National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin's Lymphomas

Version 2.2012

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Non-Hodgkin's Lymphomas

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NCCN Guidelines Panel Disclosures

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Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

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Updates to the 2.2012 version of the Non-Hodgkin's Lymphoma guidelines from the 1.2012 version include:

Mantle Cell Lymphoma

MANT-3

- Stage II_X, III, IV
  - After complete response, the treatment option for "not candidate for HDT/ASCR and treated with RCHOP" was modified as, "~~Consider~~ rituximab maintenance (See MANT-A)".

MANT-A 3 of 3

- A reference was added, "Kluin-Nelemans JC, Hoster E, Walewski J, et al. R-CHOP versus R-FC followed by maintenance with rituximab versus interferon-alfa: Outcome of the first randomized trial for elderly patients with mantle cell lymphoma [abstract]. Blood 2011;118:Abstract 439".

Post-Transplant Lymphoproliferative Disorder

PTLD-2

- Footnote "e" was revised by adding, "*Concurrent or sequential chemoimmunotherapy,* See Suggested Treatment Regimens PTLD-A.

PTLD-A

- Suggested treatment regimens were separated into "concurrent chemoimmunotherapy" and "sequential chemoimmunotherapy".
- Sequential chemoimmunotherapy, "Rituximab 375 mg/m^2 weekly x 4 weeks followed by CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone) starting Day 1 of week 9 x 4 cycles" was added as an option.

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Updates to the 1.2012 version of the Non-Hodgkin's Lymphoma guidelines from the 4.2011 version include:

New Guidelines

TPLL-1
- T-cell Prolymphocytic Leukemia is a new guideline.

HCL-1
- Hairy Cell Leukemia is a new guideline.

Global change
- Diagnosis:
  - Adequate immunophenotyping to establish diagnosis "Recommended panel for paraffin section immunohistochemistry" was changed to "IHC panel".
  - IHC panel, "cyclin D1'" and "BCL" were clarified as "CCND1".

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CSLL-1
- Informative for prognostic and/or therapy determination.
  - First bullet was modified from "cytogenetics and/or FISH to detect" to "FISH or stimulated cytogenetics".

CSLL-3
- Evaluate for indications for treatment, "Lymphocyte doubling time (LDT) ≤ 6 mo" was removed.

CSLL-4
- Heading, "relapsed/refractory therapy" was added to the page. (Also for CSLL-5 and CSLL-6)
- Response to therapy, the qualifiers "> 3 y" for long response and "< 2 y" for short response were removed and footnote 'r' was added, "Long and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff." Also for CSLL- D 1 of 5 and CSLL-D 3 of 5.
- Footnote q, "Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease" was added. Also for CSLL-5 and CSLL-6.

CSLL-6
- CLL with deletion of 11q:
  - For relapsed/refractory therapy after no response, no transplant, or disease progression, the option "followed by consideration of allogeneic stem cell transplant" was added.

CSLL-A
- Footnote a, 3rd sentence was modified as, "Alemtuzumab or high dose steroids have ~~anecdotal~~ response in del(17p) disease".

CSLL-D 1 of 5
- CLL without del (11q) or del (17p):
  - Frail patient, significant co-morbidities
    - "Chlorambucil ± prednisone" was changed to "chlorambucil ± rituximab". (Also for first-line therapy, age ≥ 70 y or younger patients with co-morbidities and relapsed/refractory therapy, short response < 2 y for age ≥ 70 y).
- Footnote f, "In patients ≥ 70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil" is new to the page.
- Footnote g, "See Discussion for further information on oral fludarabine" is new to the page.

CSLL-D 2 of 5
- CLL with del (17p):
  - First-line therapy
    - "Bendamustine + rituximab" was removed.
    - Footnote i, "Rituximab should be added unless patient is known to be refractory to rituximab" was added to "alemtuzumab ± rituximab" and "CHOP". (Also for relapsed/refractory therapy, "alemtuzumab ± rituximab")
  - Relapsed/refractory therapy
    - The order of the regimens was changed from 'in order of preference" to "in alphabetical order".
    - "High-dose dexamethasone" was changed to "high-dose methylprednisolone".
    - "Bendamustine ± rituximab" was removed.

CSLL-D 3 of 5
- CLL with del (11q):
  - First-line therapy, age ≥ 70 y or younger patients with co-morbidities
    - "Chlorambucil ± prednisone" was changed to "chlorambucil ± rituximab". (Also for relapsed/refractory therapy, short response < 2 y for age ≥ 70 y).

CSLL-E
- Table updated with Hallek M, Cheson BD, Catovsky D, et al. Blood 2008;111:5446-5456.

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Follicular Lymphoma

FOLL-1

- Footnote 'h' was modified as, "Bilateral or unilateral provided core biopsy is ~~> 2~~ *>1.6* cm".

FOLL-2

- Stage I-IV, follow-up was modified as: (Also for FOLL-3)
  - Clinical
    - *H&P and labs* every 3-6 mo for 5 y and then ~~yearly~~ *annually* or as clinically indicated
  - *Surveillance imaging*
    - *Up to 2 y post completion of treatment: CT scan no more than every 6 mo*
    - *> 2 y: No more than annually*
- Stage II[x], III, IV:
  - Indication for treatment, "Patient preference" was removed. (Also for FOLL-3)
  - No indication for treatment, "observe" was changed from a category 2A to a category 1 recommendation.

Footnotes:

- Footnote 'i' was modified as, "When determining initial treatment, consider excluding profoundly *stem cell* ~~myelo~~toxic regimens *(eg, fludarabine)*...".
- Footnote q, "Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations" was added. (Also for FOLL-3)
- Footnote, "Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated" was removed.

FOLL-3

- Headings were added to the page for clarification: optional extended therapy, follow-up, and second-line and subsequent therapy.

FOLL-A

- Footnote d, "FLIPI-2 (Federico M, Bellei M, Marcheselli L, et al. J Clin Oncol 2009;27:4555-4562) predicts for outcomes after active therapy, see Discussion" was added to the page.

FOLL-B 1 of 3

- First-line therapy:
  - Bendamustine + rituximab, the category was changed from a category 1 to a category 2A recommendation.
  - RFND (rituximab, fludarabine, mitoxantrone, dexamethasone), the category was changed from a category 2A to a category 2B recommendation.
  - Radioimmunotherapy, the category was changed from a category 2B to a category 3 recommendation.
  - "Fludarabine + rituximab" was removed.
- First-line therapy for elderly or infirm:
  - The qualifying phrase was clarified as "if none of the above are *expected to be* tolerable *in the opinion of treating physician*".
- First-line consolidation or extended dosing:
  - The qualifier "optional" was added to the heading, "First-line consolidation or extended dosing".
  - Rituximab maintenance was qualified as "Rituximab maintenance *375 mg/m^2 one dose every 8 wk* up to 2 y *for patients initially presenting with high tumor burden* (category 1)".
- Second-line and extended dosing:
  - "BVR (bendamustine, bortezomib, rituximab)" and "fludarabine + rituximab" were added.
- Second-line consolidation or extended dosing:
  - Rituximab maintenance was qualified, "Rituximab maintenance *375 mg/m^2 one dose every 12 weeks for 2 years* (category 1)*(optional)*".

Footnotes:

- Footnote d, "RFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion)" is new to the page.
- Regarding radioimmunotherapy, footnote g, "Category 3 designation is due to limited additional data such as randomized trials" is new to the page.
- Footnote, "In patients previously treated with chemotherapy, rituximab and anthracycline naive, maintenance rituximab extends disease-free, and event-free survival" was removed.
- Footnote, "Initial management of patients with follicular lymphoma should include rituximab; use caution in patients with hepatitis B" was removed.

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Mantle Cell Lymphoma

MANT-2

- Stage I, II,
  - After complete response, follow-up was added. After relapse, the algorithm was modified as "prior treatment with RT alone" then "see induction therapy on MANT-3" and "prior treatment with chemotherapy ± RT" then "second-line therapy".
  - After a partial response, the algorithm was modified as "prior treatment with RT alone" then "see induction therapy on MANT-3" and " prior treatment with chemotherapy ± RT" then "second-line therapy".

MANT-3

- Stage IIX, III, IV
  - After complete response, the treatment options for candidate for HDT/ASCR and not candidate for HDT/ASCR were clarified.
  - After partial response, "consider second-line therapy" was added.

MANT-A 1 of 3

- A new category for suggested treatment regimens was added as:
  - For patients without intention for high dose therapy with stem cell rescue consolidation
    - If treated with RCHOP, consider rituximab maintenance 375 mg/m^2 every 8 wks until progression.

Diffuse Large B-Cell Lymphoma

BCEL-1

- Useful under certain circumstances:
  - First subbullet was modified as, "...*EBER-ISH* ~~EBV~~, ALK, ~~HTLV~~ *HHV8*".
  - Second bullet was modified as, "... ~~BCL1~~ *CCND*1, BCL2, *BCL6*, MYC rearrangements *by either FISH or IHC*".
- Footnote 'a' was modified by adding, "These cases would be appropriate to evaluate for BCL2, BCL6 and MYC rearrangements".

BCEL-2

- Workup:
  - Essential, bone marrow biopsy bullet was modified as, "Adequate ~~unilateral or bilateral~~ bone marrow biopsy (~~1-2~~ >1.6 cm)...".
  - Useful in selected cases, lumbar puncture bullet was modified by adding, "and elevated LDH" to ≥ 2 extranodal sites.

BCEL-3

- Footnote 'h' was modified as, "... after completion of chemotherapy, *scrotal* RT should be given ~~to contralateral testis~~ (*25-30* ~~30-36~~ Gy).
- Footnote 'j' was modified as, "In selected ~~settings~~ cases (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≥ 2 extranodal sites *and elevated LDH*), ~~CNS prophylaxis should be given~~ *there may be an increased risk of CNS events. The optimal management of these events are uncertain, but CNS prophylaxis can be considered with* 4-8 doses of intrathecal methotrexate and/or cytarabine, *or systemic methotrexate (3-3.5 g/m^2)* during the course of treatment".
- Footnote k, "Systemic disease with concurrent CNS disease should be treated with methotrexate/cytarabine-containing regimens" was added. Also for BCEL-6.

BCEL-4

- Statge I, II, follow-up was modified as: (Also for Stage III, IV on BCEL-5)
  - Clinical
    - *H&P and labs*, every 3-6 mo for 5 y and then yearly or as clinically indicated
  - *Imaging*
    - *CT scan no more often than every 6 mo for 2 y after completion of treatment, then only as clinically indicated*
- Footnote 's' was clarified from "Wait a minimum of 8 weeks after RT to repeat PET-CT scan. The optimum timing of repeat PET-CT is unknown. False positives may occur due to posttreatment changes" to "The optimum timing of repeat PET-CT is unknown, however waiting a minimum of 8 weeks after RT to repeat PET-CT scan is suggested. False positives may occur due to posttreatment changes."

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BCEL-A
- IPI was modified as, "Serum LDH > ~~1 x~~ normal". (Also for TCEL-A)

BCEL-B
- Last bullet, second sentence was modified as, "Biopsy of PET- CT scan positive mass is recommended if additional *systemic* treatment is contemplated".

BCEL-C 1 of 3
- A new category, "Concurrent presentation with CNS disease" with treatment options was added.
  - Parenchymal: 3 g/m^2 or more of systemic methotrexate at count recovery as an alternating regimen
  - Leptomeningeal: IT methotrexate/cytarabine, consider Ommaya resevoir placement and/or systemic methotrexate (3-3.5 g/m^2)

- First-line therapy:
  - Dose dense RCHOP 14, the category was changed from a category 2B to a category 3 recommendation.

- First-line consolidation:
  - The qualifier "optional" was added to the heading "first-line consolidation".
  - High dose therapy with autologous stem cell rescue was modified as, "in *patients with age-adjusted IPI high risk disease* ~~patients~~ (category 2B)".

- Second-line therapy for patients with intention to proceed to high dose autologous stem cell rescue:
  - For GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab, "gemcitabine, dexamethasone, carboplatin ± rituximab" was added as an alternative treatment option.

- Second-line therapy for patients who are non-candidates for high dose therapy:
  - "Bendamustine ± rituximab" was added.

Burkitt Lymphoma

BURK-1
- Diagnosis, useful under certain circumstances category section was removed:
  - ISH for EBV EBER was moved to essential.
  - Molecular genetic analysis to detect: antigen receptor gene rearrangements; MYC rearrangement was removed.

Footnotes:
- Footnote 'a' was modified by adding, "Treatment of double or triple hit tumors is controversial. Optimum regimen has not been identified".
- Footnote 'c' was modified as, "...Ki67+ (~~100~~ ≥ 95%), BCL2-, BCL6+, *simple karyotype with* MYC rearrangement *as sole abnormality* ~~only by cytogenetics or FISH~~".

BURK-2
- Footnote h, "All regimens for Burkitt lymphoma include CNS prophylaxis/therapy" is new to the page. (Also for BURK-A)

BURK-A 1 of 2
- Induction therapy:
  - CALGB 9251 regimen was changed to CALGB 10002 regimen with the addition of "+ rituximab".
- Second-line therapy:
  - A statement, "While no definitive second-line therapies exists, there are limited data for the following regimens" was added.
  - "RICE (rituximab, ifosfamide, carboplatin, etoposide); intrathecal methotrexate if have not received previously" was added.

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Lymphoblastic Lymphoma

BLAST-1

- Diagnosis:
  - Essential, IHC panel was modified by adding, "CD19, CD7".
  - Essential, "cytogenetics or FISH" was changed to "cytogenetics ± FISH".
  - Useful under certain circumstances, "frozen: kappa/lambda" was removed.
- Footnotes:
  - Footnote a, "The LL category comprises two diseases, T-cell LL (90%) and B-cell LL (10%), which corresponds to T-ALL and B-ALL with presentations in extramedullary sites" is new to the page.
  - Footnote 'c' was modified by adding, "cytoplasmic CD3+, sCD3-/+".

BLAST-2

- Induction therapy heading was modified by adding "consolidation".
- Footnotes:
  - Footnote f, "All regimens for LL include CNS prophylaxis/therapy" is new to the page. (Also for BLAST-A)
  - Footnote, "For poor risk patients, consideration of high dose therapy with autologous or allogeneic stem cell rescue is appropriate" was removed.

AIDS-Related B-cell lymphoma

AIDS-1

- Diagnosis:
  - Essential, cell surface marker analysis by flow cytometry, "TdT, CD1" were removed.
- Workup:
  - Essential, "viral load" was clarified as "HIV viral load".
  - Useful in selected cases, "EBV viral load" was added.

AIDS-2

- Burkitt lymphoma:
  - CODOX-M/IVAC, "modified" was added for clarification. (Also for plasmablastic lymphoma on AIDS-3)
  - Treatment option, "HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) ± rituximab" was added.
  - A new bullet was added, "If CD4 < 100, consider eliminating rituximab".
  - Treatment option, "Consider CHOP with high-dose methotrexate ± rituximab (+ rituximab is for favorable presentation) Avoid methotrexate dose > 3 g/m^2" was removed.
  - Dose-adjusted EPOCH and CDE, "+ rituximab is for favorable presentation" was removed.
- Lymphoma associated with Castleman's disease, Diffuse large B-cell lymphoma, and Primary effusion lymphoma:
  - "+ rituximab" was added to: dose-adjusted EPOCH, CDE, CHOP, and CDOP.
  - Two new bullets were added, "If CD20-, rituximab is not indicated" and "If CD4 < 100, consider eliminating rituximab".
- Footnotes:
  - Footnote 'e' was modified as, "...for all patients *with HIV-associated DLBCL*. At other NCCN institutions, ~~patients with HIV-associated DLBCL~~ ... or ≥ 2 extranodal sites and *elevated LDH*).
  - Footnote, "Most cases are CD20 negative and addition of rituximab is not indicated" was removed.

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Updates to the 1.2012 version of the Non-Hodgkin's Lymphoma guidelines from the 4.2011 version include: (continued)

Primary Cutaneous B-Cell Lymphoma

CUTB-1

- Diagnosis:
  - Useful under certain circumstances, second subbullet was modified as, "Assessment of ~~surface~~ IgM and IgD expression...".
  - The names were clarified as "Primary Cutaneous Marginal Zone ~~B-cell~~ Lymphoma" and "Primary Cutaneous Follicle Center ~~B-~~Cell Lymphoma".

Peripheral T-Cell Lymphomas

TCEL-1

- Diagnosis:
  - Essential, IHC panel was modified as, "EBER-ISH".
  - Useful under certain circumstances, "PD1" was removed from last bullet and added next to "CD279" for clarification.
- Useful under certain circumstances, third bullet was modified as, "cytogenetics~~ or FISH~~ *to establish clonality*".
- Footnote 'a' was modified by adding, "...as these are often seen with reactive/inflammatory processes".

TCEL-2

- Workup:
  - PET-CT scan was moved from useful in selected cases to essential.

TCEL-3

- The following information about "breast implant-associated ALCL" was added to the page:
  - Emerging entity with an unknown natural history and management
  - Treatment recommendations above may not apply and individualized care is necessary

TCEL-5

- Consolidation/additional therapy:
  - "Consider" was added to both "allogeneic stem cell transplant" and "high dose therapy with autologous stem cell rescue".

TCEL-B 1 of 2

- First-line therapy:
  - The suggested treatment regimens were clarified as "for ALCL, ALK+ histology" and "other histologies (ALCL, ALK -; PTCL, NOS; AITL; EATL)".
  - For ALCL, ALK+ histology, "CHOEP-21 (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone)" was added.
  - For other histologies (ALCL, ALK -; PTCL, NOS; AITL; EATL), "CHOP every 2 or 3 wks" was clarified as "CHOP-14" and "CHOP-21".

Mycosis Fungoides/Sezary Syndrome

MFSS-1

- Diagnosis:
  - Useful under certain circumstances, IHC panel, "CD25" was added and second bullet was modified as "Molecular ~~study~~ *analysis*".
  - Footnote c, "Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative" was added to the page.

MFSS-6

- Footnote v, "Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should first be considered for therapies under SYST-CAT A before resorting to treatments listed in SYST CAT B or SYST CAT C" was added.

MFSS-7

- Footnote 'ee' was modified by removing, "Alemtuzumab can be administered by IV or subcutaneously". Also for MFSS-8.

MFSS-A 1 of 3

- Skin-directed therapies, local radiation was modified, "*12-36 Gy* ~~particularly unilesional presentation, 24-36 Gy~~".

Adult T-cell Leukemia/Lymphoma

ATLL-2

- Heading was clarified from "primary therapy" to "first-line therapy". Also for ATLL-3.

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Extranodal NK/T-cell Lymphoma, nasal type

NKTL-1

- Diagnosis:
  - "Molecular analysis for TCR gene rearrangements" was moved from essential to useful under certain circumstances.
  - "*in situ* hybridization (ISH) for (EBER-1/2)" was clarified as"EBER-ISH".
- Footnote 'c' was modified by adding, "EBV- EBER+".

NKTL-2

- Induction therapy:
  - Stage I, presence of any risk factors and stage II, "sequential chemoradiation" was added as an option.
  - RT dose "≥ 50 Gy" was removed from the page and a footnote was added to the suggested treatment regimens page.

NKTL-B

- Suggested treatment regimen:
  - "In alphabetical order" was added.
  - Combination chemotherapy regimen, "AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) (Reported as a second line regimen.)" was added as an option.
  - Sequential chemoradiation regimens were added as options
    - SMILE followed by RT 45-50.4 Gy
    - VIPD followed by RT 45-50.4 Gy

Post-Transplant Lymphoproliferative Disorder

PTLD-1

- Diagnosis:
  - Essential,
    - IHC panel, "kappa, lambda" was added.
    - Epstein-Barr virus was modified as, "evaluation by EBV-LMP1 or EBER-ISH (if EBV-LMP1 negative, EBER-ISH is recommended)".
  - Useful under certain circumstances,
    - Third bullet was modified as, "Molecular genetic analysis to detect: IgH *gene rearrangements* ~~by PCR~~".
    - Fourth bullet, "EBV by southern blot" was added.
- Workup:
  - Useful in selected cases, "EBV serology for primary versus reactivation" was added.

PTLD-2

- Heading was clarified from "primary threatment" to "first-line therapy". Also for ATLL-3.
- First-line therapy:
  - For both early lesions and polymorphic, "If EBV positive, treat with gancyclovir" was removed.
  - Polymorphic, systemic was modified as "RI, if possible *and*: Rituximab *alone or* Chemoimmunotherapy".
  - Polymorphic, localized was modified as "*RI, if possible and:* RT ± *rituximab* or Surgery ± *rituximab* or Rituximab alone".
  - Monomorphic was modified as "RI, *if possible and/or:* Rituximab alone or Chemoimmunotherapy".
- Second-line therapy:
  - Polymorphic, complete response was modified as, "Monitor EBV PCR and: Observation or Continue RI, if possible ± maintenance rituximab".
- Footnotes:
  - Footnote 'd' was modified by adding, "RI should be coordinated with the transplant team".
  - Footnote 'f' was changed from "In patients unable to tolerate chemotherapy" to "As part of a step-wise approach in patients who are not highly symptomatic or cannot tolerate chemotherapy secondary to co-morbidity".

Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms

NHODG-A

- General principles and a new introductory page were added.

NHODG-A 8 of 10

- Footnote f, "Rare T-cell lymphomas may be PAX5+. PCR analysis may be required to determine lineage in such cases" is new the page.

Principles of Radiation Therapy

NHODG-E

- A new reference was added, "Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. Radiother Oncol 2011;100:86-92".

NCCN Guidelines Version 2.2012
CLL/SLL[a]

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DIAGNOSIS

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor, if the diagnosis was made on a lymph node or bone marrow biopsy. Rebiopsy if consult material is nondiagnostic.**
- **An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IGHV and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL/SLL.**
- **Flow cytometry of blood adequate for diagnosis of CLL/SLL (biopsy not required).**

- **Adequate immunophenotyping to establish diagnosis[b,c]**
  - **IHC panel: CD3, CD5, CD10, CD20, CD23, CCND1**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10**
- **Absolute monoclonal B lymphocyte count[d]**

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:[e]

- **FISH or stimulated cytogenetics to detect: t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)**
- **Molecular analysis to detect: immunoglobulin heavy chain variable gene (IGHV) mutation status**
- **Determination of CD38 and Zap 70 expression by flow cytometry or immunohistochemistry[f]**

CLL/SLL → **See Workup for CLL/SLL (CSLL-2)**

Monoclonal B lymphocytosis (MBL)
- **Absolute monoclonal B lymphocyte count < 5000/mm^3**
- **All lymph nodes < 1.5 cm**
- **No anemia**
- **No thrombocytopenia**

→ **Observe**

[a] CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma. Cases diagnosed as B-PLL are excluded from this guideline.

[b] Typical immunophenotype: CD5+, CD23+, CD43+/-, CD10-, CD19+, CD20 dim, sIg dim+ and cyclin D1-. Note: Some cases may be sIg bright+, CD23- or dim and some MCL may be CD23+; CCND1 immunohistochemistry or FISH for t(11;14) should be considered in all cases and should be done in cases with an atypical immunophenotype (CD23 dim or negative, CD20 bright, sIg bright).

[c] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[d] Absolute monoclonal B lymphocyte count < 5000/mm^3 in the absence of adenopathy or other clinical features of lymphoproliferative disorder is monoclonal B lymphocytosis (MBL).

[e] See Prognostic Information for CLL (CSLL-A).

[f] Evaluation of ZAP 70 expression can be challenging and ZAP 70 is not recommended outside the setting of a clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

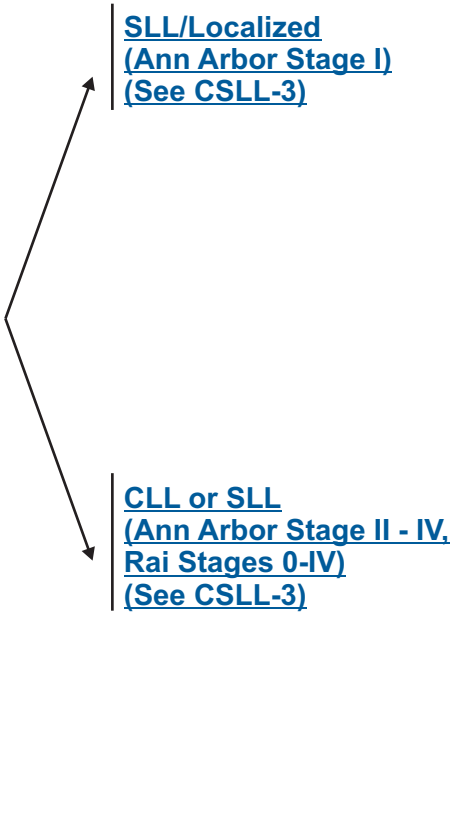
WORKUP

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Hepatitis B testing[g] if CD20 monoclonal antibody contemplated
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct Coombs' test
- Chest/abdominal/pelvic CT should be done prior to initiation of therapy (particularly when peripheral adenopathy is present and symptoms suggest bulky lymph nodes)
- Beta-2-microglobulin
- Uric acid
- Unilateral bone marrow biopsy (± aspirate) at initiation of therapy
- Discussion of fertility issues and sperm banking
- PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected



[g]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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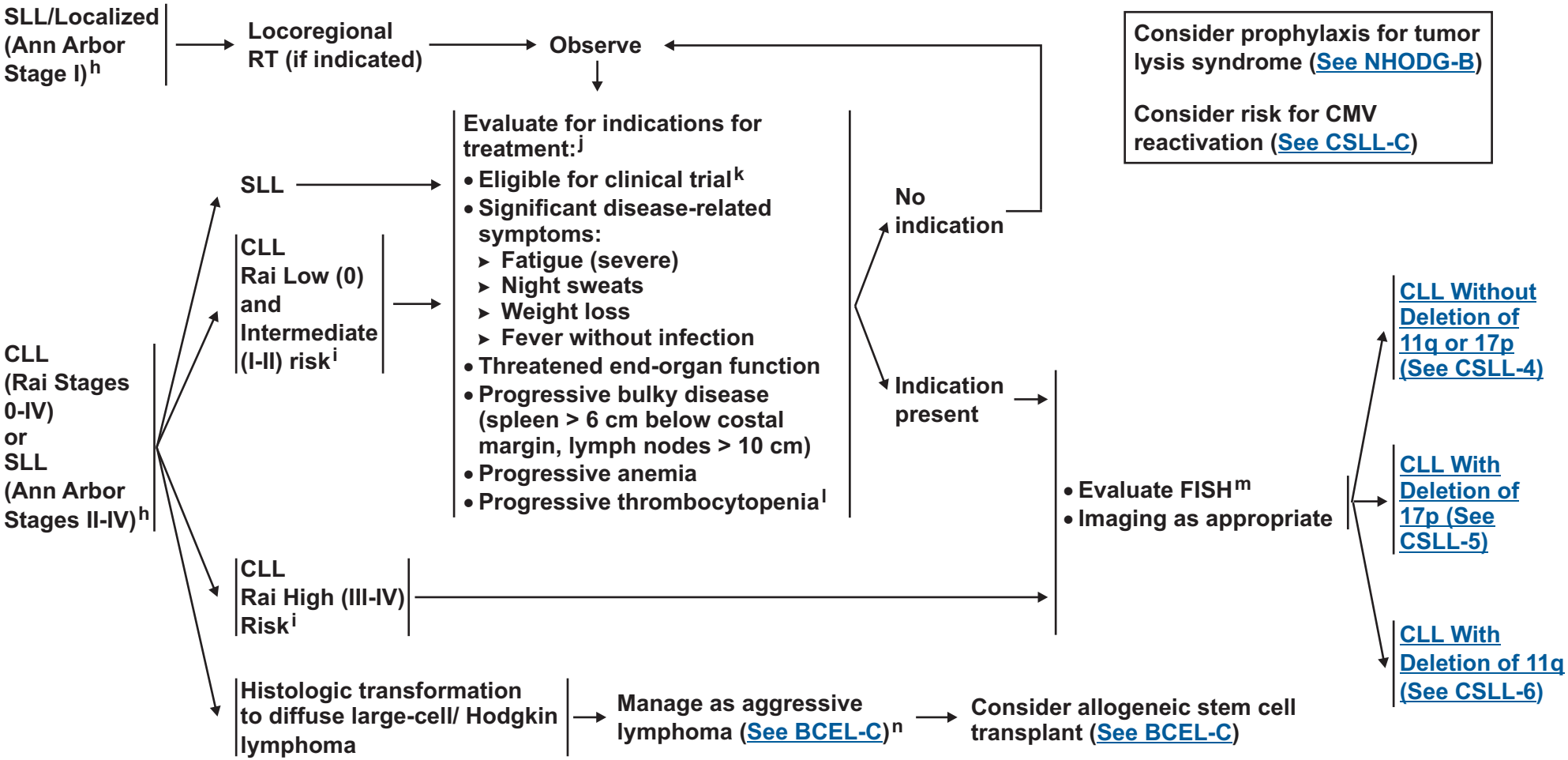
PRESENTATION



[h] See Supportive Care For Patients With CLL (CSLL-C).

[i] See Rai and Binet Classification Systems (CSLL-B).

[j] Absolute lymphocyte count alone is not an indication for treatment unless above 200- 300 x 10^9/L or symptoms related to leukostatsis.

[k] Given incurability with conventional therapy, consider a clinical trial as first line of treatment.

[l] Platelet counts >100,000 cells/mm^3 are typically not associated with clinical risk.

[m] Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] is necessary to direct treatment.

[n] In addition to the regimens listed in BCEL-C, R-HyperCVAD has also been used in this setting.

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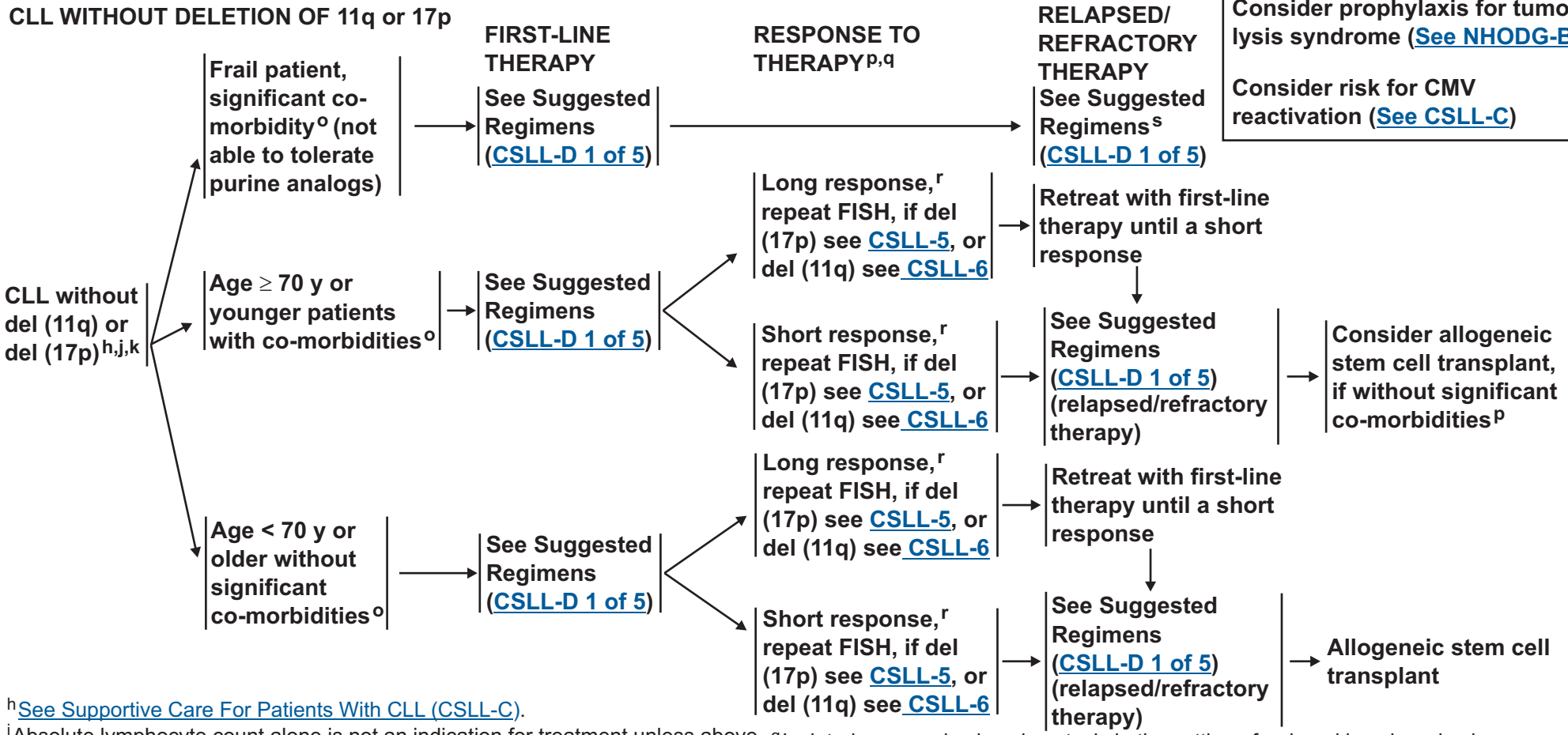
CLL WITHOUT DELETION OF 11q or 17p



[h] See Supportive Care For Patients With CLL (CSLL-C).

[j] Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10^9/L or symptoms related to leukostatsis.

[k] Given incurability with conventional therapy, consider a clinical trial as first-line of treatment.

[o] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.

[p] Keating M, Wierda W, Tam C, et al. Long term outcome following treatment failure of FCR chemoimmunotherapy as initial therapy for chronic lymphocytic leukemia [abstract]. Blood 2009;114:Abstract 2381.

[q] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

[r] Long and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff.

[s] If long response, treat with the same first-line therapy. If short response, consider alternative first-line therapy not used before.

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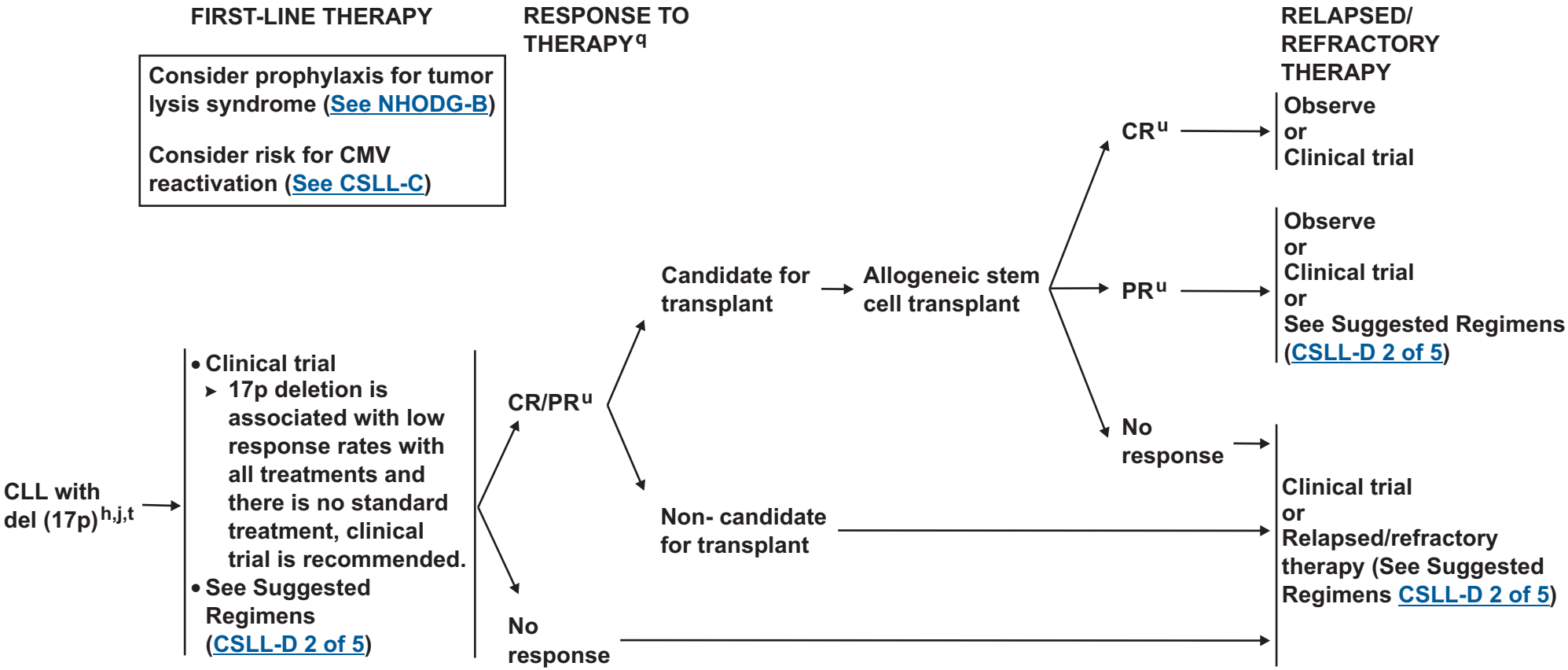
CLL WITH DELETION OF 17p



[h] See Supportive Care For Patients With CLL (CSLL-C).
[j] Absolute lymphocyte count alone is not an indication for treatment unless above 200- 300 x 10^9/L or symptoms related to leukostatsis.
[q] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.
[t] Patients with low positivity should be retested due to chance of false positive results.
[u] See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).

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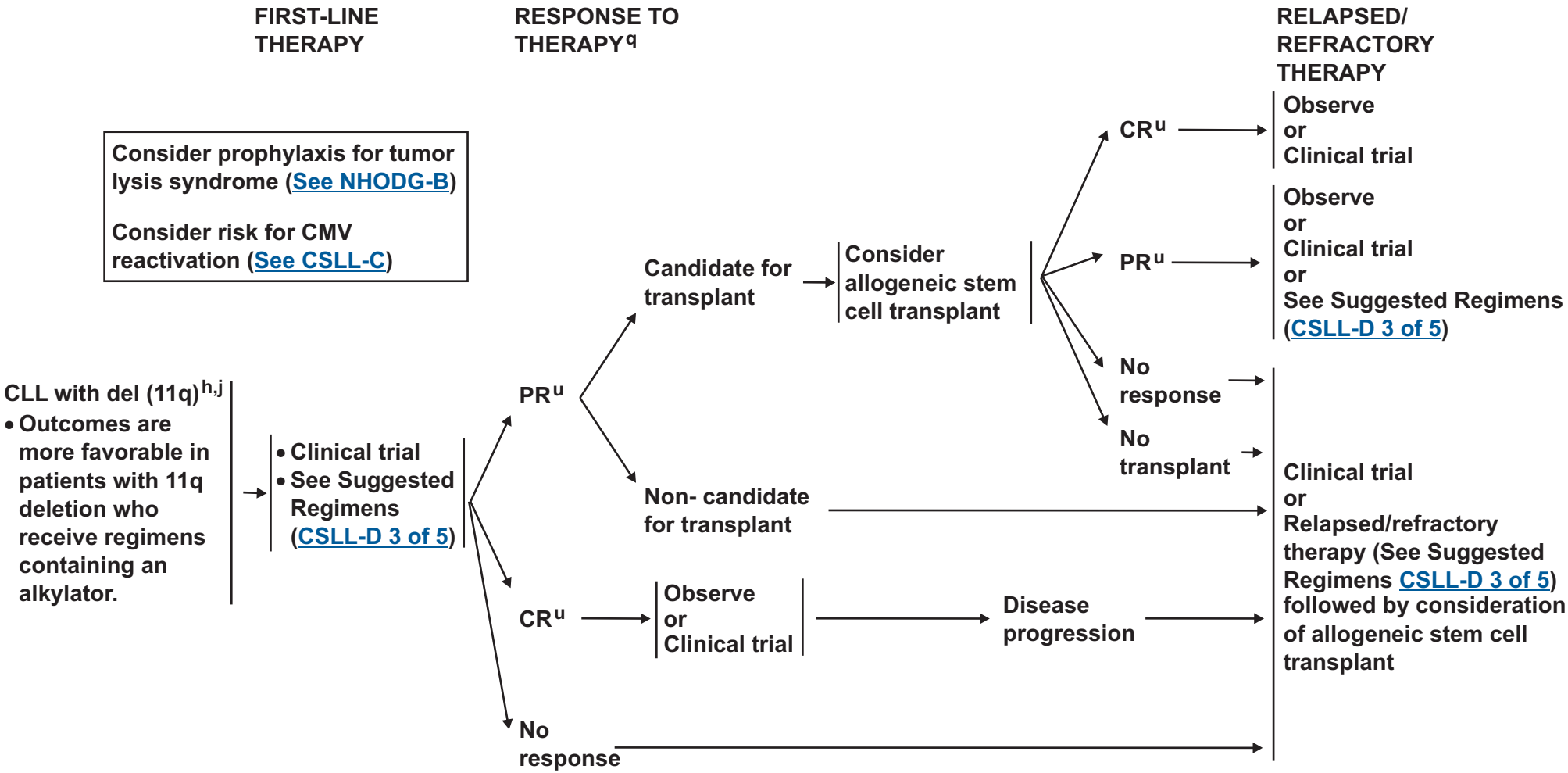
CLL WITH DELETION OF 11q



[h] See Supportive Care For Patients With CLL (CSLL-C).
[j] Absolute lymphocyte count alone is not an indication for treatment unless above 200- 300 x 10^9/L or symptoms related to leukostatsis.
[q] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.
[u] See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).

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PROGNOSTIC INFORMATION FOR CLL[a]

Immunoglobulin Variable Region (IGHV) Gene Mutation and Surrogates by Flow Cytometry

	Outcome Association	
	Favorable	Unfavorable
DNA sequencing[b] IGHV	> 2% mutation	≤ 2% mutation
Flow Cytometry		
CD38	< 30 %	≥ 30 %
Zap 70	< 20 %	≥ 20 %

Interphase Cytogenetics (FISH)[c]

Unfavorable	Neutral	Favorable
del(11q) del(17p)	Normal +12	del(13q) (as a sole abnormality)

[a]This table provides useful prognostic information relative to the time to progression where therapy is required and survival. The presence of del(11q) and/or del (17p) are associated with short progression free survival to chemotherapy and chemoimmunotherapy approaches. Alemtuzumab or high dose steroids have response in del(17p) disease.

[b]IGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated.

[c]Formal studies identifying the percentage of abnormal cells identified by FISH are ongoing although populations less than 10% appear to not have the clinical impact as noted in the table.

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CLL STAGING SYSTEMS

Rai System[a]

Stage	Description	Risk Status
0	Lymphocytosis, lymphocytes in blood > 15,000/mcL and > 40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0-I with splenomegaly, hepatomegaly, or both	Intermediate
III[c]	Stage 0-II with hemoglobin < 11.0 g/dL or hematocrit < 33%	High
IV[c]	Stage 0-III with platelets < 100,000/mcL	High

Binet System[b]

Stage	Description
A	Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm^3 and < 3 enlarged areas
B	Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm^3 and ≥ 3 enlarged areas
C[c]	Hemoglobin < 10 g/dL and/or Platelets < 100,000/mm^3 and any number of enlarged areas

[a] This research was originally published in Blood. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46(2):219-234. (c) the American Society of Hematology.

[b] From: Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.

[c] Immune-mediated cytopenias are not the basis for these stage definitions.

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SUPPORTIVE CARE FOR PATIENTS WITH CLL

Recurrent Sinopulmonary Infections (requiring IV antibiotics or hospitalization)	• Antimicrobials as appropriate • Evaluate serum IgG, if < 500 mg/dl ➤ begin monthly IVIG 0.3-0.5 g/kg, ➤ adjust dose/interval to maintain nadir level of approximately 500 mg/dl
Antiinfective Prophylaxis	• Recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter, if tolerated ➤ Herpes virus (acyclovir or equivalent) ➤ PCP (sulfamethoxazole/trimethoprim or equivalent) • Alemtuzumab: Clinicians must be aware of the high risk of CMV reactivation. The current appropriate management is controversial, some use ganciclovir (oral or IV) prophylactically if viremia present, others only if viral load is rising. CMV viremia should be measured by PCR quantitation at least every 2-3 wks. Consultation with an Infectious Disease expert may be necessary.
Autoimmune Cytopenias	• Auto-immume hemolytic anemia (AIHA): Diagnosis with reticulocyte count, haptoglobin, DAT ➤ AIHA that develops in setting of treatment with fludarabine, stop, treat, and avoid subsequent fludarabine • Immune thrombocytopenia purpura (ITP): Evaluate bone marrow for cause of low PLT • Pure red blood cell aplasia (PRCA): Evaluate for parvo B19 and bone marrow evaluation • Treatment: Corticosteroids; rituximab; IVIG; cyclosporin A; splenectomy; eltrombopag or romiplostim (ITP)
Vaccination	• Annual Influenza vaccine[a] • Pneumococcal vaccine (Prevnar preferred) every 5 yrs • Avoid all live vaccines, including Zoster
Blood Product Support	• Transfuse according to institutional or published standards • Irradiate all blood products to avoid transfusion associated GVHD

[a] In patients who have received rituximab, B-cell recovery occurs by approximately 9 months. Prior to B-cell recovery, patients generally do not respond to influenza vaccine and if given should not be considered vaccinated.

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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)
CLL without del (11q) or del (17p)

Frail patient, significant co-morbidity (not able to tolerate purine analogs)

- Chlorambucil ± rituximab
- Rituximab (single)
- Pulse corticosteroids

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

See Suggested Regimens for CLL with del (17p) (2 of 5)

See Suggested Regimens for CLL with del (11q) (3 of 5)

First-line therapy[b]

- Age ≥ 70 y or younger patients with co-morbidities
  - Chlorambucil ± rituximab
  - BR (bendamustine, rituximab)[c]
  - Cyclophosphamide, prednisone ± rituximab
  - Alemtuzumab[d]
  - Rituximab
  - Fludarabine[e,f,g] ± rituximab
  - Cladribine
- Age < 70 y or older patients without significant co-morbidities
  - Chemoimmunotherapy[c,g]
    - FCR (fludarabine,[e] cyclophosphamide, rituximab)
    - FR (fludarabine,[e] rituximab)
    - PCR (pentostatin, cyclophosphamide, rituximab)
    - BR

Relapsed/Refractory therapy

- Long response[h]
  - Retreat as in first line therapy until short response
- Short response[h] for age ≥ 70 y
  - Chemoimmunotherapy[c,g]
    - Reduced-dose FCR[e]
    - Reduced-dose PCR
    - Bendamustine ± rituximab
    - High-dose methylprednisolone (HDMP) + rituximab
  - Chlorambucil ± rituximab (if used first-line)
  - Ofatumumab
  - Alemtuzumab[d] ± rituximab
  - Dose-dense rituximab (category 2B)
- Short response[h] for age < 70 y or older patients without significant co-morbidities
  - Chemoimmunotherapy[c,g]
    - FCR[e]
    - PCR
    - BR
    - Fludarabine[e] + alemtuzumab
    - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
    - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
    - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
    - OFAR (oxaliplatin, fludarabine,[e] cytarabine, rituximab)
  - Ofatumumab
  - Alemtuzumab[d] ± rituximab
  - HDMP + rituximab

[a] See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.

[b] Antibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.

[c] Monitor for myelosuppression.

[d] Less effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.

[e] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

[f] In patients ≥ 70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.

[g] See Discussion for further information on oral fludarabine.

[h] Long and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff.

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SUGGESTED TREATMENT REGIMENS[a]
CLL with del (17p)

First-line therapy[b] (in order of preference)
- FCR (fludarabine,[e,g] cyclophosphamide, rituximab)[c]
- FR (fludarabine,[e,g] rituximab)[c]
- High-dose methylprednisolone (HDMP) + rituximab
- Alemtuzumab[d] ± rituximab[i]

Relapsed/Refractory therapy (in alphabetical order)
- Alemtuzumab[d] ± rituximab[i]
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab[c,i]
- CFAR (cyclophosphamide, fludarabine,[e,g] alemtuzumab, rituximab)[c]
- HDMP ± rituximab[i]
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab[c]
- Ofatumumab[j]
- OFAR (oxaliplatin, fludarabine,[e,g] cytarabine, rituximab)[c]

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 5)

See Suggested Regimens for CLL with del (11q) (3 of 5)

[a] See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
[b] Antibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.
[c] Monitor for myelosuppression.
[d] Less effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.
[e] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[g] See Discussion for further information on oral fludarabine.
[i] Rituximab should be added unless patient is known to be refractory to rituximab.
[j] This is not effective in patients with lymph nodes > 5 cm.

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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)
CLL with del (11q)

First-line therapy[b]

- Age ≥ 70 y or younger patients with co-morbidities
  - Chlorambucil ± rituximab
  - BR (bendamustine, rituximab)[c]
  - Cyclophosphamide, prednisone ± rituximab
  - Reduced-dose FCR (fludarabine,[e,g] cyclophosphamide, rituximab)[c]
  - Alemtuzumab[d]
  - Rituximab
- Age < 70 y or older patients without significant co-morbidities
  - Chemoimmunotherapy[c]
    - FCR[g]
    - BR
    - PCR (pentostatin, cyclophosphamide, rituximab)

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 5)

See Suggested Regimens for CLL with del (17p) (2 of 5)

Relapsed/Refractory therapy

- Long response[h]
  - Retreat as in first line therapy until short response
- Short response[h] for age ≥ 70 y
  - Chemoimmunotherapy[c,g]
    - Reduced-dose FCR[e]
    - Reduced-dose PCR
    - Bendamustine ± rituximab
    - High-dose methylprednisolone (HDMP) + rituximab
    - Chlorambucil ± rituximab (if used first line)
  - Ofatumumab
  - Alemtuzumab[d] ± rituximab
  - Dose-dense rituximab (category 2B)
- Short response[h] for age < 70 y or older patients without significant co-morbidities
  - Chemoimmunotherapy[c,g]
    - FCR[e]
    - PCR
    - BR
    - Fludarabine[e] + alemtuzumab
    - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
    - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
    - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
    - OFAR (oxaliplatin, fludarabine,[e,g] cytarabine, rituximab)
  - Ofatumumab
  - Alemtuzumab[d] ± rituximab
  - HDMP + rituximab

[a] See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.

[b] Antibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy

[c] Monitor for myelosuppression.

[d] Less effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.

[e] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

[g] See Discussion for further information on oral fludarabine.

[h] Long and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff.

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SUGGESTED TREATMENT REGIMENS
REFERENCES

Alemtuzumab

Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. Blood 2004;103:3278-3281.

Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: Results of a large international study. Blood 2002;99:3554-3561.

Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616-5623.

Alemtuzumab + rituximab

Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 2003;101:3413-3415.

Bendamustine + rituximab

Fischer K, Cramer P, Busch R et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011;29:3559-3566.

Fischer K, Cramer P, Stilgenbauer S et al. Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: A multicenter phase II trial of the German CLL Study Group (GCLLSG) [abstract]. Blood, 2009;114: Abstract 205.

Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27:4378-4384.

Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine in the treatment of chronic lymphocytic leukemia -consistent superiority over chlorambucil in elderly patients and across clinically defined risk groups [abstract]. Blood 2009;114: Abstract 2367.

Chlorambucil

Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009;114:3382-3391.

Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 2000; 343:1750-1757.

Chlorambucil + rituximab

Hillmen P, Gribben JG, Follows GA, et al. Rituximab plus chlorambucil (R-Chlorambucil) as first-line treatment for chronic lymphocytic leukaemia (CLL): Final analysis of an open-label phase II study [abstract]. Ann Oncol 2011;22:Abstract 120.

Foa R, Alietti A, Guarini A, et al. A phase II study of chlorambucil rituximab (CLB-R) followed by R maintenance vs observation in elderly patients with previously untreated chronic lymphocytic leukemia (CLL): Induction phase results [abstract]. Haematologica 2011;96:Abstract 532.

CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab)

Wierda WG, O'Brien S, Ferrajoli A, et al. Combined cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR), an active frontline regimen for high-risk patients with CLL [abstracts]. Blood 2007;110:Abstract 628.

Badoux XC, Keating MJ, Wang X, et al. Cyclophosphamide, fludarabine, rituximab and alemtuzumab (CFAR) as salvage therapy for heavily pre-treated patients with chronic lymphocytic leukemia. Blood 2011;118:2085-2093.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)

Leporrier M, Chevret S, Cazin B, et al. Randomized comparison of fludarabine, CAP, and CHOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. Blood 2001;98:2319-2325.

Continued on next page

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SUGGESTED TREATMENT REGIMENS
REFERENCES

FCR (fludarabine, cyclophosphamide, rituximab)
Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 2005;23:4079-4088.
Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 2005;23:4070-4078.
Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112:975-980.
Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomised, open-label, phase 3 trial. Lancet 2010;376:1164-1174.
Robak T, Dmoszynska A, Solal-Celigny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756-1765.

Fludarabine + alemtuzumab
Elter T, Borchmann P, Schulz H, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: Results of a Phase II trial. J Clin Oncol 2005;23:7024-7031.

Fludarabine + rituximab
Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6-14.

HDMP (high-dose methylprenisolone) + rituximab
Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. Leukemia and Lymphoma 2007;48:2412-2417.
Castro JE, James DF, Sandoval-Sus JD, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia. Leukemia 2009;23:1779-1789.

Ofatumumab
Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749-1755.
Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood 2008;111:1094-1100.

OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
Tsimberidou AM, Wierda WG, Plunkett W, et al. Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's Syndrome or fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2008;26:196-203.
Tsimberidou AM, Wierda WG, Badoux X, et al. Evaluation of oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR) combination therapy in aggressive chronic lymphocytic leukemia (CLL) and Richter's syndrome (RS) [abstract]. J Clin Oncol 2010;28: Abstract 6521.

PCR (pentostatin, cyclophosphamide, rituximab)
Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 2006;24:1575-1581.
Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood 2007;109:405-411.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RESPONSE DEFINITION AFTER TREATMENT FOR CLL[a,b]

Parameter	Complete response	Partial response	Progressive Disease
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules, Hypocellular marrow defines CR with incomplete marrow recovery (CRi)	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Blood lymphocytes	< 4000/µ/L	Decrease ≥ 50% over baseline	Increase ≥ 50% over baseline*
Group B			
Platelet count without growth factors	> 100,000/µ/L	> 100,000/µ/L or increase ≥ 50% over baseline	Decrease ≥ 50% over baseline secondary to CLL
Hemoglobin without transfusions or growth factors	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils without growth factors‡	> 1500/µ/L	> 1500/µ/L or > 50% improvement over baseline	

Group A criteria define the tumor load. Group B criteria define the function of the hematopoietic system (or marrow).
Complete remission (CR): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms;
Partial remission(PR): at least two of the criteria of group A plus one of the criteria of group B have to be met;
Stable disease is absence of progressive disease (PD) and failure to achieve at least a PR;
PD: appearance of any new lesions; at least one of the above criteria of group A or group B has to be met.
†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).
‡These parameters are irrelevant for some response categories.

[a] Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: A report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-5456.

[b] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

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Follicular Lymphoma[a] (grade 1-2)

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DIAGNOSIS[b]

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**
- **An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. Histologic grading cannot be performed on an FNA.**
- **Adequate immunophenotyping to establish diagnosis[c,d]**
  - **IHC panel: CD20, CD3, CD5, CD10, BCL2,[e] BCL6, CCND1, CD21 or CD23, or**
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: antigen gene receptor rearrangements; BCL2 rearrangement**
- **Cytogenetics or FISH: t(14;18); t(8;14) or variants**
- **IHC panel: Ki67[f]**

WORKUP

ESSENTIAL:

- **Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC, differential, platelets**
- **LDH**
- **Comprehensive metabolic panel**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **Hepatitis B testing[g]**
- **Bone marrow biopsy + aspirate to document clinical stage I-II disease[h]**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL IN SELECTED CASES:

- **MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated**
- **Neck CT**
- **Beta-2-microglobulin**
- **PET-CT scan**
- **Uric acid**
- **Discussion of fertility issues and sperm banking**
- **SPEP and/or quantitative immunoglobulin levels**
- **Hepatitis C testing**

Stage I, II → **See Initial Therapy (FOLL-2)**

Stage II, III, IV → **See Initial Therapy (FOLL-2)**

[a] Follicular lymphoma, grade 1-2. Follicular lymphoma, grade 3 is an area of controversy. The distinction between follicular grade 3a and 3b has not been shown to have clinical significance to date. Follicular lymphoma, grade 3 is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma Guideline (BCEL-1). Any area of diffuse large B-cell lymphoma (DLBCL) in a follicular lymphoma of any grade should be diagnosed and treated as a DLBCL.

[b] Germinal center or follicular center cell phenotype type is not equivalent to follicular lymphoma and occurs in Burkitt lymphoma and some DLBCL.

[c] Typical immunophenotype: CD10+, BCL2+, CD23+/-, CD43-, CD5-, CD20+, CCND1-, BCL6+. Rare cases of follicular lymphoma may be CD10- or BCL2-.

[d] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[e] In BCL2 negative young patients with localized disease, consider entity of pediatric follicular lymphoma.

[f] There are reports showing Ki67 proliferation fraction of > 30 % may be associated with a more aggressive clinical behavior but no evidence this should guide treatment decisions.

[g] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[h] Bilateral or unilateral provided core biopsy is >1.6 cm. If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy, bone marrow biopsy may be deferred.

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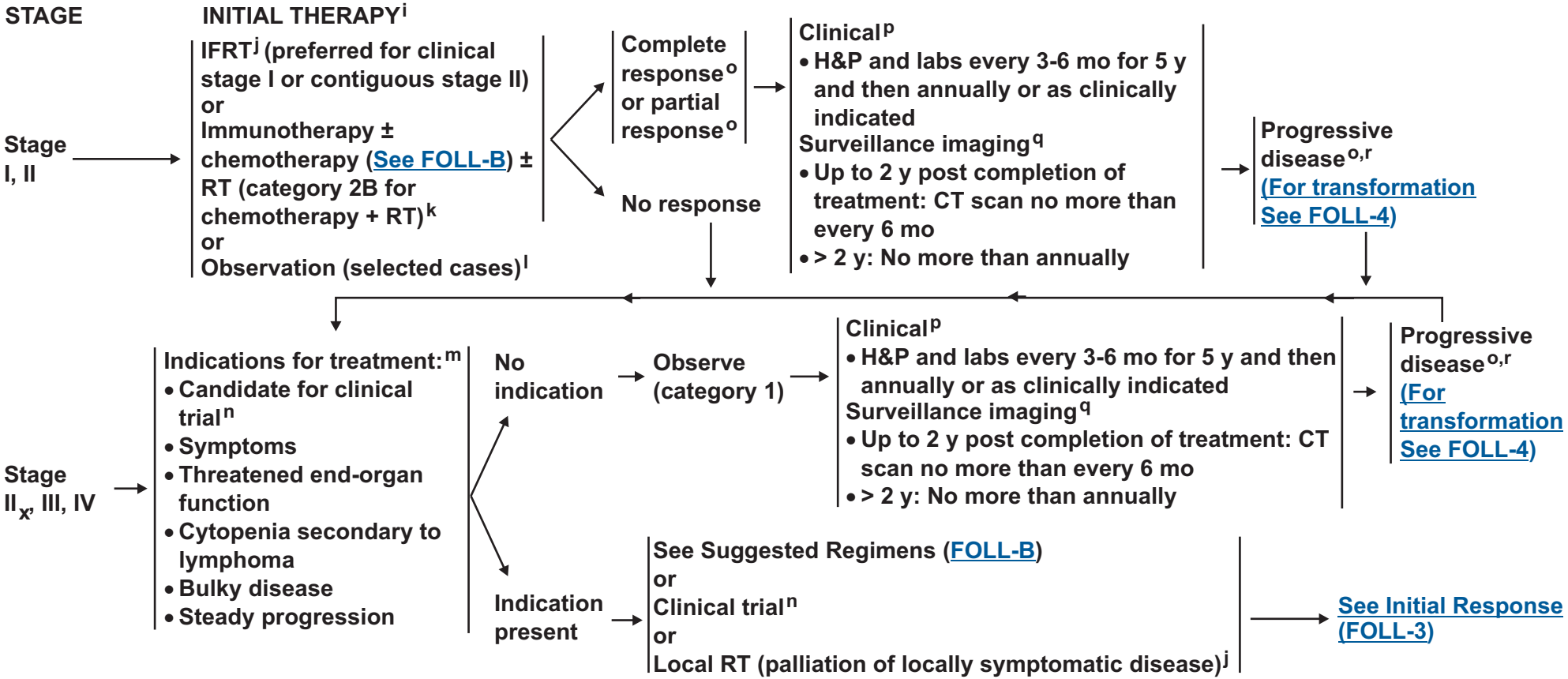

[i] When determining initial treatment, consider excluding profoundly stem cell toxic regimens (eg, fludarabine) for patients who may be eligible for high dose therapy with autologous stem cell rescue.

[j] See Principles of Radiation Therapy (NHODG-E).

[k] Initiation of chemotherapy or more extended RT can improve FFS (failure-free survival), but has not been shown to improve overall survival. These are options for therapy.

[l] Observation may be appropriate in circumstances where toxicity of involved-field RT outweighs potential clinical benefit.

[m] See GELF criteria (FOLL-A).

[n] Given incurability with conventional therapy, consider investigational therapy as first-line of treatment.

[o] See Response Criteria for Lymphoma (NHODG-C).

[p] Consider clinical trials appropriate for patients on observation.

[q] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.

[r] Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy or marked increase in FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, new B symptoms develop, or there is marked heterogeneity or sites of intense FDG avidity on PET scan. A directed biopsy should be performed of a suspicious area. If transformation is histologically confirmed, treat with anthracycline-based therapy. Positive functional imaging does not replace biopsy to diagnose transformation. See Management of Transformation (FOLL-4).

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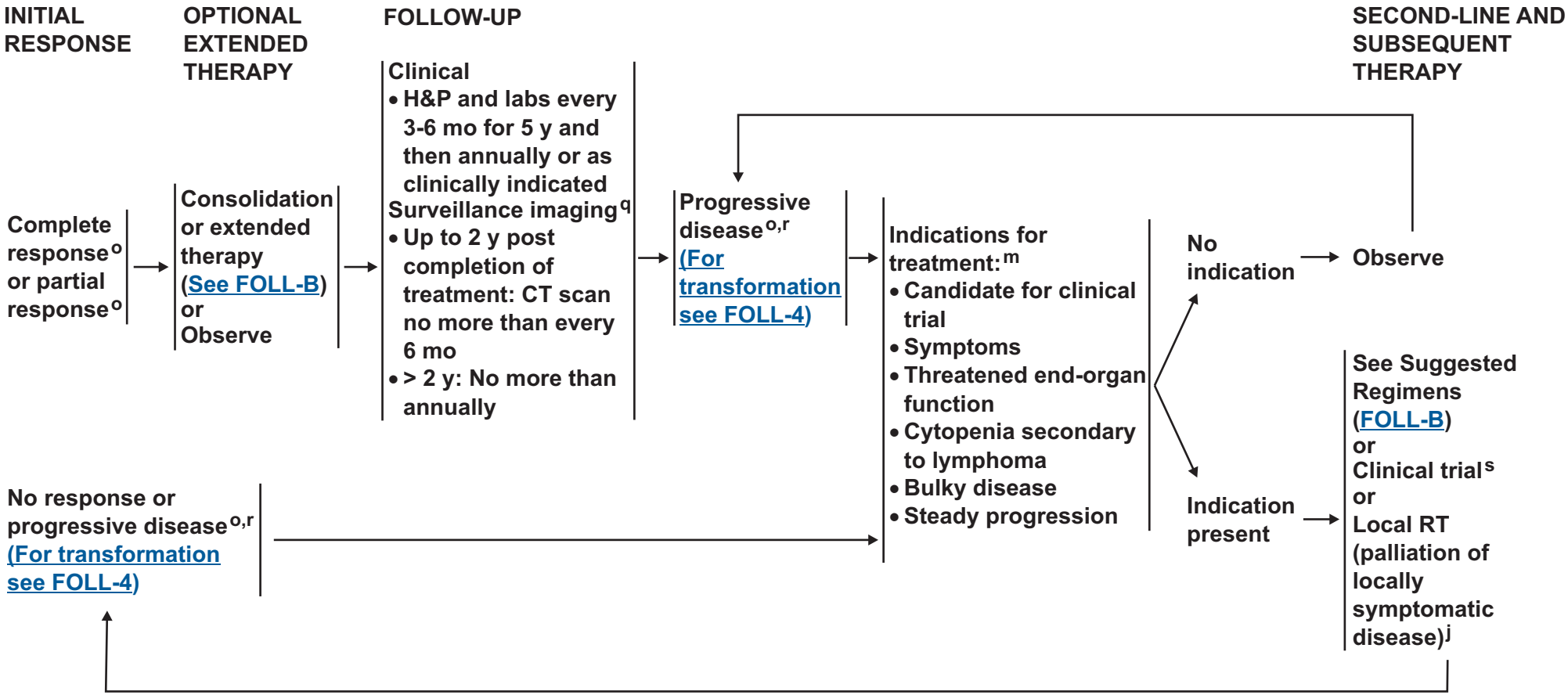
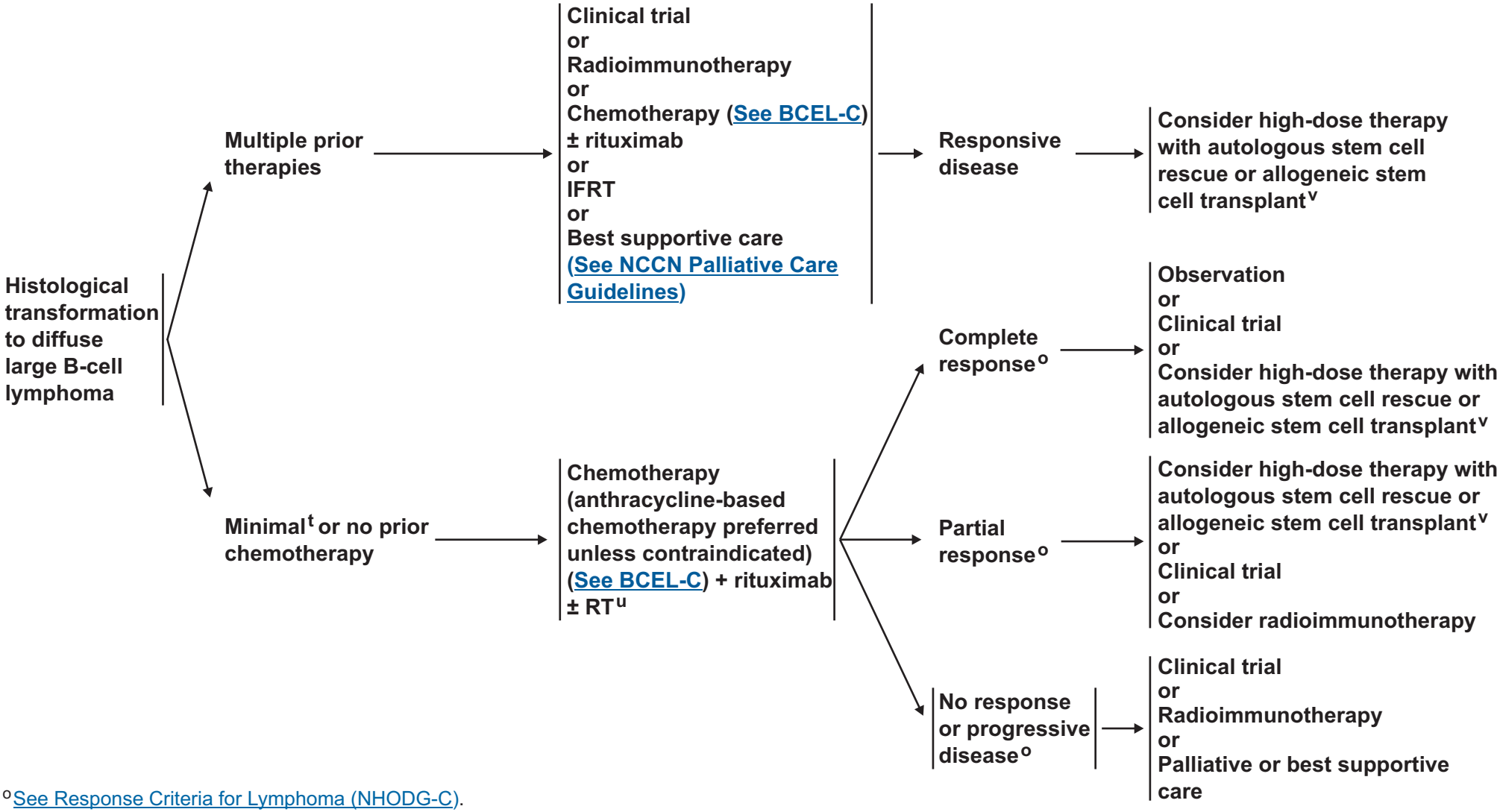


[j] See Principles of Radiation Therapy (NHODG-E).
[m] See GELF criteria (FOLL-A).
[o] See Response Criteria for Lymphoma (NHODG-C).
[q] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[r] Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy or marked increase in FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, new B symptoms develop, or there is marked heterogeneity or sites of intense FDG avidity on PET scan. A directed biopsy should be performed of a suspicious area. If transformation is histologically confirmed, treat with anthracycline-based therapy. Positive functional imaging does not replace biopsy to diagnose transformation. See Management of Transformation (FOLL-4).
[s] Clinical trials may involve novel agents, regimens, or transplantation.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

HISTOLOGICAL TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA



[o] See Response Criteria for Lymphoma (NHODG-C).
[t] Involved-field RT alone or one course of single agent therapy including rituximab.
[u] If locoregional transformation, consider adding RT.
[v] Strongly recommend this treatment be given in the context of a clinical trial; nonmyeloblative approaches may also be considered.

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GELF CRITERIA[a,b]

- Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
- Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L)
- Leukemia (> 5.0 x 10^9/L malignant cells)

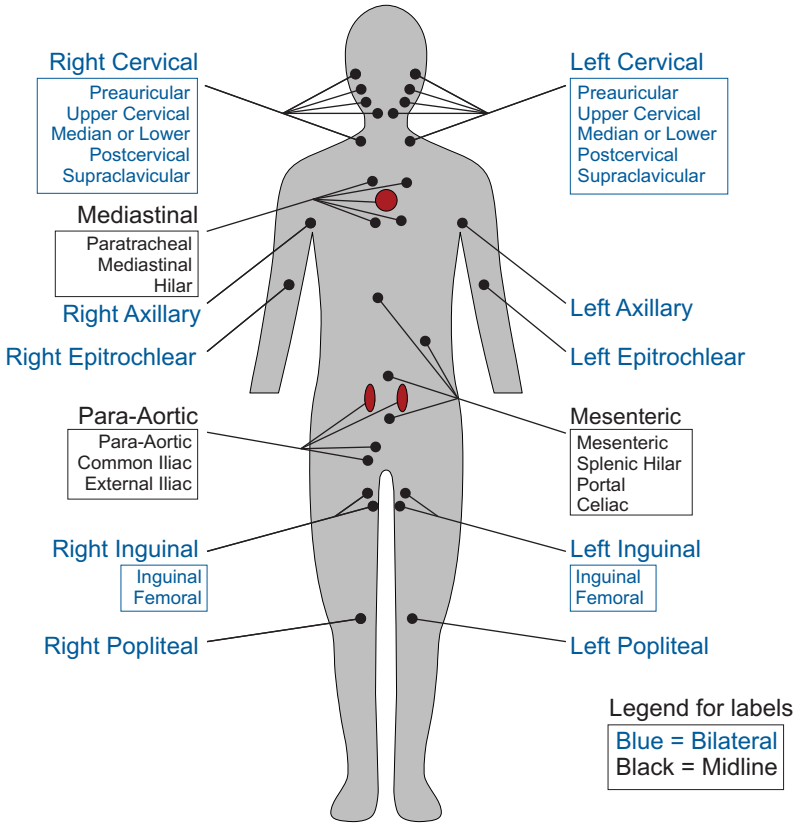
FLIPI - 1 CRITERIA[a,c,d]

Age	≥ 60 y
Ann Arbor stage	III-IV
Hemoglobin level	< 12 g/dL
Serum LDH level	> ULN (upper limit of normal)
Number of nodal sites[d]	≥ 5

Risk group according to FLIPI chart

	Number of factors
Low	0-1
Intermediate	2
High	≥ 3

Nodal Areas



Mannequin used for counting the number of involved areas.[e]

[a] This provides useful prognostic information which may be used to guide therapeutic decisions.

[b] Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin containing regimen with or without interferon alfa 2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaire 86 trial. J Clin Oncol 1998;16:2332-2338.

[c] This research was originally published in Blood. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-1265. (c) the American Society of Hematology.

[d] FLIPI-2 (Federico M, Bellei M, Marcheselli L, et al. J Clin Oncol 2009;27:4555-4562) predicts for outcomes after active therapy, see Discussion.

[e] The map is used to determine the number of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.

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SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

First-line Therapy[c,d]
- Bendamustine + rituximab
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- RFND (rituximab, fludarabine, mitoxantrone, dexamethasone)[d] (category 2B)
- Radioimmunotherapy[e,f] (category 3)[g]
- Rituximab

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)
- Radioimmunotherapy
- Rituximab (preferred)
- Single agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab

For patients with locally bulky or symptomatic disease, consider IFRT 4-30 Gy ± additional systemic therapy.

First-line Consolidation or Extended Dosing (optional)
- Chemotherapy followed by radioimmunotherapy[e,f,h] (category 1)
- Rituximab maintenance 375 mg/m^2 one dose every 8 wk up to 2 y for patients initially presenting with high tumor burden (category 1)

Second-line and Subsequent Therapy
- BVR (bendamustine, bortezomib, rituximab)
- Chemoimmunotherapy (as in first-line therapy)
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- Fludarabine + rituximab
- Radioimmunotherapy[e,f] (category 1)
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3)[i]

Second-line Consolidation or Extended Dosing
- High dose therapy with autologous stem cell rescue[j]
- Allogeneic stem cell transplant for highly selected patients[k]
- Rituximab maintenance 375 mg/m^2 one dose every 12 weeks for 2 years (category 1) (optional)

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[a] See references for regimens FOLL-B 2 of 3 and FOLL-B 3 of 3.

[b] The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.

[c] In combination chemotherapy, addition of rituximab has consistently increased overall response rate, response duration, and progression-free survival. In addition some studies have demonstrated an overall survival benefit.

[d] RFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion).

[e] Selection of patients requires adequate marrow cellularity > 15% and < 25% involvement of lymphoma in bone marrow, and platelets > 100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for radioimmunotherapy.

[f] If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Cytogenetics ± FISH for known MDS markers. Updates as of 2010 suggest a trend towards an increased risk of MDS with RIT treatment.

[g] Category 3 designation is due to limited additional data such as randomized trials.

[h] The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.

[i] These agents can be administered without restriction for transplantability.

[j] High dose therapy with autologous stem cell rescue is an appropriate consolidative therapy to patients in second or third remission.

[k] In highly selected patients, trials of fully ablative and nonmyeloablative allogeneic stem cell transplant have shown long term survival advantage, although there is a 2-year treatment-related mortality rate of approximately 25% for non-myeloablative and 40% for fully ablative.

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SUGGESTED TREATMENT REGIMENS
References

First-line therapy

Bendamustine + rituximab

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany) [abstract]. Blood 2009;114:Abstract 405.

Cyclophosphamide

Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5-15.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 2004;22:4711-4716.

Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-3732.

CVP (cyclophosphamide, vincristine, prednisone) + rituximab

Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579-4586.

FND (fludarabine, mitoxantrone, dexamethasone) + rituximab

McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. Semin Oncol 2000;27:37-41.

Rituximab

Hainsworth JD, Litchy S, Burris HA, III, et al. Rituximab as first-line and maintenance therapy for patients with indolent Non-Hodgkin's lymphoma. J Clin Oncol 2002;20:4261-4267.

Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: Clinical and molecular evaluation. Blood 2001;97:101-106.

Radioimmunotherapy

Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005;352:441-449.

Kaminski MS, Tuck M, Estes J, et al. Tositumomab and iodine I-131 tositumomab for previously untreated, advanced-stage, follicular lymphoma: Median 10 year follow-up results. Blood 2009;114:3759.

First-line consolidation or extended dosing

Chemotherapy followed by radioimmunotherapy

Press OW, Unger JM, Braziel RM, et al. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: Five-year follow-up of Southwest Oncology Group Protocol S9911. J Clin Oncol 2006;24:4143-4149.

Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with Yttrium-90–Ibritumomab Tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008;26:5156-5164.

Hagenbeek A, Radford J, Van Hoof A, et al. 90Y-Ibritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-hodgkin's lymphoma: Updated results after a median follow-up of 66.2 months from the international, randomized, phase III First-Line Indolent Trial (FIT) in 414 Patients [abstract]. Blood 2010;116:Abstract 594.

Chemotherapy followed by rituximab

Salles GA, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. The Lancet 2011;377:42-51.

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Note: All recommendations are category 2A unless otherwise indicated.
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SUGGESTED TREATMENT REGIMENS
References

Second-line and subsequent therapy

BVR (bendamustine, bortezomib, rituximab)

Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood 2011;117:2807-2812.

Fowler N, Kahl BS, Lee P, et al. Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: The phase II VERTICAL study. J Clin Oncol 2011;29:3389-3395.

FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)

Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas - results of a prospective randomized study of the German low grade lymphoma study group (GLSG). Blood 2004;104:3064-3071.

Fludarabine + rituximab

Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade of follicular lymphoma. J Clin Oncol 2005;23:694-704.

Radioimmunotherapy

Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20:3262-3269.

Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453-2463.

Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001;19:3918-3928.

Fisher RI, Kaminski MS, Wahl RL, et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. J Clin Oncol 2005;23:7565-7573.

Second-line consolidation or extended dosing

Rituximab maintenance

van Oers MHJ, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-hodgkin's lymphoma: Long-term outcome of the EORTC 20981 Phase III randomized Intergroup Study. J Clin Oncol 2010;28:2853-2858.

Forstpointer R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-4008.

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Marginal Zone Lymphomas

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Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

- **Gastric** → See Diagnosis and Workup (MALT-1)
- **Nongastric** → See Diagnosis and Workup (NGMLT-1)

Nodal marginal zone lymphoma → See Diagnosis and Workup (NODE-1)

Splenic marginal zone lymphoma → See Diagnosis and Workup (SPLN-1)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.[a,b]
- Diagnosis of gastric MALT lymphoma requires an endoscopic biopsy and an FNA is never adequate.
- Adequate immunophenotyping to establish diagnosis[c,d]
  - IHC Panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, CCND1, BCL6
    or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter Pylori stain (gastric), if positive, then PCR or FISH for t(11;18)[e]

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements
- Cytogenetics or FISH: t(1;14), t(14;18), t(3;14)

→

WORKUP

ESSENTIAL:

- Physical exam with attention to nongastric sites (eyes, skin)
- Performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- If H. pylori negative by histopathology, then use noninvasive H. pylori testing (stool antigen test, urea breath test, blood antibody test)
- Hepatitis B testing[f] if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Endoscopy with ultrasound (if available) with multiple biopsies of anatomical sites
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

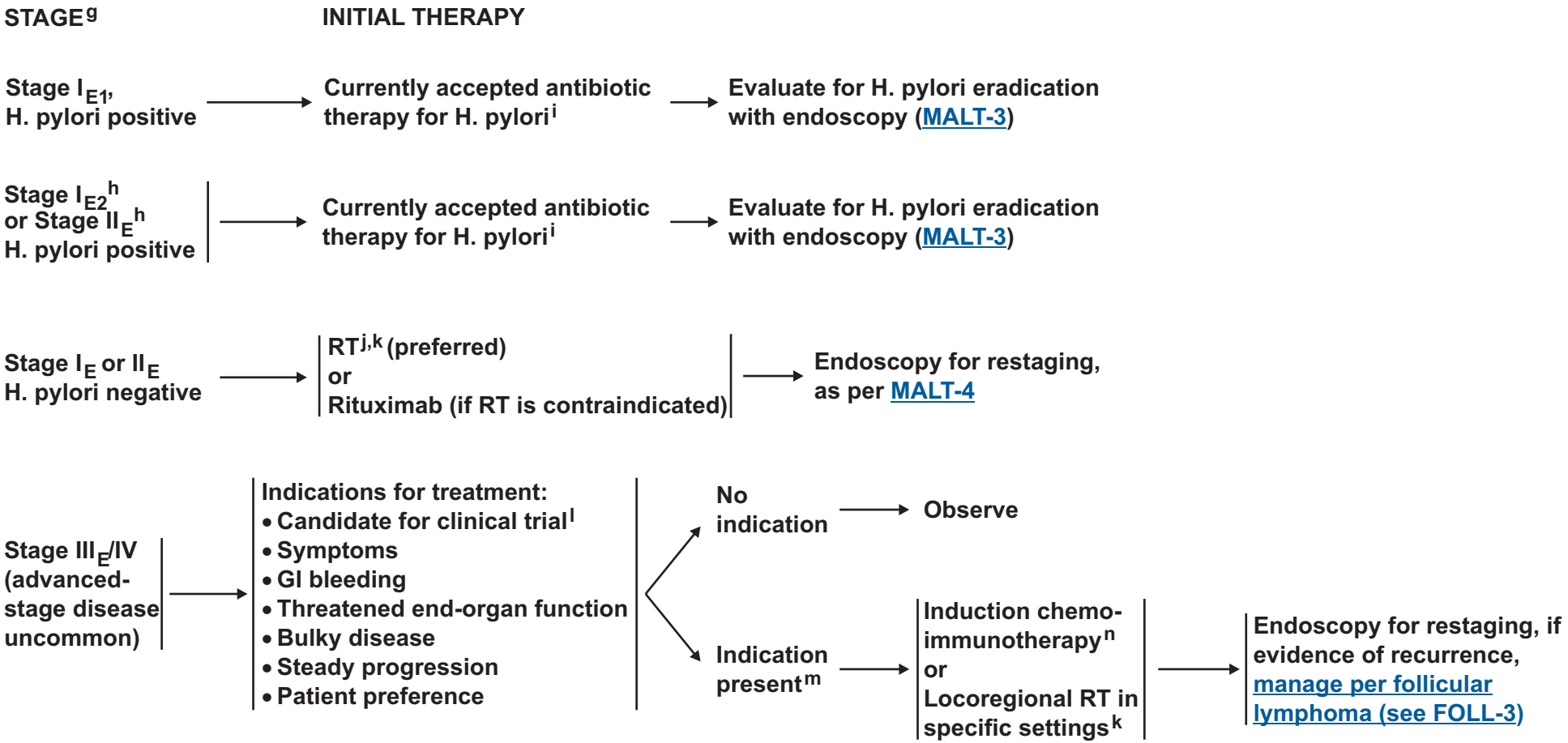
USEFUL IN SELECTED CASES

- Bone marrow biopsy ± aspirate
- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

→ See Initial Therapy (MALT-2)

[a] Nondiagnostic atypical lymphoid infiltrates that are H. Pylori positive, should be rebiopsied to confirm or exclude lymphoma prior to treatment of H. Pylori.
[b] Any area of DLBCL should be treated according to the NCCN Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).
[c] Typical immunophenotype: CD10-, CD5-, CD20+, CCND1-, BCL2 follicles-.
[d] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).
[e] Locally advanced disease is more likely in patients with gastric MALT lymphoma with t(11;18).
[f] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[g] See Lugano Staging System for gastrointestinal lymphoma (MALT-A).
[h] Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course.
[i] t(11;18) is a predictor for lack of response to antibiotics. These patients should be considered for alternative therapy.
[j] If negative by both histology and serum antibodies, RT recommended.
[k] See Principles of Radiation Therapy (NHODG-E).
[l] Given incurability with conventional therapy, consider investigational therapy as first-line of treatment.
[m] Surgical resection is generally limited to specific clinical situations, ie, life-threatening hemorrhage.
[n] See Suggested Treatment Regimens (FOLL-B).

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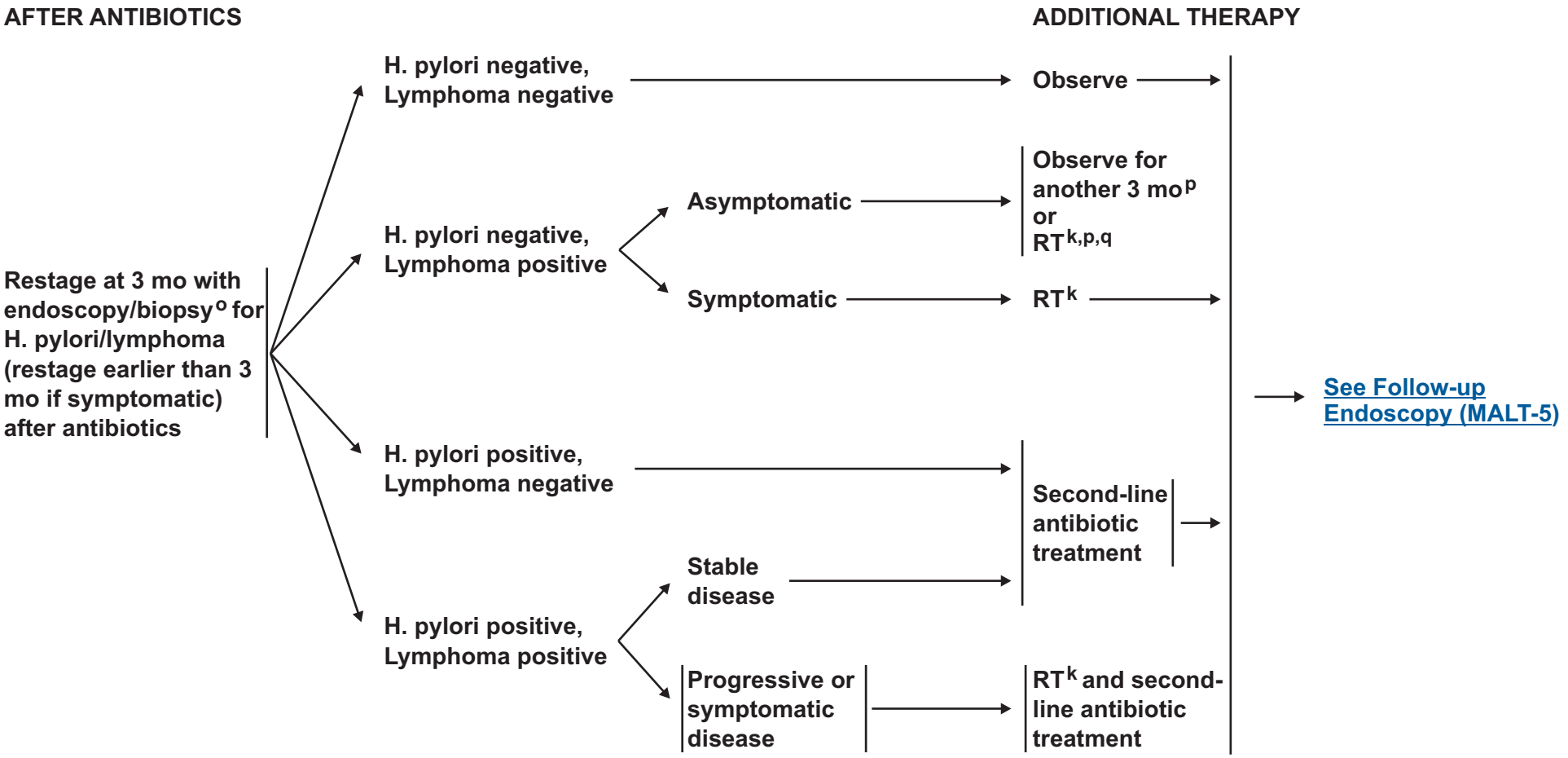
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

3-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY



[k] See Principles of Radiation Therapy (NHODG-E).

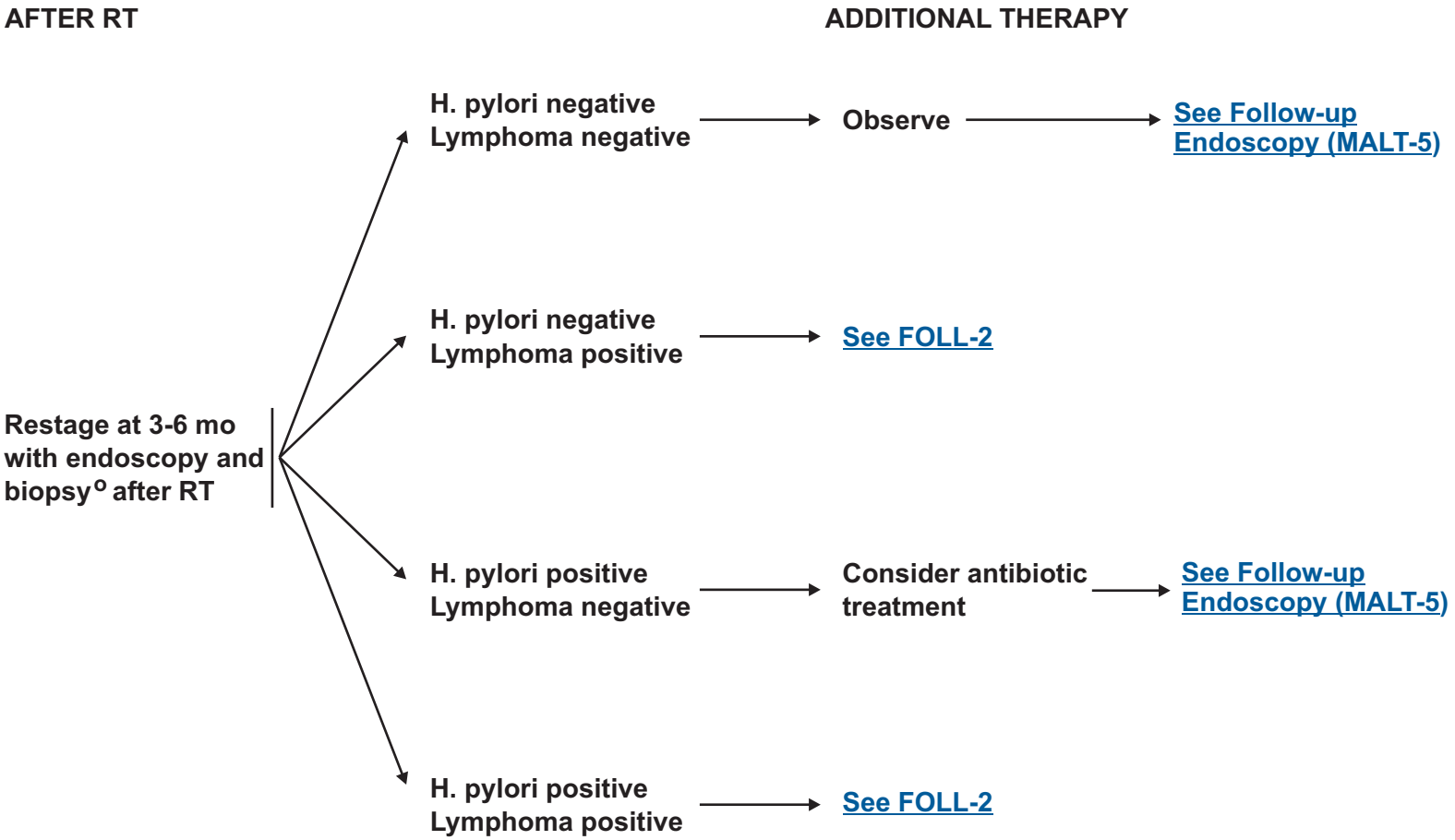
[o] Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).

[p] If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted. RT can be considered as early as 3 mo after observation but can be prolonged to 18 mo (category 2B).

[q] If patient originally had clinical Stage I_{E2} or Stage II_{E}, early RT should be considered if there is no response to antibiotics.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

3-6 MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY



[o]Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).

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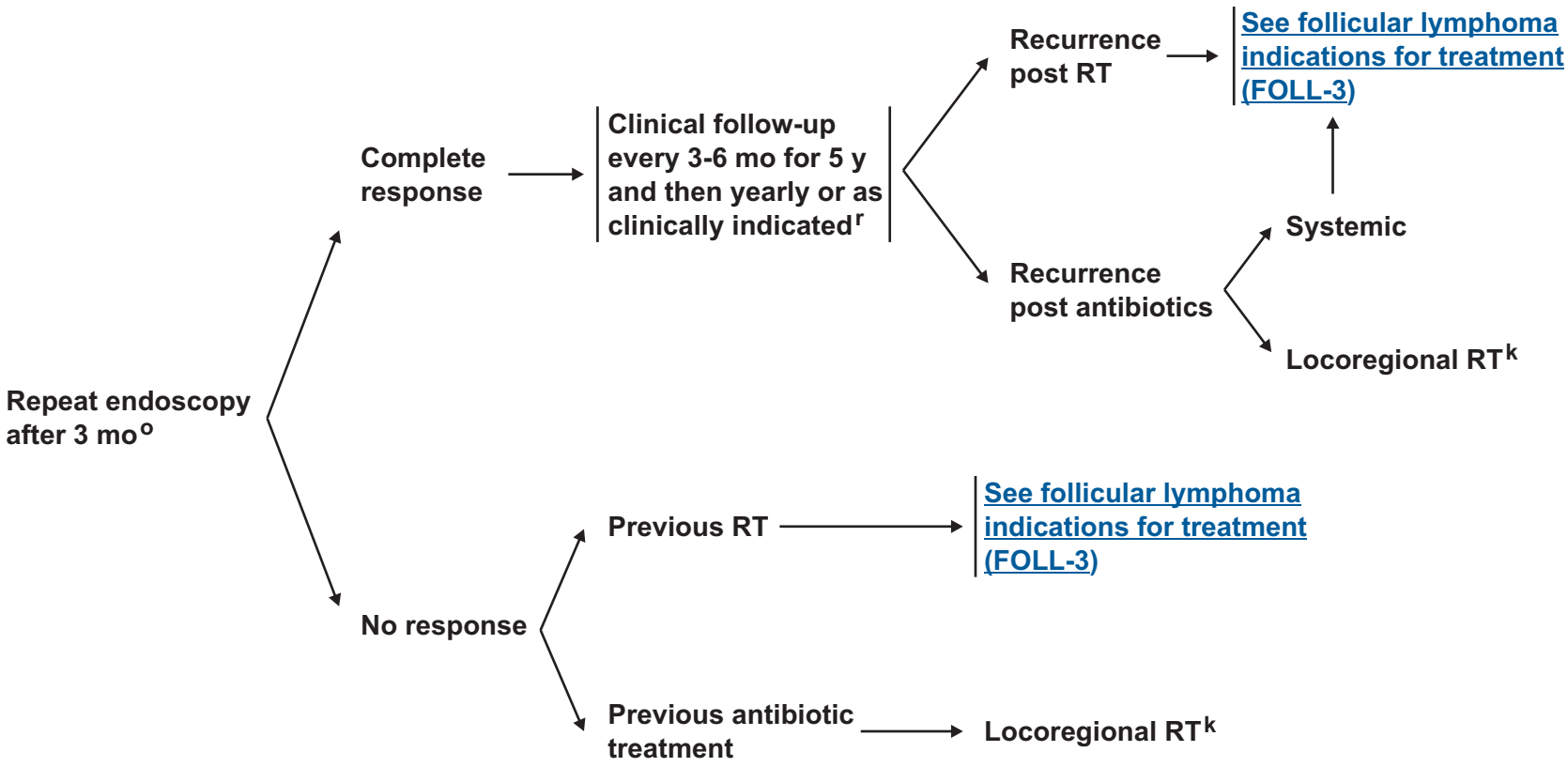
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLLOW-UP ENDOSCOPY



[k] See Principles of Radiation Therapy (NHODG-E).
[o] Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).
[r] Optimal interval for follow-up endoscopy and imaging is not known. Follow-up endoscopy and imaging at NCCN institutions is driven by symptoms.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

STAGING OF GASTRIC MALT LYMPHOMA: COMPARISON OF DIFFERENT SYSTEMS

Lugano Staging System for gastrointestinal lymphomas		Ann Arbor Stage	TNM Staging System adapted for gastric lymphoma	Tumor extension
Stage I_E	Confined to GI tract[a]			
	I_{E1} = mucosa, submucosa	I_E	T1 N0 M0	Mucosa, submucosa
	I_{E2} = muscularis propria, serosa	I_E	T2 N0 M0	Muscularis propria
		I_E	T3 N0 M0	Serosa
Stage II_E	Extending into abdomen			
	II_{E1} = local nodal involvement	II_E	T1-3 N1 M0	Perigastric lymph nodes
	II_{E2} = distant nodal involvement	II_E	T1-3 N2 M0	More distant regional lymph nodes
Stage II_E	Penetration of serosa to involve adjacent organs or tissues	II_E	T4 N0 M0	Invasion of adjacent structures
Stage III-IV[b]	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement	III_E	T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

Yahalom et al. Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT lymphoma) in Mauch et al eds. Non-Hodgkin's Lymphomas. Philadelphia: Lippincott, 2004:352. (http://lww.com)

[a] Single primary or multiple, noncontiguous.

[b] Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvement in other lymphomas, and these patients may be managed by treating each site separately with excision or RT. In contrast, cases with disseminated nodal involvement appear to behave more like nodal MZL or like disseminated FL.

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Extranodal Marginal Zone B-Cell Lymphoma[a]

Nongastric MALT Lymphoma[b]

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DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- Adequate immunophenotyping to establish diagnosis[c,d]
  - IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa lambda, CD21 or CD23, CCND1
    or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements; PCR for t(11;18)
- Cytogenetics or FISH: t(11;18); t(11;14); t(3;14); t(14;18)

WORKUP

ESSENTIAL:

- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing[e] if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES

- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- Bone marrow biopsy ± aspirate (for patients with multifocal disease)
- Endoscopy with multiple biopsies of anatomical sites
- PET-CT scan
- MRI
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

See Initial Therapy (NGMLT-2)

[a] Typical sites of extranodal marginal zone lymphoma other than the stomach include the following: bowel (small and large), breast, head and neck, lung, ocular adenxa, ovary, parotid, prostate, and salivary gland. Infectious agents have been reported to be associated with many nongastric sites but testing for these agents is not required for management.

[b] This guideline pertains to non-cutaneous, for primary cutaneous marginal zone lymphoma, see CUTB.

[c] Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+, CCND1-, BCL2 follicles-.

[d] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[e] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
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NCCN Guidelines Version 2.2012

Extranodal Marginal Zone B-Cell Lymphoma

Nongastric MALT Lymphoma

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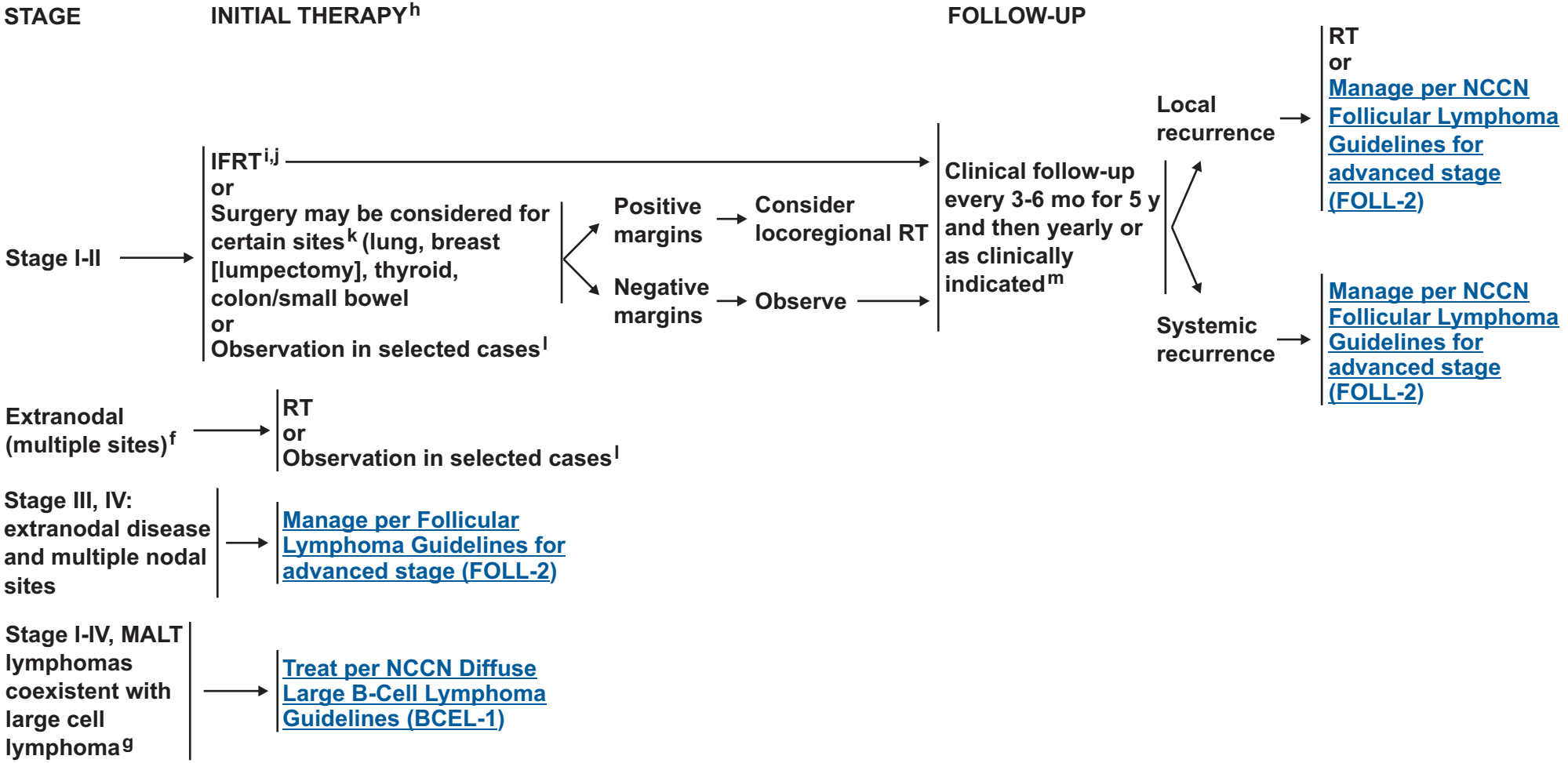

[f] Treatment of each site may be indicated (eg, bilateral conjunctiva) both at diagnosis and at relapse.

[g] DLBCL coexistent with MALT cell lymphoma is managed as DLBCL. See Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).

[h] Based on anecdotal responses to antibiotics in ocular and cutaneous marginal zone lymphomas, some physicians will give an empiric course of doxycycline prior to initiating other therapy.

[i] Dose is site dependent with lower dose reserved for eye involvement.

[j] See Principles of Radiation Therapy (NHODG-E).

[k] Surgical excision for adequate diagnosis may be appropriate treatment for disease.

[l] Observation may be considered for patients whose diagnostic biopsy was excisional or involved-field RT or systemic treatment could result in significant comorbidity.

[m] Follow-up includes diagnostic tests and imaging as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Guidelines Version 2.2012
Nodal Marginal Zone Lymphoma

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Discussion

DIAGNOSIS[a]

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. Histologic grading cannot be performed on an FNA.
- Adequate immunophenotyping to establish diagnosis[b,c]
  - IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, CCND1
    or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Pediatric nodal marginal zone lymphoma should be considered with localized disease in a young patient.

USEFUL UNDER CERTAIN CIRCUMSTANCES FOR CLARIFICATION OF DIAGNOSIS:

- Molecular analysis to detect: antigen receptor gene rearrangements; PCR for t(11;18)
- Cytogenetics or FISH: t(11;18); t(1;14); t(14;18); del(13q); del(7q)

WORKUP

ESSENTIAL:

- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing[d] if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Bone marrow biopsy + aspirate to document clinical stage I-II disease[e]
- Evaluation to rule out extranodal primary sites
  - Neck nodes: ocular, parotid, thyroid, and salivary gland
  - Axillary nodes: lung, breast, and skin
  - Mediastinal/hilar nodes: lung
  - Abdominal nodes: splenic and GI
  - Inguinal/iliac nodes: GI and skin
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES

- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Additional imaging as appropriate
- PET-CT scan
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

→ See Management as per Follicular Lymphoma (FOLL-2)

[a] Nodal MZL is rare and occurs most commonly as spread from extranodal MALT; must also be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma, and CLL, all of which are more common.

[b] Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and CCND1-, BCL2 follicles-.

[c] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[e] Bilateral or unilateral provided core biopsy is > 2 cm. If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy, bone marrow biopsy may be deferred.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2012
Splenic Marginal Zone Lymphoma

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Discussion

DIAGNOSIS

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.[a]**
- **An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[b,c]**
  - **IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, CCND1, IgD, CD43, annexin-1**
    or
  - **Cell surface marker analysis by flow cytometry (peripheral blood, bone marrow, or tissue):**
    kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD43, CD103

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: antigen receptor gene rearrangements; PCR for t(11;18)**
- **Cytogenetics or FISH: CLL panel; t(11;18); t(11;14); t(14;18); del(7q)**

WORKUP

ESSENTIAL:

- **Physical exam with performance status**
- **CBC, differential, platelets**
- **Comprehensive metabolic panel**
- **LDH**
- **Hepatitis B testing[d] if rituximab contemplated**
- **Hepatitis C testing**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **Bone marrow biopsy ± aspirate**
- **SPEP and/or quantitative immunoglobulin levels**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL IN SELECTED CASES

- **Additional imaging as appropriate**
- **PET-CT scan**
- **Discussion of fertility issues and sperm banking**
- **Immunofixation of blood (for elevated immunoglobulins or positive SPEP)**
- **Cryoglobulins**
- **Directs Coombs testing**

See Management (SPLN-2)

[a] SMZL is most definitively diagnosed at splenectomy, since the immunophenotype is nonspecific and morphologic features on the bone marrow may not be diagnostic. However, the diagnosis of SMZL may be made on the basis of bone marrow ± peripheral blood involvement by small lymphoid cells with immunoglobulin (Ig) light chain restriction that lack characteristic features of other small B-cell neoplasms (CD5, CD10, CCND1). Plasmacytoid differentiation with cytoplasmic Ig detectable on paraffin sections may occur. In such cases, the differential diagnosis may include lymphoplasmacytic lymphoma. With a characteristic intrasinusoidal lymphocytic infiltration of the bone marrow, the diagnosis can strongly be suggested on bone marrow biopsy alone, if the immunophenotype is consistent.

[b] Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and CCND1-, BCL2 follicles-, annexin-1, CD103- (distinction from hairy cell leukemia) with expression of both IgM and IgD.

[c] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2012
Splenic Marginal Zone Lymphoma

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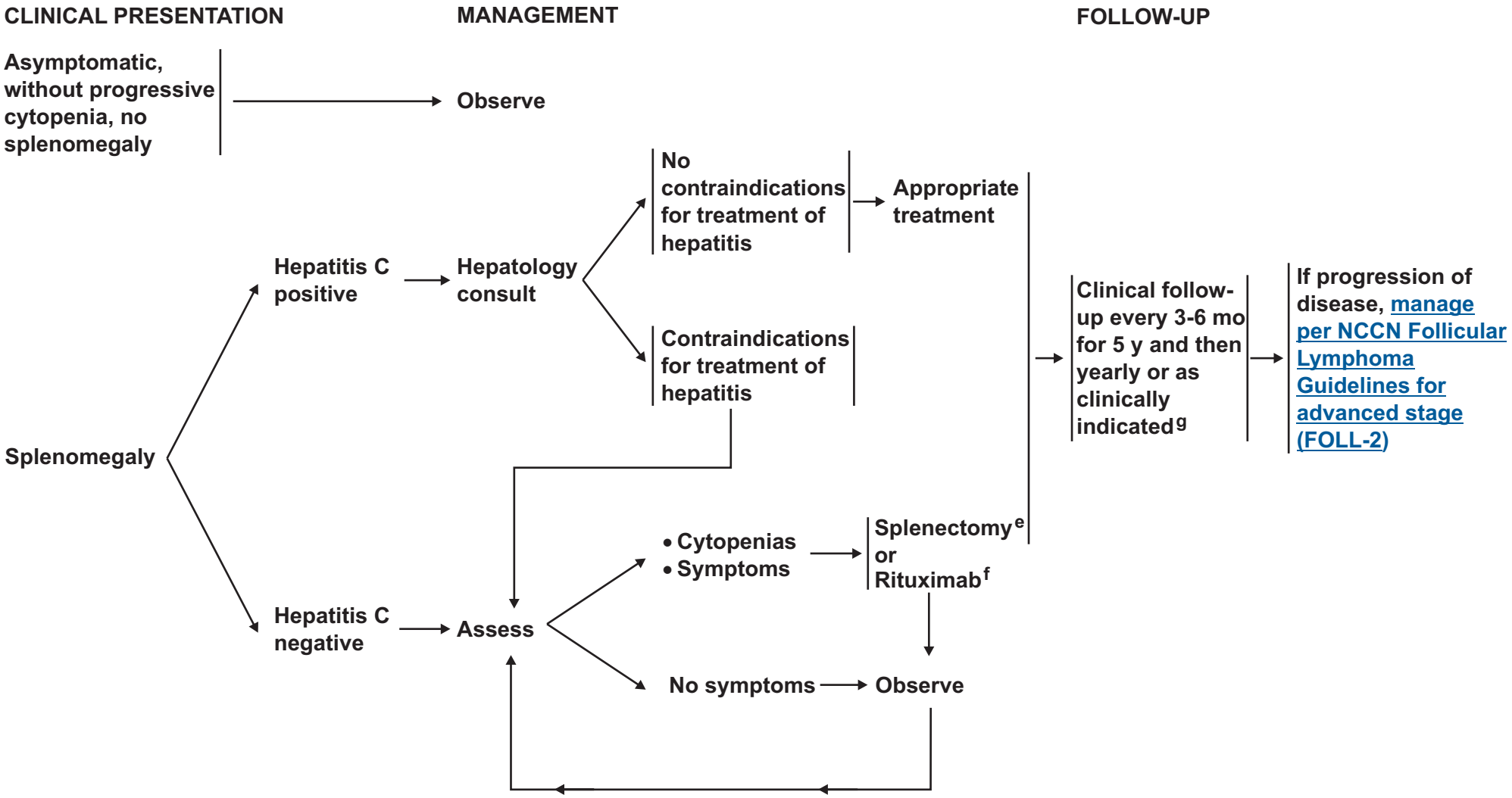

[e] Pneumococcal and meningococcal vaccination should be performed at least 2 weeks before splenectomy.

[f] Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer 2006;107:125-135.

[g] Follow-up includes diagnostic tests and imaging as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2012
Mantle Cell Lymphoma

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Discussion

DIAGNOSIS

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**
- **An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis(immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[a,b]**
  - **IHC panel: CD20, CD3, CD5, CCND1, CD10, CD21, CD23, BCL2, BCL6, Ki67[c]**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: antigen receptor gene rearrangements; CCND1 rearrangements**
- **Cytogenetics or FISH: t(11;14); t(14;18); CLL panel**

→

WORKUP

ESSENTIAL:

- **Physical exam: Attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC, differential, platelets**
- **Comprehensive metabolic panel**
- **LDH**
- **Bone marrow biopsy ± aspirate**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **Hepatitis B testing[d] if rituximab contemplated**
- **MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL UNDER CERTAIN CIRCUMSTANCES

- **Endoscopy/colonoscopy[e]**
- **Neck CT**
- **Uric acid**
- **Discussion of fertility issues and sperm banking**
- **Lumbar puncture (for blastic variant or CNS symptoms)**
- **Beta-2-microglobulin**
- **PET-CT scan**

→ **See Induction Therapy (MANT-2)**

[a] Typical immunophenotype: CD5+, CD20+, CD43+, CD23-/+, CCND1+, CD10-/+ Note: Some cases of MCL may be CD5- or CD 23+. If the diagnosis is suspected, CCND1 staining or FISH for t(11;14) should be done.

[b] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[c] Ki67 proliferation fraction of < 30% is associated with a more favorable prognosis. However, it is not used to guide treatment.

[d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[e] Essential for confirmation of stage I- II disease. See discussion for details.

Note: All recommendations are category 2A unless otherwise indicated.
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Mantle Cell Lymphoma

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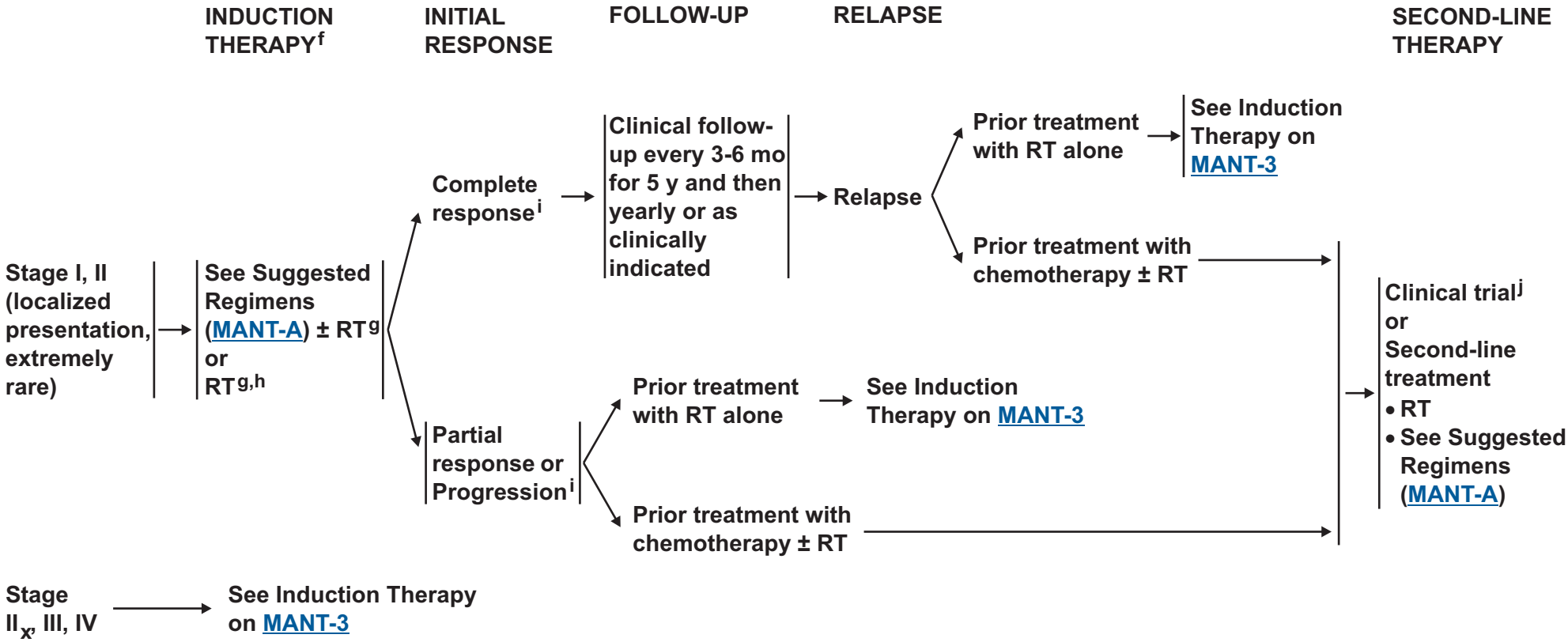

[f] Early referral for high dose therapy with stem cell rescue is advisable for planning purposes.

[g] See Principles of Radiation Therapy (NHODG-E).

[h] Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. Ann Oncol 2003;14:1555-1561.

[i] See Response Criteria for Lymphoma (NHODG-C).

[j] Option for clinical trials of adjuvant therapy or for relapsed disease involving high dose therapy with autologous or allogeneic stem cell rescue, immunotherapy with nonmyeloablative stem cell rescue, or evaluation of treatment with new agents are appropriate.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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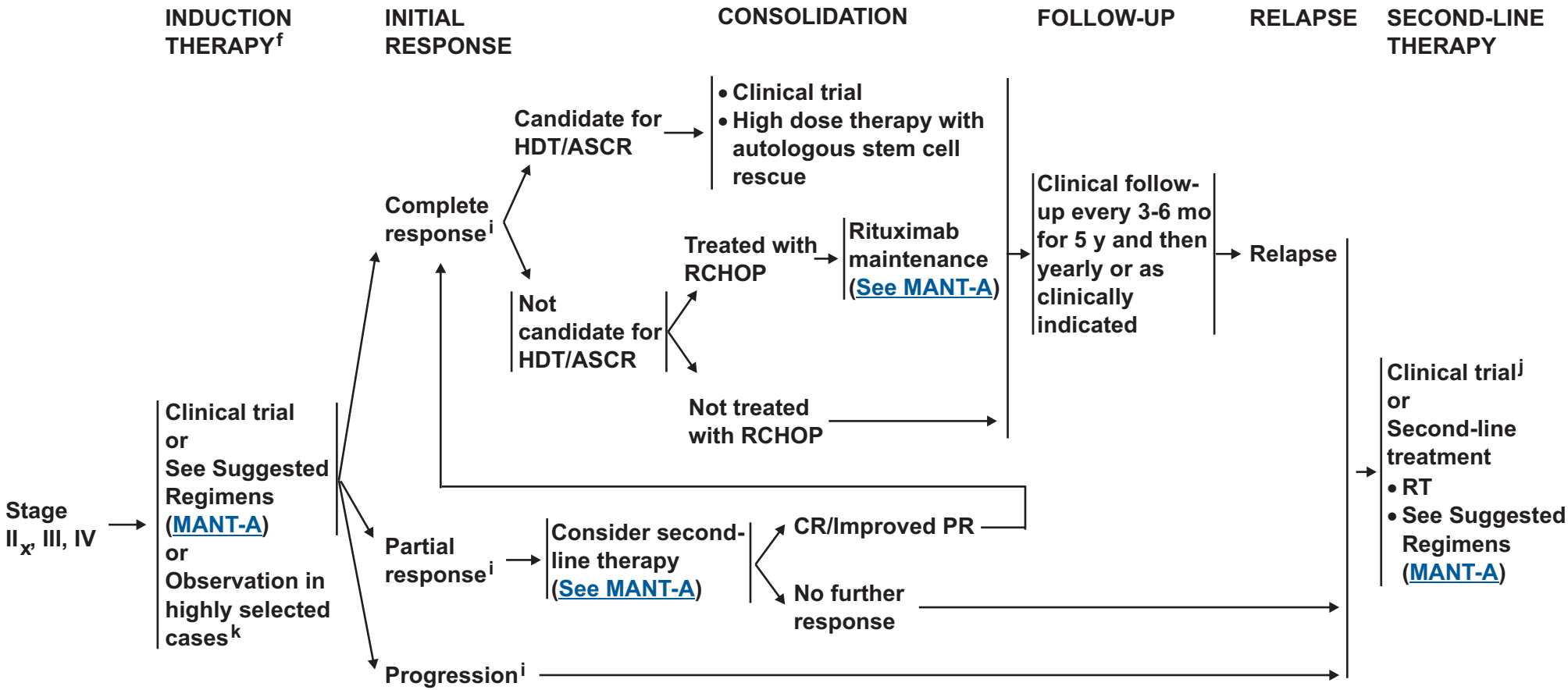

[f]Early referral for high dose therapy with stem cell rescue is advisable for planning purposes.
[i]See Response Criteria for Lymphoma (NHODG-C).
[j]Option for clinical trials of adjuvant therapy or for relapsed disease involving high dose therapy with autologous or allogeneic stem cell rescue, immunotherapy with nonmyeloablative stem cell rescue, or evaluation of treatment with new agents are appropriate.
[k]Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol 2009;27:1209-1213.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

Induction Therapy

- **Aggressive therapy**
  - **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab**
  - **NORDIC regimen[b] (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)**
  - **CALGB regimen[b] (rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone]) (rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone])**
  - **Sequential RCHOP/RICE[b] (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (rituximab, ifosfamide, carboplatin, etoposide)**
  - **Alternating RCHOP/RDHAP[b] (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)**
- **Less aggressive therapy**
  - **Bendamustine + rituximab**
  - **CHOP + rituximab[c]**
  - **Cladribine + rituximab**
  - **CVP (cyclophosphamide, vincristine, prednisone) + rituximab**
  - **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab**
  - **Modified rituximab-HyperCVAD with rituximab maintenance in patients older than 65 y**

First-line Consolidation[d]

- **Clinical trial**
- **High dose therapy with autologous stem cell rescue[e]**

For patients without intention for high dose therapy with stem cell rescue consolidation

- **If treated with RCHOP, consider rituximab maintenance 375 mg/m^2 every 8 wks until progression**

Second-line Therapy

- **Bendamustine ± rituximab**
- **Bortezomib ± rituximab**
- **Cladribine + rituximab**
- **FC (fludarabine, cyclophosphamide) ± rituximab**
- **FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)**
- **FMR (fludarabine, mitoxantrone, rituximab)**
- **Lenalidomide ± rituximab**
- **PCR (pentostatin, cyclophosphamide, rituximab)**
- **PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab**
- **See Second-line Therapy for DLBCL (BCEL-C 1 of 3)[f]**

Second-line Consolidation

- **Allogeneic stem cell transplant (nonmyeloablative or myeloablative)**

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[a] See references for regimens MANT-A 2 of 3 and MANT-A 3 of 3.

[b] These regimens include first-line consolidation with high dose therapy and autologous stem cell rescue (HDT/ASCR).

[c] There is a randomized trial that demonstrated that RCHOP was not superior to CHOP.

[d] Typically patients will receive an aggressive induction regimen prior to consolidation; however, less aggressive regimens followed by consolidation with high dose therapy may also result in a good long-term outcome.

[e] Randomized data with anthracycline-containing regimens suggest an improvement in progression free survival with the addition of first-line high dose therapy with autologous stem cell consolidation.

[f] These agents can be administered without restriction for transplantability.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

InductionTherapy

Aggressive therapy

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine) + rituximab

Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005;23:7013-7023.

Nordic trial regimen (Dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)

Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma following intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A non-randomized phase-II multicenter study by the Nordic Lymphoma Group. Blood 2008;112:2687-2693.

CALGB regimen (rituximab + methotrexate with augmented CHOP)

Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol 2009;27:6101-6108.

RCHOP/RICE

Schaffel R, Hedvat CV, Teruya-Feldstein J, et al. Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. Ann Oncol 2010;21:133-139.

RCHOP/RDHAP

Pott C, Hoster E, Beldjord K, et al. R-CHOP/R-DHAP compared to R-CHOP induction followed by high dose therapy with autologous stem cell transplantation induces higher rates of molecular remission in MCL: Results of the MCL Younger Intergroup Trial of the European MCL Network [abstract]. Blood 2010;116:Abstract 965.

Less aggressive therapy

Bendamustine + rituximab

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany) [abstract]. Blood 2009;114:Abstract 405.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005;23:1984-1992.

Cladribine + rituximab

Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. Cancer 2008;113:108-116.

CVP + rituximab

Teodorovic I, Pittaluga S, Kluin-Nelemans J, et al. Efficacy of four different regimens in 64 mantle-cell lymphoma cases: Clinicopathologic comparison with 498 other non-Hodgkin's lymphoma subtypes. European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group. J Clin Oncol 1995;13:2819-2826.

Martin P, Chadburn A, Christos P, et al. Intensive treatment strategies may not provide superior outcomes in mantle cell lymphoma: Overall survival exceeding 7 years with standard therapies. Ann Oncol 2008;19:1327-1330.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) + rituximab

Wilson WH, Gutierrez M, O'Connor P, et al. The role of rituximab and chemotherapy in aggressive B-cell lymphoma: a preliminary report of dose-adjusted EPOCH-R. Semin Oncol 2002;29:41-47.

Modified HyperCVAD with rituximab maintenance

Kahl BS, Long WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: A pilot study from the Wisconsin Oncology Network. Ann Oncol 2006;17:1418-1423.

First-line consolidation

High dose therapy with autologous stem sell rescue

Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005;105:2677-2684.

Thieblemont C, Antal D, Lacotte-Thierry L, et al. Chemotherapy with rituximab followed by high-dose therapy and autologous stem cell transplantation in patients with mantle cell lymphoma. Cancer 2005;104:1434-1441.

Ritchie D, Seymour J, Grigg A, et al. The hyper-CVAD–rituximab chemotherapy programme followed by high-dose busulfan, melphalan and autologous stem cell transplantation produces excellent event-free survival in patients with previously untreated mantle cell lymphoma. Ann Hematol 2007;86:101-105.

Kluin-Nelemans JC, Hoster E, Walewski J, et al. R-CHOP versus R-FC followed by maintenance with rituximab versus interferon-alfa: Outcome of the first randomized trial for elderly patients with mantle cell lymphoma [abstract]. Blood 2011;118:Abstract 439.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued on next page

SUGGESTED TREATMENT REGIMENS
References

For patients without intention for high dose therapy with stem cell rescue consolidation

Kluin-Nelemans JC, Hoster E, Walewski J, et al. R-CHOP versus R-FC followed by maintenance with rituximab versus interferon-alfa: Outcome of the first randomized trial for elderly patients with mantle cell lymphoma [abstract]. Blood 2011;118:Abstract 439.

Second-line Therapy

Bendamustine

Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell Non-Hodgkin's Lymphoma. J Clin Oncol 2008; 26:4473-4479.

Rummel MJ, Al-Batran SE, Kim S-Z, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-hodgkin's lymphoma. J Clin Oncol 2005;23:3383-3389.

Bortezomib

Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 2009;20:520-525.

Cladribine

Rummel MJ, Chow KU, Jager E, et al. Treatment of mantle-cell lymphomas with intermittent two-hour infusion of cladribine as first-line therapy or in first relapse. Ann Oncol 1999;10:115-117.

Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. Cancer 2008;113:108-116.

FC (fludarabine and cyclophosphamid) ± rituximab

Cohen BJ, Moskowitz C, Straus D et al. Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 2001;42:1015-1022.

FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)

Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicular and mantle cell lymphoma - results of a prospective randomized study of the German low grade lymphoma study group (GLSG). Blood 2004;104:3064-3071.

FMR (fludarabine, mitoxantrone, rituximab)

Levine AM, Tulpule A, Smith L, Espina BM, Mohrbacher AF, Feinstein DI. Results of a pilot trial of fludarabine, mitoxantrone and rituxan in mantle cell lymphoma [abstract]. Blood 2005;106:Abstract 945.

Lenalidomide

Habermann TM, Lossos IS, Justice G, et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. Br J Haematol 2009;145:344-349.

Reeder CB, Witzig TE, Zinzani PL, et al. Efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory mantle-cell lymphoma: Results from an international study (NHL-003) [abstract]. J Clin Oncol 2009;27:Abstract 8569.

Lenalidomide + rituximab

Wang L, Fayad L, Hagemeister FB, et al. A phase I/II study of lenalidomide in combination with rituximab in relapsed/refractory mantle cell lymphoma [abstract]. Blood 2009;114: Abstract 2719.

PEP-C (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab

Coleman M, Martin P, Ruan J, et al. Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy. Cancer 2008;112:2228-2232.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Diffuse Large B-Cell Lymphoma

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DIAGNOSIS[a,b]

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**
- **An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[c,d]**
  - **IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Additional immunohistochemical studies to establish lymphoma subtype**
  - **IHC panel: CCND1, kappa/lambda, CD138, EBER-ISH, ALK, HHV8**
- **Molecular analysis to detect: antigen receptor gene rearrangements; CCND1, BCL2, BCL6, MYC[e] rearrangements by either FISH or IHC**
- **Cytogenetics or FISH: t(14;18);[e] t(3;v); t(8;14)**

SUBTYPES

- **Subtypes included:**
  - **Diffuse large B-cell lymphoma (DLBCL), NOS[f]**
  - **DLBCL coexistent with follicular lymphoma of any grade**
  - **DLBCL coexistent with gastric MALT lymphoma**
  - **DLBCL coexistent with nongastric MALT lymphoma**
  - **Follicular Lymphoma grade 3**
  - **Intravascular large B-cell lymphoma**
  - **DLBCL associated with chronic inflammation**
  - **ALK positive DLBCL**
  - **EBV positive DLBCL of the elderly**
  - **T-cell/histiocyte rich large B-cell lymphoma**

→ **See Workup (BCEL-2)**

- **Subtypes *not* included:**
  - **Cutaneous B-cell lymphoma (See CUTB-1)**
  - **Primary DLBCL of the CNS**

Primary Mediastinal Large B-Cell Lymphoma (PMBL), see BCEL-B.

[a] Burkitt lymphoma intermediate histology or DLBCL CD10 + tumors with very high proliferation > 90% with or without Burkitt lymphoma-like features might be considered for more aggressive treatment as per BURK-A. These cases would be appropriate to evaluate for BCL2, BCL6 and MYC rearrangements.

[b] See International Prognostic Index (BCEL-A).

[c] Typical immunophenotype: CD20+, CD45+, CD3-; other markers used for subclassification.

[d] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[e] Standard of care is not established for DLBCL with t(14;18) with concurrent MYC rearrangements.

[f] Germinal center (or follicle center) cell phenotype is not equivalent to follicular lymphoma and can occur in DLBCL and Burkitt lymphoma. Morphology is required to establish diagnosis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

WORKUP

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Adequate bone marrow biopsy (>1.6 cm) ± aspirate
- Calculation of International Prognostic Index (IPI)[b]
- Hepatitis B testing[g]
- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- PET-CT scan
- Pregnancy testing in women of child-bearing age
- Beta-2-microglobulin (category 2B)

USEFUL IN SELECTED CASES:

- Neck CT, Head CT, or MRI
- Discussion of fertility issues and sperm banking
- HIV
- Lumbar puncture, if paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≥ 2 extranodal sites and elevated LDH

→ See Induction Therapy (BCEL-3)

[b] See International Prognostic Index (BCEL-A).

[g] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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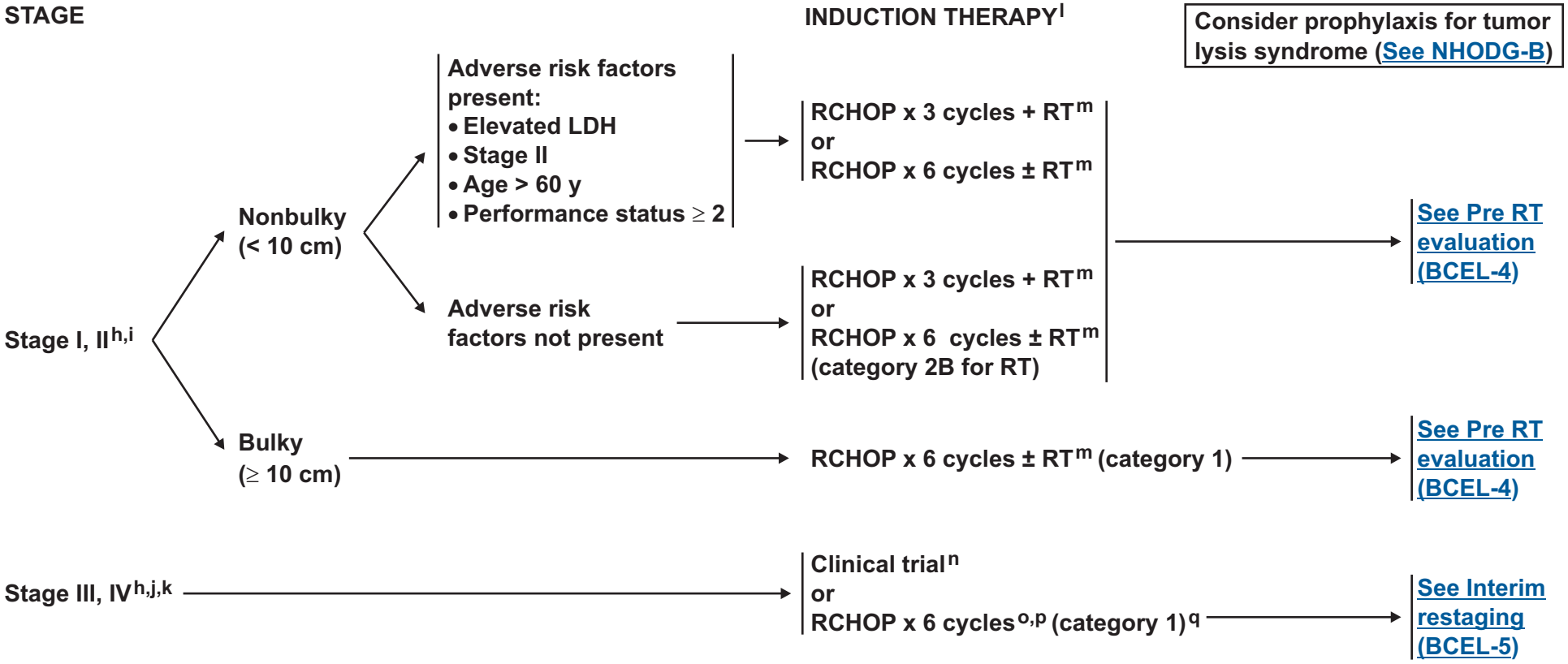

[h] In testicular lymphoma, after completion of chemotherapy, scrotal RT should be given (25-30 Gy).

[i] In patients who are not candidates for chemotherapy involved field radiation therapy (IFRT) is recommended.

[j] In selected cases (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≥ 2 extranodal sites and elevated LDH), there may be an increased risk of CNS events. The optimal management of these events are uncertain, but CNS prophylaxis can be considered with 4-8 doses of intrathecal methotrexate and/or cytarabine, or systemic methotrexate (3-3.5 g/m^2) during the course of treatment. Recent data regarding Stage IE DLBCL of breast has been suggested as a potential risk for CNS disease.

[k] Systemic disease with concurrent CNS disease should be treated with methotrexate/cytarabine-containing regimens.

[l] Recommendations are for HIV-negative lymphoma only. for HIV-positive DLBCL, see AIDS-2.

[m] See Principles of Radiation Therapy (NHODG-E).

[n] May include high-dose therapy.

[o] Based on current clinical trials, CHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are acceptable.

[p] For other regimens, see BCEL-C.

[q] In selected cases, RT to initially bulky sites of disease may be beneficial (category 2B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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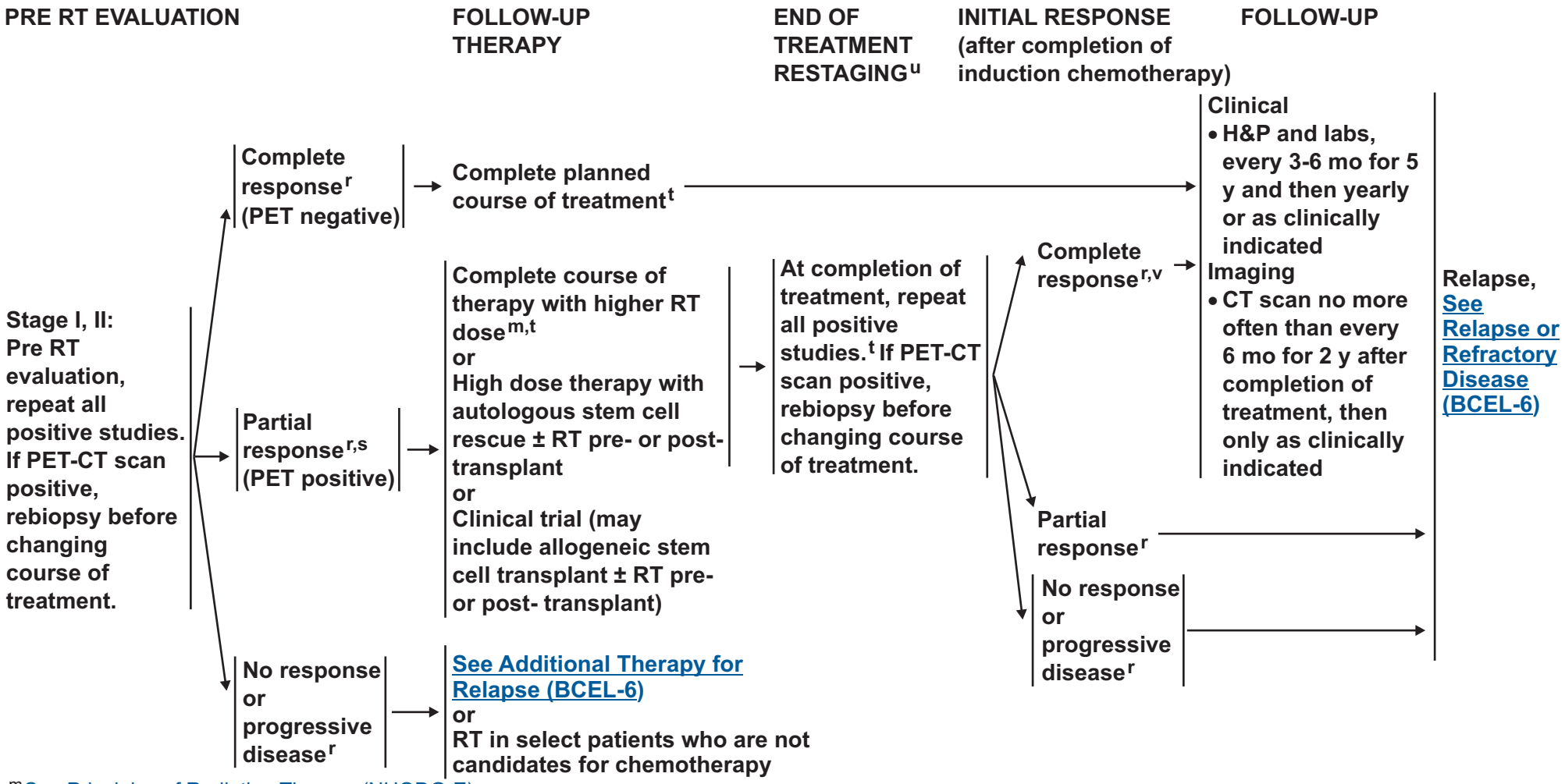


[m] See Principles of Radiation Therapy (NHODG-E).

[r] See Response Criteria for Lymphoma (NHODG-C).

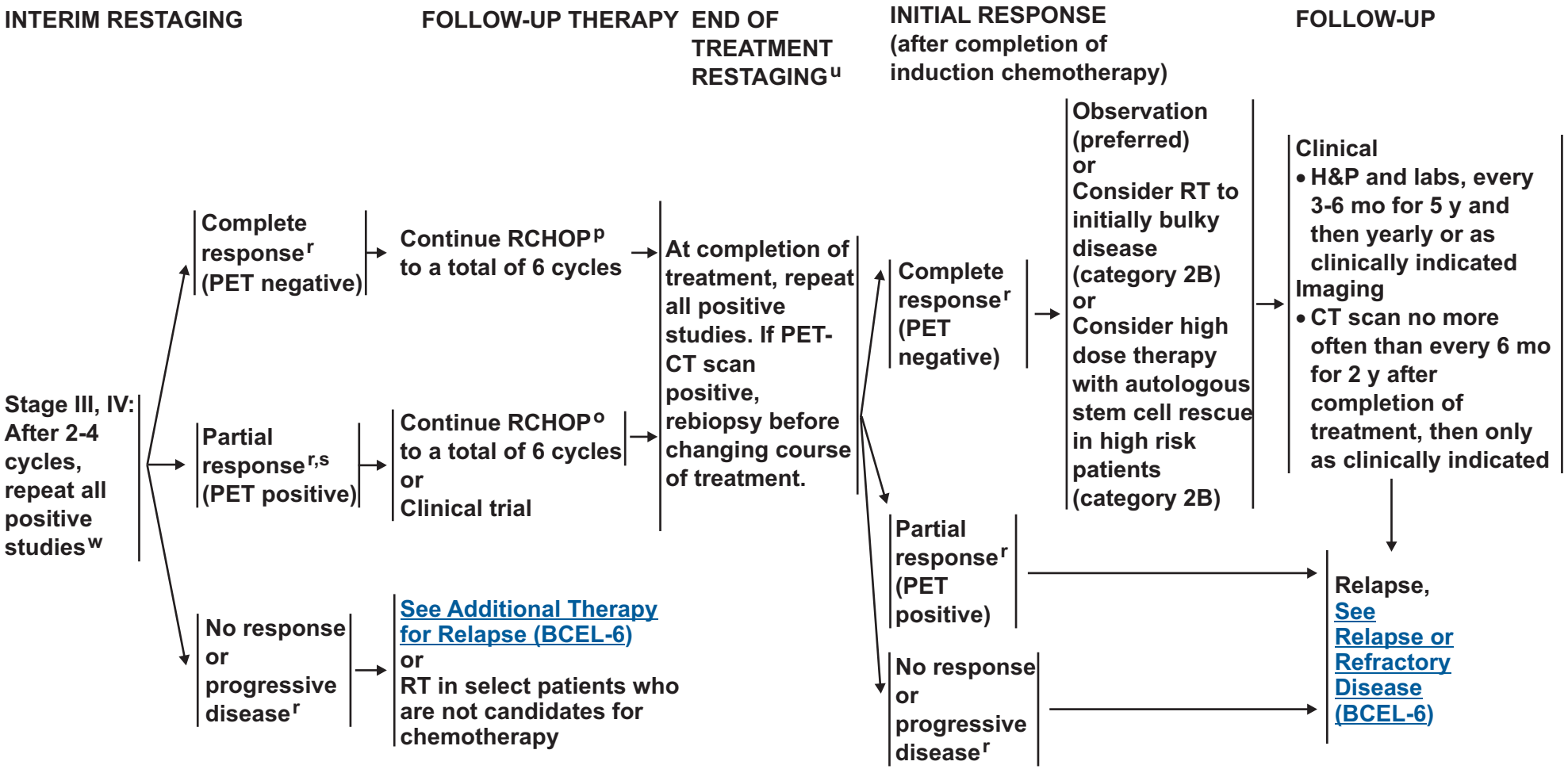
[s] Documented PR includes a biological measure of disease: positive PET-CT scan, or ideally positive biopsy.

[t] The optimum timing of repeat PET-CT is unknown, however waiting a minimum of 8 weeks after RT to repeat PET-CT scan is suggested. False positives may occur due to posttreatment changes.

[u] There is evidence that addition of maintenance rituximab does not improve survival.

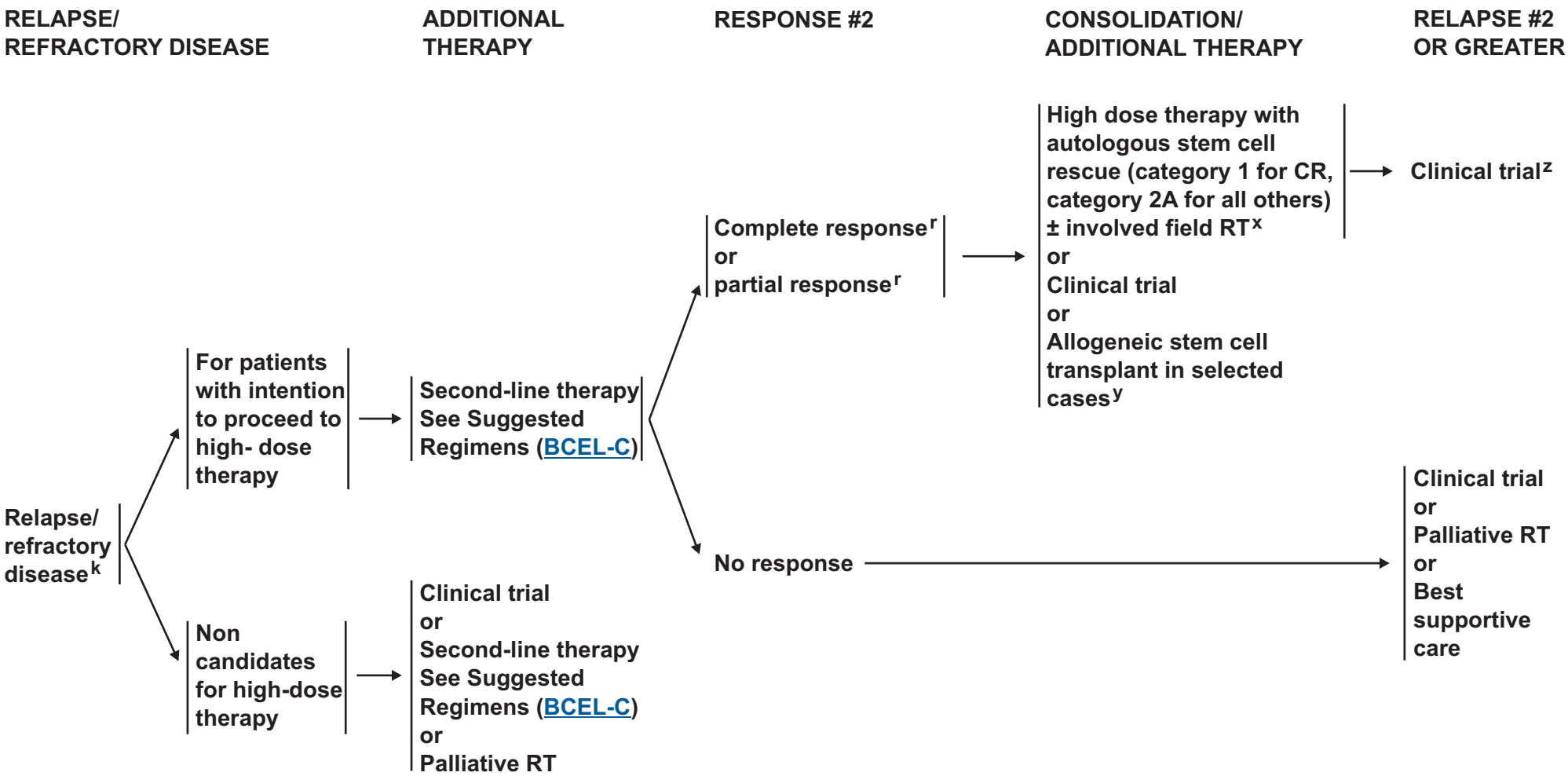
[v] Patients in first remission may be candidates for consolidation trials including high dose therapy with autologous stem cell rescue.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[p] For other regimens, see BCEL-C.
[r] See Response Criteria for Lymphoma (NHODG-C).
[s] Documented PR includes a biological measure of disease: positive PET-CT scan, or ideally positive biopsy.
[u] There is evidence that the addition of maintenance rituximab does not improve survival.
[w] PET-CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET-CT scan performed and positive, rebiopsy before changing course of treatment.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[k] Systemic disease with concurrent CNS disease should be treated with methotrexate/cytarabine-containing regimens.

[r] See Response Criteria for Lymphoma (NHODG-C).

[x] Additional RT can be given before or after high dose therapy with stem cell rescue to sites of previous positive disease.

[y] Selected cases include mobilization failures and persistent bone marrow involvement.

[z] Clinical trials or individual regimens: Patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age > 60 years
- Serum LDH > normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

INTERNATIONAL INDEX, ALL PATIENTS:

• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤ 60 YEARS:
- Stage III or IV
- Serum LDH > normal
- Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤ 60 YEARS:

• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

[a] The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med1993; 329:987-994.

Back to Workup (BCEL-1)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Primary Mediastinal Large B-Cell Lymphoma (PMBL)

PMBL can be defined as a clinical entity presenting with primary site of disease in mediastinum with or without other sites and has histology of DLBCL.

- **Clinical pathologic correlation is required to establish diagnosis.**
- **Optimal first-line therapy is more controversial than other subtypes of NHL.**
- **Because of relative rarity of PMBL, the role of R-CHOP-21 is not established as the definitive treatment option for this disease. However, R-CHOP-21 is widely used in NCCN institutions based on data in DLBCL and other regimens have been used (see BCEL-C). There are data suggesting that more intense therapy may be better based on non-randomized comparisons.**
- **Role of RT is controversial; if PET-CT scan negative at the end of treatment, may be observed.**
- **Residual mediastinal masses are common. PET-CT scan is essential post-treatment. Biopsy of PET- CT scan positive mass is recommended if additional systemic treatment is contemplated.**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

First-line Therapy
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- Dose-dense RCHOP 14 (category 3)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (category 2B)

First-line Therapy for patients with poor left ventricular function[b,c]
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- RCNOP (rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisone)
- DA-EPOCH[d] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)

First-line Consolidation (optional)
- High dose therapy with autologous stem cell rescue in patients with age-adjusted IPI high risk disease (category 2B)

Second-line Therapy[b,e,f] (For patients with intention to proceed to high dose therapy with autologous stem cell rescue)
- DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

Second-line Therapy[b,e,f] (non candidates for high dose therapy)
- Bendamustine ± rituximab
- Clinical trial
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV
- DA-EPOCH ± rituximab
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- GDP ± rituximab
- GemOx ± rituximab
- Lenalidomide ± rituximab
- Rituximab

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

Concurrent presentation with CNS disease
- Parenchymal: 3 g/m² or more of systemic methotrexate at count recovery as an alternating regimen
- Leptomeningeal: IT methotrexate/cytarabine, consider Ommaya resevoir placement and/or systemic methotrexate (3-3.5 g/m²)

[a] See references for regimens BCEL-C 2 of 3 and BCEL-C 3 of 3.
[b] Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[c] There is limited published data regarding the use of these regimens, however, they are used at NCCN institutions for the first-line treatment of DLBCL for patients with poor ventricular left function.
[d] If upward dose adjustment is necessary, doxorubicin should be maintained at base dose and not increased.
[e] If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
[f] Rituximab would be included in second-line therapy if there is relapse after a reasonable remission (> 6 mo), however rituximab would often be omitted in patients with primary refractory disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

First-line Therapy

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab with RT

Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-hodgkin's lymphoma. N Engl J Med 1998;339:21-26.

Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-hodgkin's lymphoma: Eastern Cooperative Oncology Group Study 1484. J Clin Oncol 2004;22:3032-3038.

Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group Study 0014. J Clin Oncol 2008;26:2258-2263.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045.

Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-4126.

Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379-391.

Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105-116.

Dose-dense CHOP 14 + rituximab

Blayney DW, LeBlanc ML, Grogan T, et al. Dose-intense chemotherapy every 2 weeks with dose-intense cyclophosphamide, doxorubicin, vincristine, and prednisone may improve survival in intermediate- and high-grade lymphoma: a phase II study of the Southwest Oncology Group (SWOG 9349). J Clin Oncol 2003;21:2466-2473

Cunningham D, Smith P, Mouncey P, et al. R-CHOP14 versus R-CHOP21: Result of a randomized phase III trial for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma [abstract]. J Clin Oncol 2011;29: Abstract 8000.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab

Purroy N, Lopez A, Vallespi T, Gironella M, Bergua J, Sancho JM. Dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor risk large B-cell lymphoma. A phase 2 study conducted by the Spanish PETHEMA Group [Abstract]. Blood 2009;114:Abstract 2701.

Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol 2008;26:2717-2724.

First-line Therapy for patients with poor ventricular left function

CDOP (cyclophosphamide, liposomal doxorubicin, vincristine and prednisone) + rituximab

Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: Results from a prospective phase II study. Haematologica 2002;87:822-827.

Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2006;47:2174-2180.

CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone) + rituximab

Bessell EM, Burton A, Haynes AP, et al. A randomised multicentre trial of modified CHOP versus MCOP in patients aged 65 years and over with aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14:258-267.

Bezwoda W, Rastogi RB, Erazo Valla A, et al. Long-term results of a multicentre randomised, comparative phase III trial of CHOP versus CNOP regimens in patients with intermediate- and high-grade non-Hodgkin's lymphomas. Novantrone International Study Group. Eur J Cancer 1995;31A:903-911.

Sonneveld P, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 1995;13:2530-2539.

RCEOP (ritximab, cyclophosphamide, etoposide, vincristine, prednisone)

Moccia A, Schaff K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): Excellent outcome in diffuse large B cell lymphoma for patients with a contraindication to anthracyclines [abstract]. Blood 2009;114:Abstract 408.

First-line consolidation

Stiff PJ, Unger JM, Cook J, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP {+/-} R for eight cycles to CHOP {+/-} R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin lymphoma (NHL) [abstract]. J Clin Oncol 2011;29: Abstract 8001.

Continued on next page

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

Second-line Therapy

Bendamustine ± rituximab

Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1285-1289.

Vacirca J, Tabbara I, Acs P, Shumaker G. Bendamustine + rituximab as treatment for elderly patients with relapsed or refractory diffuse large B-cell lymphoma [abstract]. Blood 2010;116: Abstract 2806.

Ogura M, Ando K, Taniwaki M, et al. Feasibility and pharmacokinetic study of bendamustine hydrochloride in combination with rituximab in relapsed or refractory aggressive B cell non-Hodgkin's lymphoma. Cancer Sci 2011;102:1687-1692.

DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab

Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-122.

Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006;24:593-600.

Gisselbrecht C, Glass B, Mounier N, et al. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study [abstract]. J Clin Oncol 2009;27:Abstract 8509.

ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab

Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP - an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994;12:1169-1176.

Martin A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica 2008;93:1829-1836.

GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab

Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842.

GDP (gemcitabine, dexamethasone, carboplatin) ± rituximab

Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leuk Lymphoma 2010;51:1523-1529.

GemOX (gemcitabine, oxaliplatin) + rituximab

Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. Eur J Haematol 2008;80:127-132.

ICE (ifosfamide, carboplatin, etoposide) ± rituximab

Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14[suppl 1]:i5-10.

Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE (RICE) as second-line therapy prior to autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-8.

Vose J, Sneller V. Outpatient regimen rituximab plus ifosfamide, carboplatin and etoposide (R-ICE) for relapsed non-Hodgkin's lymphoma. Ann Oncol 2003;14 Suppl 1:i17-20.

Gisselbrecht C, Glass B, Mounier N, et al. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study [abstract]. J Clin Oncol 2009;27:Abstract 8509.

Lenalidomide

Czuczman MS, Vose J, Zinzani P, et al. Efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma: Results from an international study (NHL-003) [abstract]. J Clin Oncol 2009;27:Abstract e19504.

Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive Non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-4957.

CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab

Chao NJ, Rosenberg SA, and Horning SJ. CEPP(B): An effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. Blood 1990;76:1293-1298.

EPOCH + rituximab

Gutierrez M, Chabner BA, Pearson D, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: An 8-year follow-up study of EPOCH. J Clin Oncol 2000;18:3633-3642.

Jermann M, Jost LM, Taverna C, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: Results of a phase II study. Ann Oncol 2004;15:511-516.

RGemOx (rituximab, gemcitabine, oxaliplatin)

Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol 2009;64:907-916.

El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: An effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol 2007;18:1363-1368.

Note: All recommendations are category 2A unless otherwise indicated.
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Burkitt Lymphoma

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DIAGNOSIS[a,b]

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**
- **An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[c,d]**
  - **IHC panel: CD45 (LCA), CD20, CD3, CD10, Ki-67, BLC2, BCL6, TdT**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD20, CD3, CD5, CD19, CD10, TdT**
- **Cytogenetics ± FISH: t(8;14) or variants; MYC;BCL2; BCL6 rearrangements**
- **ISH for EBV EBER**

→

WORKUP

ESSENTIAL:

- **Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC, differential, platelets**
- **LDH**
- **Comprehensive metabolic panel**
- **Uric acid**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **Lumbar puncture**
- **Flow cytometry of cerebrospinal fluid**
- **Unilateral or bilateral bone marrow biopsy ± aspirate**
- **HIV testing**
- **Hepatitis B testing[e]**
- **MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL IN SELECTED CASES:

- **Neck CT**
- **Discussion of fertility issues and sperm banking**
- **Beta-2-microglobulin**
- **PET-CT scan[f]**

→ **See Risk Assessment and Induction Therapy (BURK-2)**

[a] WHO 2008 classification recognizes that it may not always be possible to distinguish between DLBCL and Burkitt lymphoma. In the setting where it is not possible to distinguish, aggressive therapy per this guideline is appropriate in selected cases. Treatment of double or triple hit tumors is controversial. Optimum regimen has not been identified.

[b] This disease is complex and curable; it is preferred that treatment occur at centers with expertise in the management of the disease.

[c] Typical immunophenotype: sIg+, CD10+, CD20+, TdT-, Ki67+ (≥ 95%), BCL2-, BCL6+, simple karyotype with MYC rearrangement as sole abnormality.

[d] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[e] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[f] Initiation of therapy should not be delayed in order to obtain a PET-CT scan.

Note: All recommendations are category 2A unless otherwise indicated.
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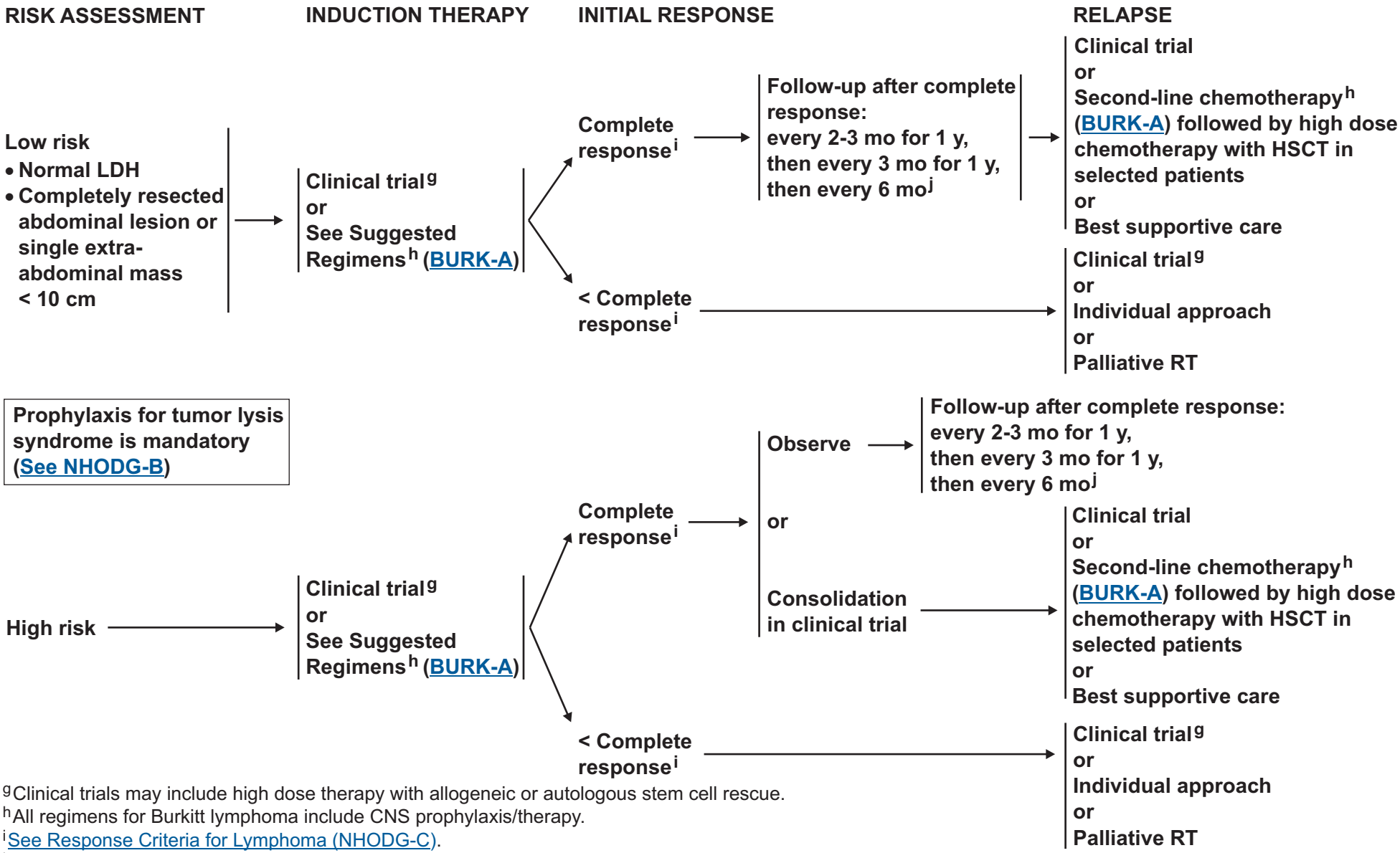

[g] Clinical trials may include high dose therapy with allogeneic or autologous stem cell rescue.
[h] All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.
[i] See Response Criteria for Lymphoma (NHODG-C).
[j] Relapse after 2 y is rare, therefore, follow-up should be individualized according to patient characteristics.

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SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

CHOP is not adequate therapy.

Induction therapy

Low Risk- Combination Regimens

- **CALGB 10002 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine and hydrocortisone]) + rituximab.**
- **CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) ± rituximab (3 cycles)**
- **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data is for patients without CNS disease.)**
- **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)**

High Risk- Combination Regimens

- **CALGB 10002 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine and hydrocortisone] with prophylactic CNS irradiation in select patients) + rituximab**
- **CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) alternating with IVAC (ifosfamide, cytarabine, etoposide and intrathecal methotrexate) ± rituximab**
- **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (For high risk patients not able to tolerate aggressive treatments) (regimen includes intrathecal methotrexate) (Data is for patients without CNS disease.)**
- **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)**

Second-line therapy (select patients with reasonable remission)

While no definitive second-line therapies exists, there are limited data for the following regimens:

- **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data is for patients without CNS disease.)**
- **RICE (rituximab, ifosfamide, carboplatin, etoposide); intrathecal methotrexate if have not received previously**
- **RIVAC (rituximab, ifosfamide, cytarabine, etoposide); intrathecal methotrexate if have not received previously**
- **RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)**
- **HDAC (high-dose cytarabine)**

[a] See references for regimens BURK-A 2 of 2.

[b] All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

Low and High Risk- Combination Regimens

CALGB 10002

Rizzieri DA, Johnson JL, Byrd JC, et al. Efficacy and toxicity of rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or Burkitt-like leukemia/lymphoma: Cancer and Leukemia Group B (CALGB) Study 10002 [abstract]. Blood 2010;116: Abstract 858.

CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) with (for high-risk) or without (for low-risk) alternating IVAC (ifosfamide, cytarabine, etoposide and intrathecal methotrexate ± rituximab

LaCasce A, Howard O, Lib S, et al. Modified magrath regimens for adults with Burkitt and Burkitt-like lymphoma: preserved efficacy with decreased toxicity. Leuk Lymphoma 2004;45:761-767.

Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002;13:1264-1274.

Barnes JA, Lacasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 2011;22:1859-1864.

Dose-adjusted EPOCH plus rituximab (regimen includes IT methotrexate)

Dunleavy K, Pittaluga S, Wayne AS, et al. MYC+ aggressive B-cell lymphomas: A novel therapy of untreated Burkitt lymphoma (BL) and MYC+ diffuse large B-cell lymphoma (DLBCL) with DA-EPOCH-R [abstract]. Ann Oncol 2011;22 (Supple 4): Abstract 71.

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab

Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580.

Thomas DA, Kantarjian HM, Cortes J, et al. Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for Burkitt (BL) or Burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukemia (ALL) [abstract]. Blood 2008;112:Abstract 1929

Second-line therapy

RICE (rituximab, ifosfamide, carboplatin, etoposide)

Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: A report from the Children's Oncology Group. Pediatr Blood Cancer 2009;52:177-181.

Note: All recommendations are category 2A unless otherwise indicated.
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Lymphoblastic Lymphoma[a]

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Discussion

DIAGNOSIS[b]

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**
- **An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[c]**
  - **IHC panel: CD45 (LCA), CD19, CD20, CD79a, CD3, CD2, CD5, CD7, TdT, CD1a, CD10, CCND1**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD4, CD7, CD8, CD19, CD20, CD10, TdT, CD13, CD33, CD1a, cytoplasmic CD3, CD22, myeloperoxidase**
- **Cytogenetics ± FISH: MYC; t(9;22); t(8;14) and variants**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Additional immunohistochemical studies to establish lymphoma subtype**
  - **Paraffin panel: CD22, CD4, CD8, CCND1**
- **Molecular analysis to detect: antigen receptor gene rearrangements**

WORKUP

ESSENTIAL:

- **Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC, differential, platelets**
- **LDH**
- **Comprehensive metabolic panel**
- **Uric acid, phosphate**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **Lumbar puncture**
- **Flow cytometry of cerebrospinal fluid**
- **Bilateral or unilateral bone marrow biopsy ± aspirate with flow and cytogenetics**
- **Hepatitis B testing[d]**
- **MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL IN SELECTED CASES:

- **Head MRI**
- **Discussion of fertility issues and sperm banking**
- **Beta-2-microglobulin**
- **PET-CT scan[e]**

See Clinical Assessment and Induction Therapy (BLAST-2)

[a] The LL category comprises two diseases, T-cell LL (90%) and B-cell LL (10%), which corresponds to T-ALL and B-ALL with presentations in extramedullary sites.

[b] This disease is complex and curable; it is preferred that treatment occur at centers with expertise in the management of the disease.

[c] Typical immunophenotype: *LL-B*: sIg-, CD10+/-, CD19+, CD20-/+, TdT+. *LL-T*: sIg-, CD10-, CD19/20-, CD3-/+, CD4/8+/+, CD1a+/-, TdT+, CD2+, CD7+ cytoplasmic CD3+, sCD3-/+.

[d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[e] Initiation of therapy should not be delayed in order to obtain a PET-CT scan.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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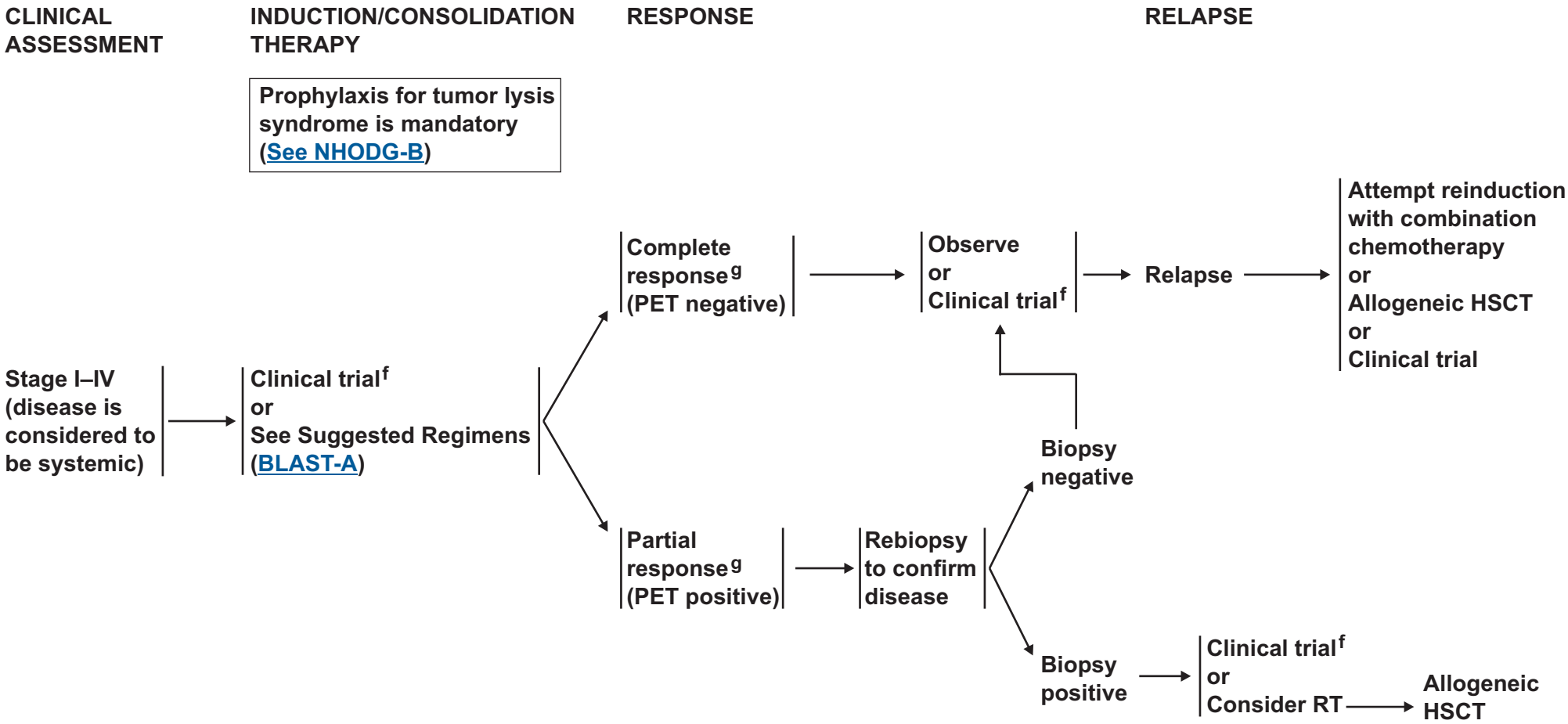

[f]All regimens for LL include CNS prophylaxis/therapy.
[g]See Response Criteria for Lymphoma (NHODG-C).

Note: All recommendations are category 2A unless otherwise indicated.
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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

BFM (Berlin–Frankfurt–Munster)

- **Standard BFM regimen:**
  - **Induction phase:**
    - **Vincristine, daunomycin, prednisone, L-asparaginase, cytarabine (IT), and methotrexate (IT).**
  - **Consolidation phase (5 weeks):**
    - **Prednisone, cyclophosphamide, mercaptopurine, vincristine, cytarabine, IT methotrexate, and RT.**
  - **Interim Maintenance phase (8 weeks):**
    - **Mercaptopurine and methotrexate (PO)**
  - **Delayed intensification (7 weeks):**
    - ***Reinduction phase (4 weeks):***
      - **Dexamethasone, vincristine, and doxorubicin.**
    - ***Reconsolidation phase (3 weeks)*:**
      - **L-asparaginase, vincristine, cyclophosphamide, thioguanine, cytarabine, and intrathecal methotrexate.**
  - **Long-term maintenance (12 weeks):**
    - **Vincristine, prednisone, mercaptopurine, methotrexate (PO and IT).**
- **Augmented BFM regimen:**
  - **Induction I:**
    - **Prednisone, vincristine, daunorubicin, L-asparaginase, methotrexate (IT).**
  - **Induction II:**
    - **Cyclophosphamide, cytarabine, 6-mercaptopurine, methotrexate (IT)**
  - **Consolidation I:**
    - **Cytarabine, mitoxantrone, methotrexate, asparaginase, 6-mercaptopurine**
  - **Reinduction I**
    - **Prednisolone, vincristine, doxorubicin**
    - **Triple prophylaxis: methotrexate, cytarabine, dexamethasone**
  - **Reinduction II**
    - **Cyclophosphamide, cytarabine, 6-thioguanine**
    - **Triple prophylaxis: methotrexate, cytarabine, dexamethasone**
  - **Consolidation II**
    - **Etoposide, cytarabine**
    - **Cyclophosphamide, cytarabine**

Suggested Treatment Regimens continued on BLAST-A 2 of 3

[a] See references for regimens BLAST-A 3 of 3.
[b] All regimens for LL include CNS prophylaxis/therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

- **CALGB ALL regimen**
  - Induction therapy (4 weeks):
    - Cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase.
    - For patients 60 years and older: the doses of cyclophsphamide, daunorubicin, and prednisone are modified (see reference for details).
  - Early intensification (4 weeks):
    - Intrathecal methotrexate, cyclophosphamide, 6-mercaptopurine, cytarabine, vincristine, and L-asparaginase.
  - CNS prophylaxis and interim maintenance:
    - Cranial irradiation in select cases, intrathecal methotrexate, 6-mercaptopurine, and methotrexate (PO).
  - Late intensification (8 weeks):
    - Doxorubicin, vincristine, dexamethasone, cyclophosphamide, 6-thioguanine, and cytarabine.
  - Prolonged maintenance (until 24 months from diagnosis):
    - Vincristine, prednisone, methotrexate (PO), and 6-mercaptopurine.

- **HyperCVAD[c] (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with methotrexate + cytarabine, including intrathecal methotrexate**
  - Maintenance therapy
    - 6-mercaptopurine, methotrexate, vincristine, and prednisone (POMP)
  - In the cases of CD20 positive (≥ 20%) acute lymphoblastic lymphoma (ALL), the addition of rituximab should be considered.
  - In cases of Philadelphia chromosome positive ALL, imatinib should be incorporated into regimen.

- **LMB-86 regimen**
  - Cytoreductive therapy
    - COP (cyclophosphamide, vincristine, and prednisone)
  - Induction therapy
    - COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, and high-dose methotrexate)
  - Consolidation therapy
    - CYVE (cytarabine and etoposide; regimen includes high-dose cytarabine)

- **Maintenance chemotherapy**
  - Up to 2 y of maintenance based on the treatment protocol is recommended.

[a] See references for regimens BLAST-A 3 of 3.

See Suggested Treatment Regimens on BLAST-A 1 of 3

[b] All regimens for LL include CNS prophylaxis/therapy.

[c] For T-cell lymphoblastic lymphomas with primary mediastinal presentation, residual masses are irradiated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

BFM (Berlin–Frankfurt–Munster)
Standard BFM
Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood 2008;112:1646-1654.
Augmented BFM
Hoelzer D, Gokbuget N, Digel W, et al. Outcome of adult patients with T-lymphoblastic lymphoma treated according to protocols for acute lymphoblastic leukemia. Blood 2002;99:4379-4385.

CALGB ALL regimen
Larson R, Dodge R, Burns C, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood 1995;85:2025-2037.

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate-cytarabine) followed by POMP (mercaptopurine, methotrexate, vincristine, and prednisone) maintenance
Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000;18:547-561.
Thomas DA, O'Brien S, Cortes J, et al. Outcome with the hyper-CVAD regimens in lymphoblastic lymphoma. Blood 2004;104:1624-1630.

LMB-86 regimen
Soussain C, Patte C, Ostronoff M, et al. Small noncleaved cell lymphoma and leukemia in adults. A retrospective study of 65 adults treated with the LMB pediatric protocols. Blood 1995;85:664-674.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2012
AIDS-Related B-Cell Lymphomas

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Discussion

DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis[a]
  - IHC panel: CD45 (LCA), CD20, CD3, CD10, BCL2, BCL6, Ki-67, CD138, kappa/lambda, HHV8
    or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20
- Epstein-Barr virus (EBER-ISH)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - DLBCL, Burkitt, Plasmablastic, Primary effusion: CD10, BCL2, Ki-67, BCL6, CD138
- Molecular analysis to detect: antigen receptor gene rearrangements; BCL2, BCL6, MYC rearrangements
- Cytogenetics or FISH: BCL2; BCL6; MYC

→

WORKUP

ESSENTIAL

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid, phosphate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- PET-CT scan
- Bone marrow biopsy ± aspirate
- CD4 count
- LP
- HIV viral load
- Hepatitis B testing[b]
- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES

- UGI/barium enema/endoscopy
- Neck CT
- Plain bone radiographs and bone scan
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin
- Brain MRI with gadolinium, or head CT
- EBV viral load

→ See Treatment and Follow-up (AIDS-2) and (AIDS-3)

[a] See Use of Immunophenotyping and Genetic Tesitng in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[b] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT

Antiretrovirals can be administered safely with chemotherapy, however some regimens have recommended discontinuation. Any change in antiviral therapy should be done in consultation with an infectious disease specialist.

Burkitt lymphoma →

- **Suggested regimens:**[c]
  - **CODOX-M/IVAC (modified): cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab**[d]
  - **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) ± rituximab**[d]
  - **CDE (cyclophosphamide, doxorubicin, etoposide) ± rituximab**[d]
  - **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) ± rituximab**[d]
- **If CD4 < 100, consider eliminating rituximab**[d]
- **GCSF for all patients**

- **Lymphoma associated with Castleman's disease**
- **Diffuse large B-cell lymphoma**
- **Primary effusion lymphoma**

→

- **Suggested regimens:**[c]
  - **Dose-adjusted EPOCH + rituximab**
  - **CDE + rituximab**
  - **CHOP + rituximab**
  - **CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, prednisone) + rituximab**
- **GCSF for all patients**
- **Intrathecal therapy (IT)**[e]
- **If CD20-, rituximab is not indicated**
- **If CD4 < 100, consider eliminating rituximab**[d]

→ **For DLBCL relapse, see BCEL-6**

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[c] See references for regimens AIDS-A.

[d] Patients on active antiretrovirals with persistently low CD4 count of <100 tend to have poor prognosis and higher risk of infection associated with the addition of rituximab. Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. Blood 2005;105:1891-1897. Sparano JA, Lee JY, Kaplan LD et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood 2010;115:3008-3016. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood 2005;106:1538-1543.

[e] Prophylactic IT methotrexate is used at some NCCN institutions for all patients with HIV-associated DLBCL. At other NCCN institutions, patients receive IT methotrexate in selective settings (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV-lymphoma, or ≥ 2 extranodal sites and elevated LDH).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT

Antiretrovirals can be administered safely with chemotherapy however some regimens have recommended discontinuation. Any change in antiviral therapy should be done in consultation with an infectious disease specialist.

Plasmablastic lymphoma[f] →

- **Suggested regimens:[c]**
  - **CODOX-M/IVAC (modified)**
  - **Dose-adjusted EPOCH**
  - **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)**
- **Standard CHOP is not adequate therapy**

Primary CNS lymphoma →

- **Consider high-dose methotrexate**
- **Consider RT alone**
- **For select patients with good performance status on HAART, see NCCN CNS Guidelines- Primary CNS Lymphoma**
- **Best supportive care (See NCCN Palliative Care Guidelines)**

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[c]See references for regimens AIDS-A.
[f]Management can also apply to HIV negative plasmablastic lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine)
Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. Cancer 2003;98:1196-1205
Barnes JA, LaCasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: A retrospective analysis. Ann Oncol 2011; 22:1859-1864.

Dose- adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. Blood 2003;101:4653-4659.

CDE (cyclophosphamide, doxorubicin, and etoposide)
Sparano JA, Lee S, Chen MG, et al. Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's Lymphoma: An Eastern Cooperative Oncology Group Trial (E1494). J Clin Oncol 2004;22:1491-1500.

CDE + rituximab
Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: Pooled results from 3 phase 2 trials. Blood 2005;105:1891-1897.
Spina M, Simonelli C, Vaccher E, et al. Long-term follow-up of rituximab and infusional cyclophosphamide, doxorubicin, and etoposide (CDE) in combination with HAART in HIV related Non-Hodgkin's Lymphomas (NHL). Blood 2008;112:Abstract 1467.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
Ratner L, Lee J, Tang S, et al. Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's Lymphoma in combination with highly active antiretroviral therapy. J Clin Oncol 2001;19:2171-2178.

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) ± rituximab
Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. Cancer 2002;94:1492-1499.
Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580.
Thomas DA, Kantarjian HM, Cortes J, et al. Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for Burkitt (BL) or Burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukemia (ALL) [abstract]. Blood 2008;112:Abstract 1929.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2012
Primary Cutaneous B-Cell Lymphomas[a]

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DIAGNOSIS

ESSENTIAL:

- **Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of primary cutaneous B-cell lymphoma. Rebiopsy if consult material is nondiagnostic.**
- **Histopathology review of adequate biopsy (punch, incisional, excisional).**
- **Adequate immunophenotyping to establish diagnosis[b,c]**
  - **IHC panel: CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, Ki-67, kappa/lambda, IRF4/MUM1**

USEFUL IN CERTAIN CIRCUMSTANCES:

- **Additional immunohistochemical studies to establish lymphoma subtype**
  - **Paraffin panel: CCND1**
  - **Assessment of IgM and IgD expression (to further help in distinguishing DLBCL, leg type from follicle center lymphoma)**
- **Molecular analysis to detect: antigen receptor gene rearrangements; IgH gene rearrangement by PCR**
- **Cytogenetics or FISH: t(14;18)**

NOTE: A germinal (or follicle) center phenotype and large cells in a skin lesion is *not* equivalent to DLBCL but is consistent with primary cutaneous germinal/follicle center lymphoma.

WORKUP

ESSENTIAL:[d]

- **Complete history and physical examination-including complete skin exam**
- **CBC, differential, comprehensive metabolic panel**
- **LDH**
- **Hepatitis B testing[e] if rituximab considered**
- **Chest/abdominal/pelvic CT**
- **Bone marrow biopsy, if PC-DLBCL, Leg type**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL IN SELECTED CASES:

- **PET-CT scan**
- **Bone marrow biopsy**
  - **Consider if PCFCL**
  - **Optional if PCMZL**
- **Peripheral blood flow cytometry, if CBC demonstrates lymphocytosis**
- **SPEP/quantitative immunoglobulins for PCMZL**

→ **See Initial Therapy for Primary Cutaneous Marginal Zone Lymphoma (CUTB-2)**

→ **See Initial Therapy for Primary Cutaneous Follicle Center Lymphoma (CUTB-2)**

→ **See Initial Therapy for Primary Cutaneous B-Cell Lymphoma, Leg Type (CUTB-4)**

PC-DLBCL, Leg type: Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg type
PCMZL: Primary Cutaneous Marginal Zone Lymphoma
PCFCL: Primary Cutaneous Follicle Center Cell Lymphoma

[a] For non-cutaneous, see Nongastric MALT Lymphoma (NGMLT-1).

[b] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

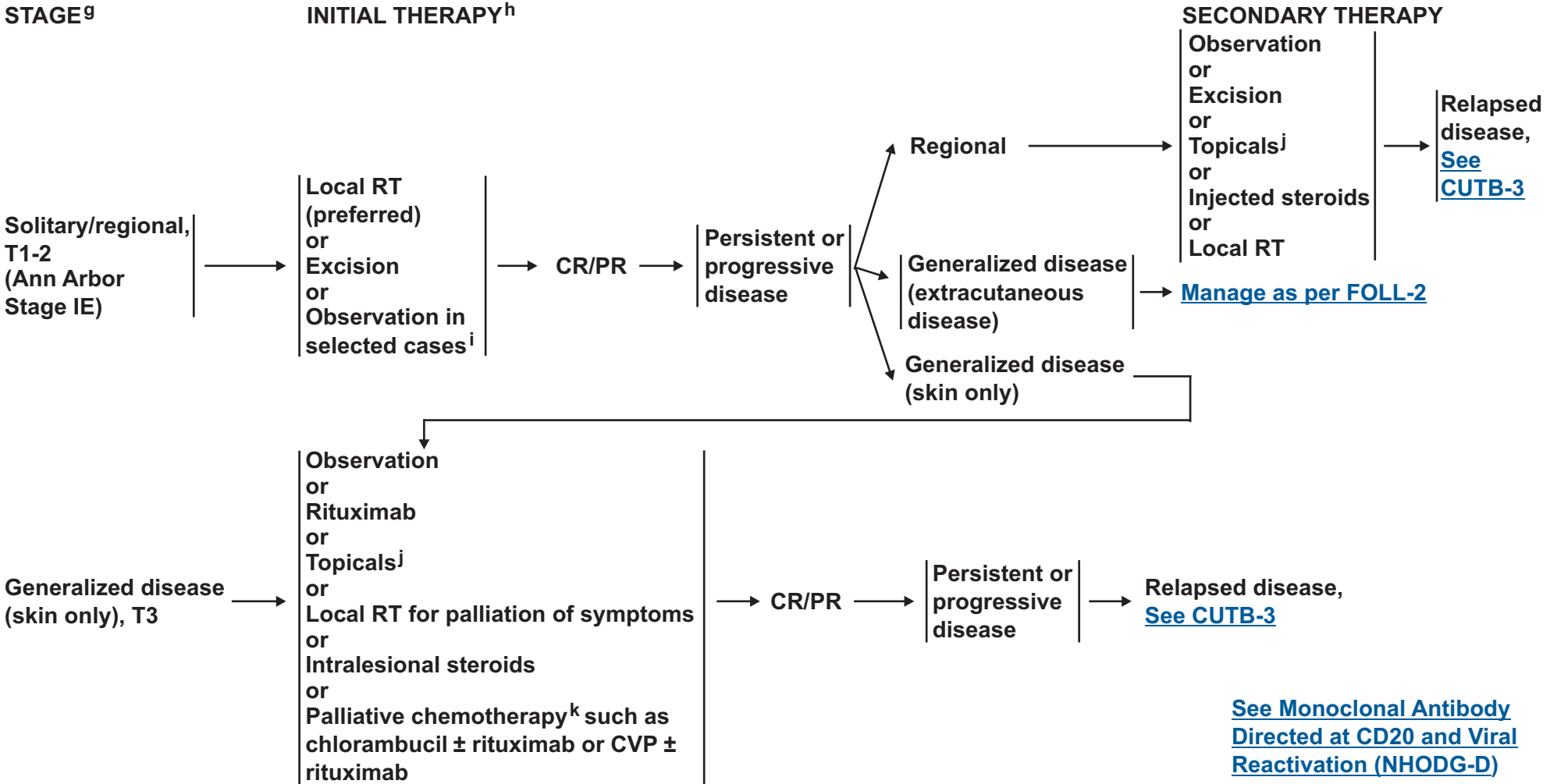
[c] Typical immunophenotype: PC-DLBCL: CD20+ Bcl2+ CD10- Bcl6+/- IRF4/MUM1+/- ; PCFCL: CD20+ Bcl2- CD10-/+ Bcl6+ IRF4/MUM1-; PCMZL: CD20+ Bcl2+/- CD10- Bcl6- IRF4/MUM1+/- cytoplasmic kappa+ or lambda+ in about 40%.

[d] Rule out drug-induced cutaneous lymphoid hyperplasia.

[e] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER CELL LYMPHOMA[f]



[f] Unless clinically indicated, additional imaging studies during the course of treatment are not needed.

[g] See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).

[h] See Treatment References (CUTB-B).

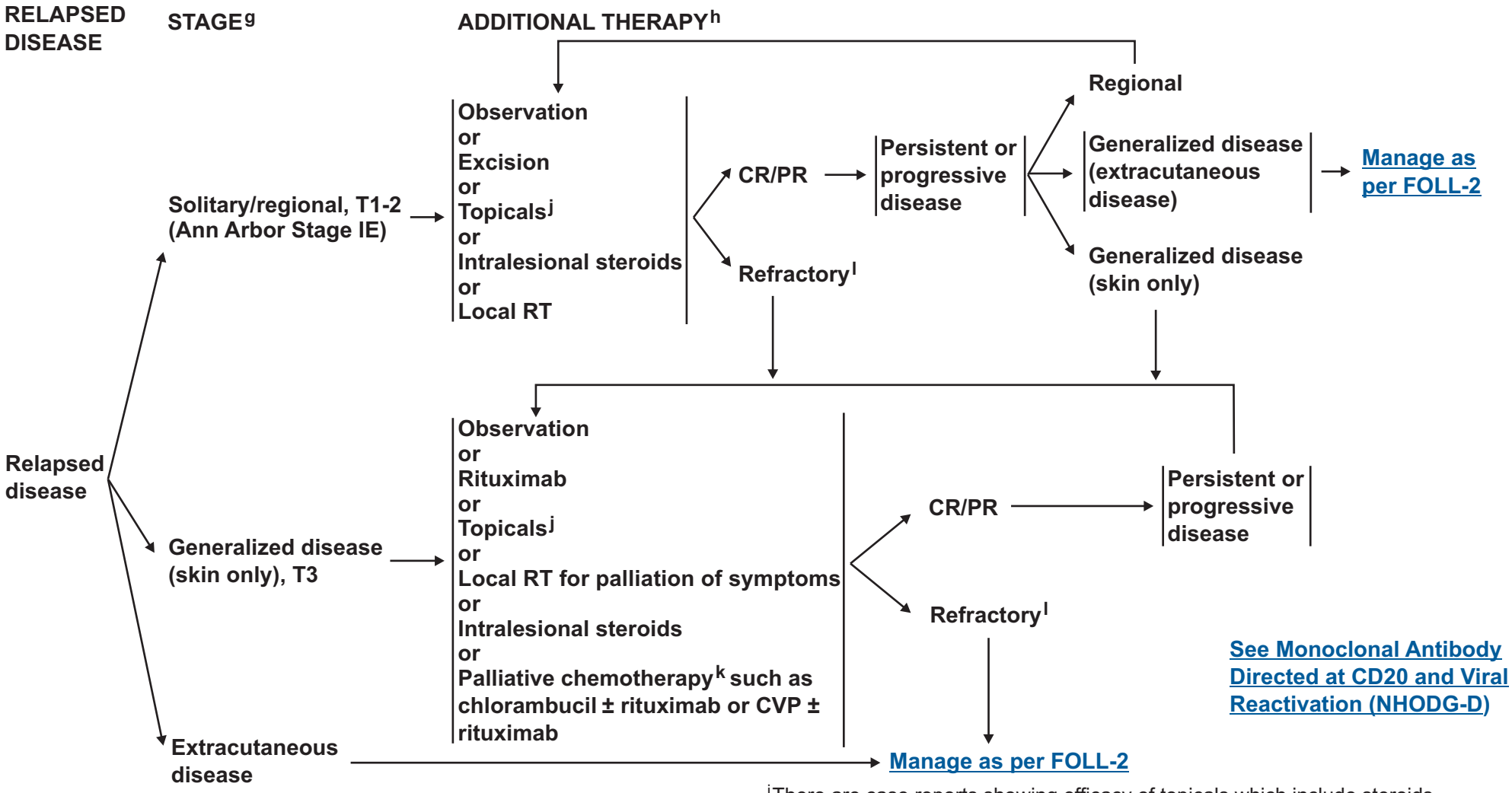
[i] When RT or surgical treatment is neither not feasible nor desired.

[j] There are case reports showing efficacy of topicals which include steroids, imiquimod, nitrogen mustard, bexarotene.

[k] In rare circumstances for very extensive disease, other combination chemotherapy regimens listed in FOLL-B are used.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER CELL LYMPHOMA[f]

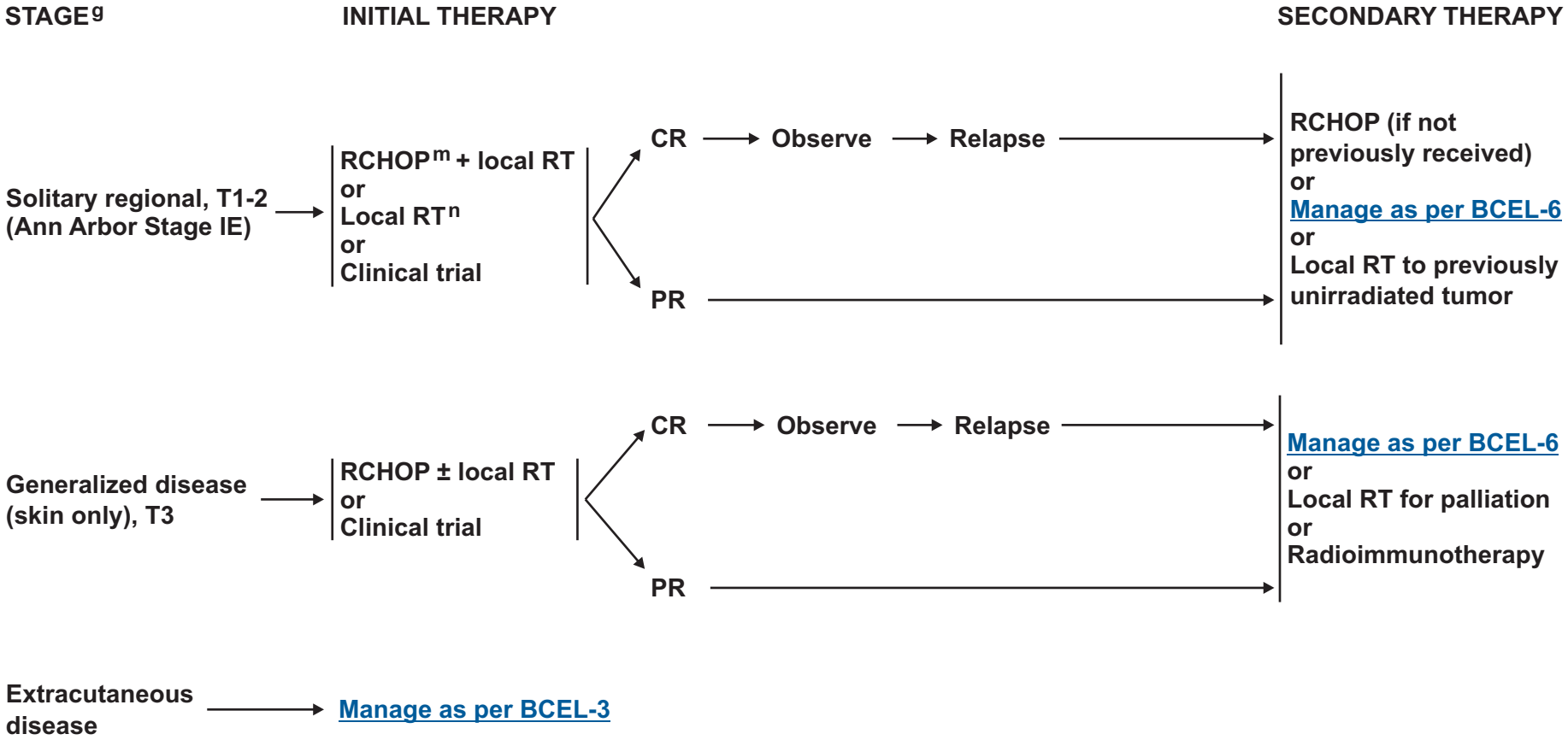


[f]Unless clinically indicated, additional imaging studies during the course of treatment is not needed.
[g]See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[h]See Treatment References (CUTB-B).

[j]There are case reports showing efficacy of topicals which include steroids, imiquimod, nitrogen mustard, bexarotene.
[k]In rare circumstances for very extensive disease, other combination chemotherapy regimens listed in FOLL-B are used.
[l]Refractory to all previous treatments.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE



See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[g] See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[m] For alternate regimens, see BCEL-C.
[n] For patients not able to tolerate chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS[a,b]

T	
T1	**Solitary skin involvement** **T1a: a solitary lesion < 5 cm diameter** **T1b: a solitary > 5 cm diameter**
T2	**Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions[b]** **T2a: all-disease-encompassing in a < 15-cm-diameter circular area** **T2b: all-disease-encompassing in a > 15- and < 30-cm-diameter circular area** **T2c: all-disease-encompassing in a > 30-cm-diameter circular area**
T3	**Generalized skin involvement** **T3a: multiple lesions involving 2 noncontiguous body regions[b]** **T3b: multiple lesions involving ≥ 3 body regions[b]**
N	
N0	**No clinical or pathologic lymph node involvement**
N1	**Involvement of 1 peripheral lymph node region[c] that drains an area of current or prior skin involvement**
N2	**Involvement of 2 or more peripheral lymph node regions[c] or involvement of any lymph node region that does not drain an area of current or prior skin involvement**
N3	**Involvement of central lymph nodes**
M	
M0	**No evidence of extracutaneous non–lymph node disease**
M1	**Extracutaneous non-lymph node disease present**

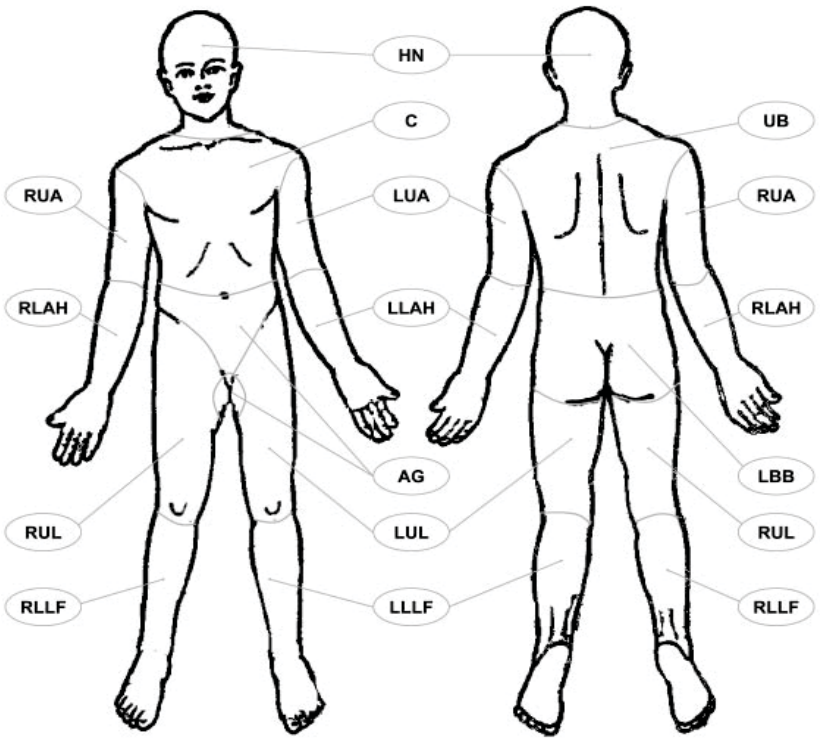
[a] This work was originally published in Blood. Kim YH, Willemze R, Pimpinell Ni, et al, for the ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) Blood 2007;110:479-484. © the American Society of Hematology.

[b] For definition of body regions, see Body Regions for the Designation of T (skin involvement) Category (CUTB-A 2 of 2).

[c] Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraortic, iliac.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY[a,b,c]



HN	Head & Neck
C	Chest
LUA	Left Upper Arm
LLAH	Left Lower Arm & Hand
AG	Abdominal & Genital
LUL	Left Upper Leg
LLLF	Left Lower Leg & Feet
RUA	Right Upper Arm
RLAH	Right Lower Arm & Hand
RUL	Right Upper Leg
RLLF	Right Lower Leg & Feet
UB	Upper Back
LBB	Lower Back & Buttock

[a] Kim YH, Willemze R, Pimpinell Ni, et al, for the ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:479-484.

[b] Left and right extremities are assessed as separate body regions. The designation of these body regions are based on regional lymph node drainage patterns.

[c] Definition of body regions: Head and neck: inferior border—superior border of clavicles, T1 spinous process. Chest: superior border—superior border of clavicles; inferior border—inferior margin of rib cage; lateral borders—midaxillary lines, glenohumeral joints (inclusive of axillae). Abdomen/genital: superior border—inferior margin of rib cage; inferior border—inguinal folds, anterior perineum; lateral borders—mid-axillary lines. Upper back: superior border—T1 spinous process; inferior border—inferior margin of rib cage; lateral borders—mid-axillary lines. Lower back/buttocks: superior border—inferior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—midaxillary lines. Each upper arm: superior borders—glenohumeral joints (exclusive of axillae); inferior borders—ulnar/radial-humeral (elbow) joint. Each lower arm/hand: superior borders—ulnar/radial-humeral (elbow) joint. Each upper leg (thigh): superior borders—inguinal folds, inferior gluteal folds; inferior borders—mid-patellae, midpopliteal fossae. Each lower leg/foot: superior borders—mid-patellae, mid-popliteal fossae.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT REFERENCES

Rituximab

Morales AV, Advani R, Horwitz SM, et al. Indolent primary cutaneous B-cell lymphoma: experience using systemic rituximab. J Am Acad Dermatol 2008;59:953-957.

Heinzerling LM, Urbanek M, Funk JO, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. Cancer 2000;89:1835-1844.

Valencak J, Weihsengruber F, Rappersberger K, et al. Rituximab monotherapy for primary cutaneous B-cell lymphoma: Response and follow-up in 16 patients. Ann Oncol 2009;20:326-330.

Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 2008;112:1600-1609.

Heinzerling L, Dummer R, Kempf W, Schmid MH, Burg G. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell lymphoma. Arch Dermatol 2000;136:374-378.

Topicals

Topical/intralesional corticosteroids

Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 1999;17:2471-2478.

Topical nitrogen mustard

Bachmeyer C, Orlandini V, Aractingi S. Topical mechlorethamine and clobetasol in multifocal primary cutaneous marginal zone-B cell lymphoma. British Journal of Dermatology 2006;154:1207-1209.

Topical bexarotene

Trent JT, Romanelli P, Kerdel FA. Topical Targretin and Intralesional Interferon Alfa for Cutaneous Lymphoma of the Scalp. Arch Dermatol 2002;138:1421-1423.

Topical imiquimod

Coors EA, Schuler G, Von Den Driesch P. Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 2006;16:391-393.

Stavrakoglou A, Brown VL, Coutts I. Successful treatment of primary cutaneous follicle centre lymphoma with topical 5% imiquimod. Br J Dermatol 2007;157:620-622.

Chemotherapy

Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Primary cutaneous marginal zone B-cell lymphoma: Clinical and therapeutic features in 50 cases. Arch Dermatol 2005;141:1139-1145.

Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 1999;17:2471-2478.

Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 2008;112:1600-1609.

Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 2007;143:1144-1150.

Brice P, Cazals D, Mounier N, et al. Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. Groupe d'Etude des Lymphomes de l'Adulte. Leukemia 1998;12:213-219.

Rijlaarsdam JU, Toonstra J, Meijer OW, Noordijk EM, Willemze R. Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: A clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy. J Clin Oncol 1996;14:549-555.

Vermeer MH, Geelen FA, van Haselen CW, et al. Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. Dutch Cutaneous Lymphoma Working Group. Arch Dermatol 1996;132:1304-1308.

Note: All recommendations are category 2A unless otherwise indicated.
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DIAGNOSIS

ESSENTIAL:

- **Review of all slides with at least one paraffin block representative of the tumor should be done by a hematopathologist with expertise in the diagnosis of PTCL. Rebiopsy if consult material is nondiagnostic.**
- **An FNA alone is not sufficient for the initial diagnosis of peripheral T-cell lymphoma.**
- **Adequate immunophenotyping to establish diagnosis[a,b]**
  - **IHC panel: CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD57 CD21, CD23, EBER-ISH, ALK**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: antigen receptor gene rearrangements; t(2;5) and variants**
- **Additional immunohistochemical studies to establish lymphoma subtype: βF1, CD279 (PD1)**
- **Cytogenetics to establish clonality**
- **CXCL-13**

SUBTYPES

Subtypes included:

- **Peripheral T-cell lymphoma (PTCL), NOS**
- **Angioimmunoblastic T-cell lymphoma (AITL)[c]**
- **Anaplastic large cell lymphoma (ALCL), ALK positive**
- **Anaplastic large cell lymphoma (ALCL), ALK negative**
- **Enteropathy associated T-cell lymphoma (EATL)**

→ **See Workup (TCEL-2)**

Subtypes *not* included:

- **Primary cutaneous ALCL**
- **All other T-cell lymphomas**

Extranodal NK/T-cell lymphoma, nasal type (See NKTL-1)

[a] Molecular diagnosis for T-cell receptor rearrangements should be done in most circumstances to confirm clonality. T-cell receptors rearrangements alone are not sufficient for diagnosis as these are often seen with reactive/inflammatory processes.

[b] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[c] AITL may occasionally present with concurrent DLBCL. EBV and appropriate immunohistochemistry should be performed.

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WORKUP

ESSENTIAL:[d]
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, size of liver and spleen, skin rash and nasopharynx
- Performance status
- B symptoms
- CBC, differential, platelets
- Bone marrow biopsy
- LDH
- Comprehensive metabolic panel
- Uric acid
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- PET-CT scan
- Calculation of International Prognostic Index (IPI)[e]
- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- Neck CT
- Head CT or MRI
- Skin biopsy
- Discussion of fertility issues and sperm banking
- HIV, HTLV-1

→ See Induction Therapy (TCEL-3)

[d] The role of intrathecal prophylaxis in PTCL is largely unknown.
[e] See International Prognostic Index (TCEL-A).

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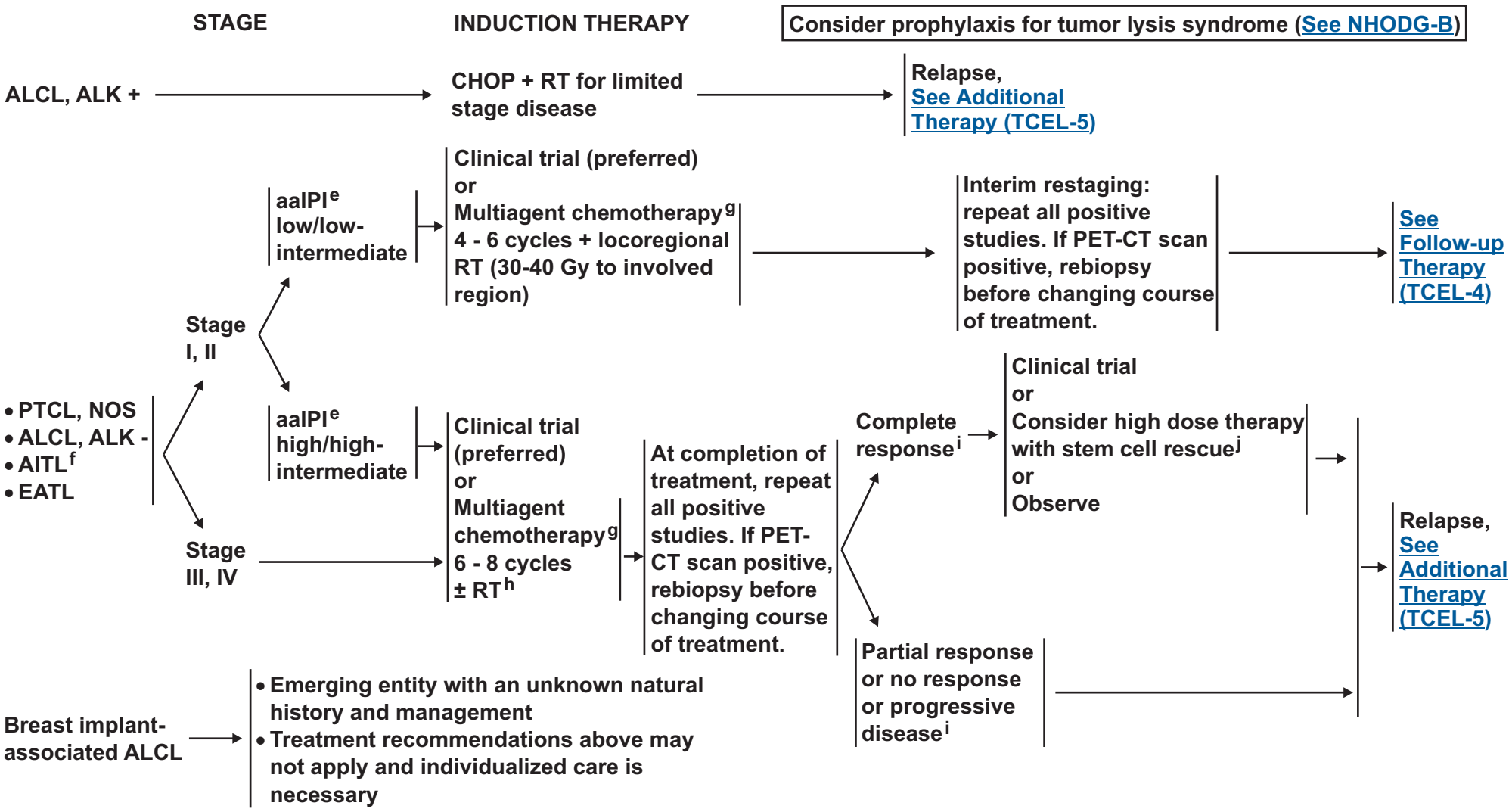

[e] See International Prognostic Index (TCEL-A).
[f] For selected patients (elderly, comorbid conditions), a trial of single agent corticosteroid may be considered for symptom management.
[g] See Suggested Treatment Regimens (TCEL-B).
[h] Patients with locoregional disease receive RT.
[i] See Response Criteria for Lymphoma (NHODG-C).
[j] Localized areas can be irradiated before or after high dose therapy.

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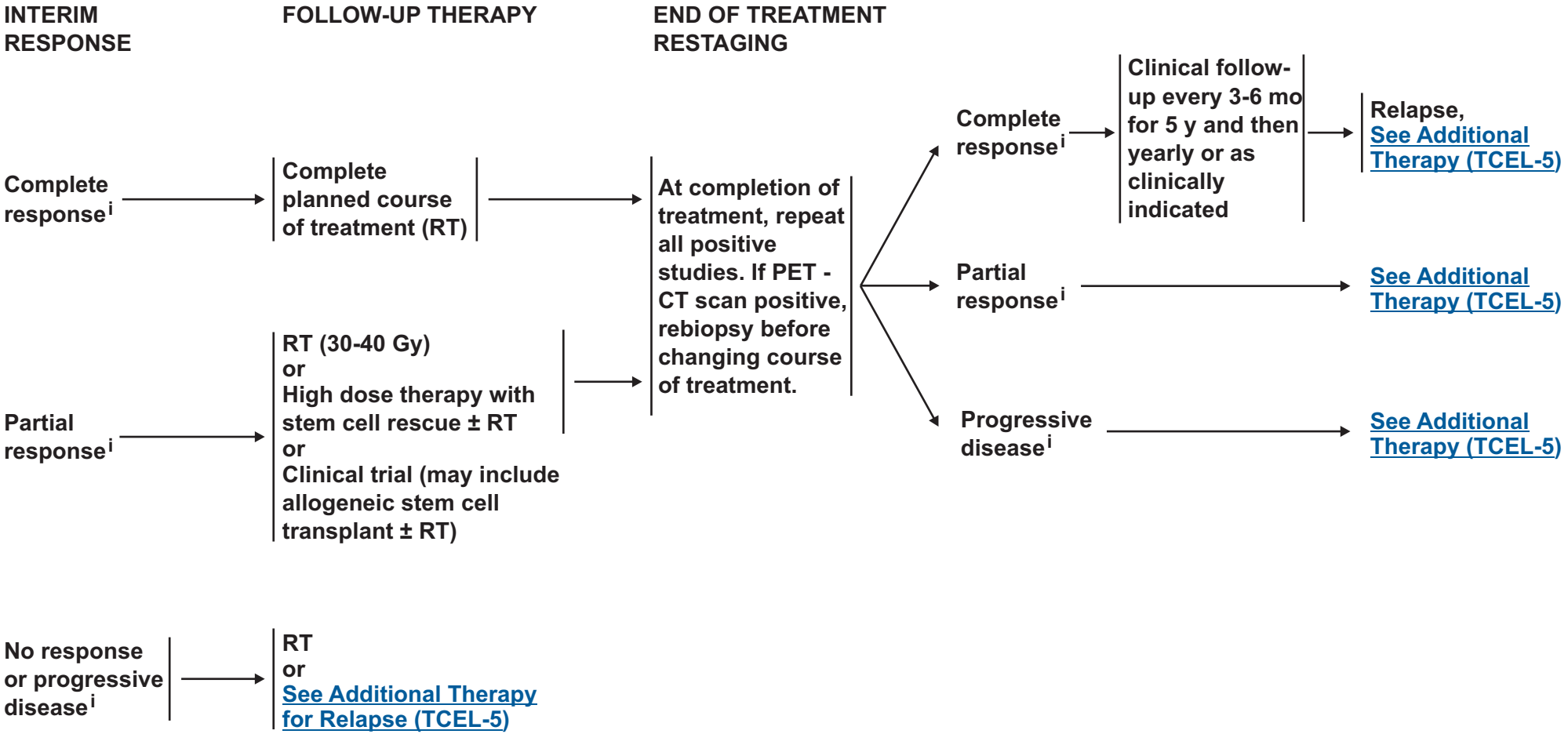
STAGE I/II, LOW/LOW- INTERMEDIATE



[i] See Response Criteria for Lymphoma (NHODG-C).

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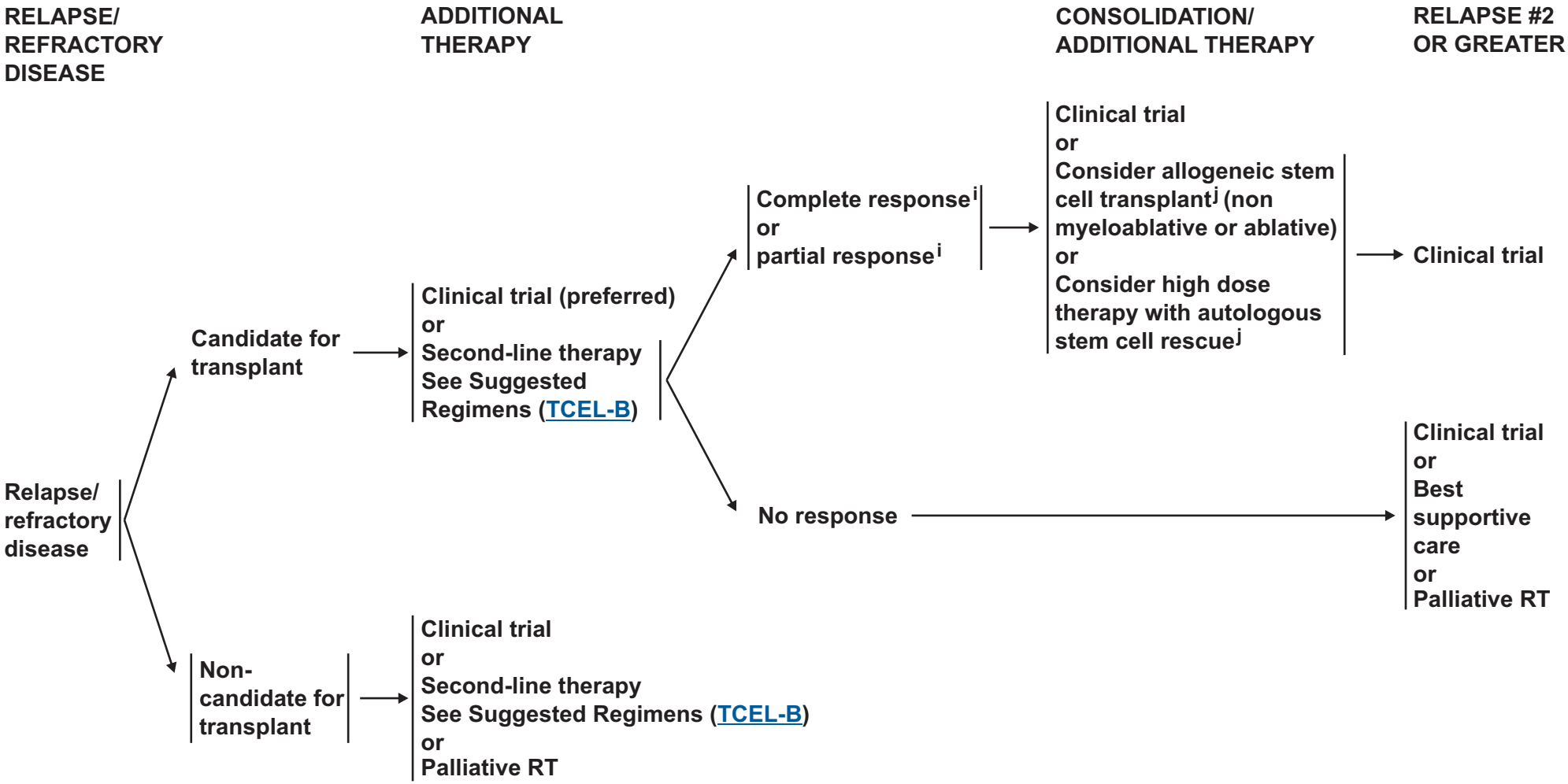

[i] See Response Criteria for Lymphoma (NHODG-C).

[j] Localized areas can be irradiated before or after high dose therapy.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
• Age > 60 years
• Serum LDH > normal
• Performance status 2-4
• Stage III or IV
• Extranodal involvement > 1 site

INTERNATIONAL INDEX, ALL PATIENTS:	
• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤ 60 YEARS:
• Stage III or IV
• Serum LDH > normal
• Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤ 60 YEARS:	
• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

Prognostic Index for PTCL-U (PIT)[b]

RISK FACTORS:
• Age > 60 years
• Serum LDH > normal
• Performance status 2-4
• Bone marrow involvement

PROGNOSTIC RISK:	
• Group 1	0
• Group 2	1
• Group 3	2
• Group 4	3 or 4

[a] The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med1993;329:987-994.
[b] Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-2479.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

First-line therapy:[b]
- Clinical trial (preferred)
- ALCL, ALK+ histology
  - CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone)
  - CHOEP-21 (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone)
- Other histologies (ALCL, ALK -; PTCL, NOS; AITL; EATL), regimens that can be used include:
  - CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone)
  - CHOP-14
  - CHOP-21
  - CHOP followed by ICE (ifosfamide, carboplatin, etoposide)
  - CHOP followed by IVE (ifosfamide, etoposide and epirubicin) alternating with intermediate dose methotrexate [New Castle Regimen]
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine

First-line Consolidation:
- All patients, except low risk (aaIPI), consider consolidation with high dose therapy and stem cell rescue. (ALCL, ALK positive is a subtype with good prognosis and does not need consolidative transplant if in remission.)

Second-line therapy (candidate for transplant):
- Clinical trial preferred
- Brentuximab vedotin for nodal ALCL only (excluding cutaneous ALCL)
- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOx (gemcitabine, oxaliplatin)
- ICE (ifosfamide, carboplatin, etoposide)
- MINE (mesna, ifosfamide, mitoxantrone, etoposide)
- Pralatrexate (category 2B)[c]
- Romidepsin

Second-line therapy (non-candidate for transplant):
- Clinical trial preferred
- Alemtuzumab[d]
- Bortezomib[d]
- Brentuximab vedotin for nodal ALCL only (excluding cutaneous ALCL)
- Cyclosporine for AITL only[e]
- Denileukin diftitox
- Gemcitabine
- Pralatrexate[c]
- Radiation therapy
- Romidepsin

[a] See references for regimens TCEL-B 2 of 2.
[b] Standard induction for PTCL remains undefined with the exception of ALCL, ALK + for which CHOP-21 remains the standard. Clinical trial is preferred for all other subtypes.
[c] In AITL, pralatrexate has limited activity.
[d] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[e] With close follow-up of renal function.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

First-line therapy

CHOP

Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004;15:1467-1475.

CHOP or CHOP-14 with or without etoposide

Pfreundschuh M, Trümper L, Kloess M, Schmits R, et al. German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004;104:626-33.

Pfreundschuh M, Trümper L, Kloess M, Schmits R, et al. German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634-41.

Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010;116:3418-3425.

CHOP followed by ICE

Horwitz S, Moskowitz C, Kewalramani T, et al. Second-line therapy with ICE followed by high dose therapy and autologous stem cell transplantation for relapsed/refractory peripheral T-cell lymphomas: Minimal benefit when analyzed by intent to treat [abstract]. Blood 2005;106:Abstract 2679.

CHOP followed by IVE

Sieniawski M, Lennard J, Millar C, et al. Aggressive primary chemotherapy plus autologous stem cell transplantation improves outcome for peripheral T cell lymphomas compared with CHOP-like regimens [abstract]. Blood 2009;114:Abstract1660.

HyperCVAD alternating with high-dose methotrexate and cytarabine

Escalon MP, Liu NS, Yang Y, et al. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer 2005;103:2091-2098.

Pozadzides JV, Perini G, Hess M, et al. Prognosis and treatment of patients with peripheral T-cell lymphoma: The M. D. Anderson Cancer Center experience [abstract]. J Clin Oncol 2010;28: Abstract 8051.

Second-line therapy

Alemtuzumab

Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004;103:2920-2924.

Brentuximab

Shustov AR, Advani R, Brice P, et al. Complete remissions with brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma [abstract]. Blood 2010;116:Abstract 961.

Cyclosporine for AILT

Advani R, Horwitz S, Zelenetz A, Horning SJ. Angioimmunoblastic T cell lymphoma: treatment experience with cyclosporine. Leuk Lymphoma 2007;48:521-525.

Denileukin diftitox

Talpur R, Apisarnthanarax N, Ward S, Duvic M. Treatment of refractory peripheral T-cell lymphoma with denileukin diftitox (ONTAK). Leuk Lymphoma 2002;43:121-126.

Dang NH, Pro B, Hagemeister FB, et al. Phase II trial of denileukin diftitox for relapsed/refractory T-cell non-Hodgkin lymphoma. Br J Haematol 2007;136:439-447.

DHAP (dexamethasone, cisplatin, cytarabine)

Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-122.

Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006;24:593-600.

ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)

Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP - an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994;12:1169-1176.

Gemcitabine

Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine Treatment in Pretreated Cutaneous T-Cell Lymphoma: Experience in 44 Patients. J Clin Oncol 2000;18:2603-2606.

Zinzani PL, Magagnoli M, Bendandi M, et al. Therapy with gemcitabine in pretreated peripheral T-cell lymphoma patients. Ann Oncol 1998;9:1351-1353.

GDP (gemcitabine, dexamethasone, cisplatin)

Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842.

GemOX (gemcitabine, oxaliplatin)

Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: A phase II study. Eur J Haematol 2008;80:127-132.

ICE (ifosfamide, carboplatin, etoposide)

Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14[suppl 1]:i5-10.

Pralatrexate

O'Connor O, Pro B, Pinter-Brown L, et al. PROPEL: Results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) [abstract]. J Clin Oncol 2009;27:Abstract 8561.

Romdepsin

Coiffier B, Pro B, Prince HM, et al. Final results from a pivotal, multicenter, international, open-label, phase 2 study of romidepsin in progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic therapy [abstract]. Blood 2010;116:Abstract114.

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Mycosis Fungoides/Sezary Syndrome

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DIAGNOSIS

ESSENTIAL:

- Biopsy of suspicious skin sites
- Dermatopathology review of slides

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- IHC of skin biopsy[a,b,c] (CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD26, CD56, TIA1, granzyme B, βF1)
- Molecular analysis for T-cell receptor (TCR) gene rearrangements (assessment of clonality) of skin biopsy;[a] PCR methods[d]
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including Sezary cell prep, flow cytometry and PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
- Assessment of ATLL serology or PCR in at-risk populations

WORKUP

ESSENTIAL:

- Complete physical examination
  - Examination of entire skin: assessment of %BSA (palm plus digits ≈ 1%BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
  - Palpation of peripheral lymph node regions
  - Palpation for organomegaly/masses
- Laboratory studies:[e]
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1); CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype including loss of CD7 or CD26
  - TCR gene rearrangement of peripheral blood lymphocytes if Sezary Syndrome suspected
  - Comprehensive metabolic panel
  - LDH
- Imaging studies
  - Neck/chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT (≥ T2, large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies)
- Pregnancy testing in women of child-bearing age[f]

USEFUL IN SELECTED CASES:

- Bone marrow biopsy (not required for staging but used to document visceral disease in those suspected to have marrow involvement including B2 blood involvement and in patients with unexplained hematologic abnormality)
- Biopsy of suspicious lymph nodes or identical clones (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites
- Rebiopsy if suspicious of large cell transformation

STAGE (MFSS-2)

Stage IA	See Primary Treatment (MFSS-4)
Stage IB-IIA	See Primary Treatment (MFSS-5)
Stage IIB	See Primary Treatment (MFSS-6)
Stage III	See Primary Treatment (MFSS-7)
Stage IV	See Primary Treatment (MFSS-8)

[a] Clinically or histologically non-diagnostic cases. Pimpinelli N, Olsen EA, Santucci M, et al., for the International Society for Cutaneous Lymphoma. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063.

[b] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[c] Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative.

[d] TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of Mycosis Fungoides/Sezary Syndrome. Demonstration of identical clones in skin, blood and/or lymph node may be helpful in selected cases.

[e] Sezary syndrome (B2) is as defined on MFSS-2.

[f] Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.

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TNMB[g]		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome[h]
Skin	T1	Limited patches,[i] papules and/or plaques[j] covering < 10 % of the skin surface
	T2	Patches,[i] papules and/or plaques[j] covering ≥ 10 % of the skin surface
	T3	One or more tumors[k] (≥ 1 cm in diameter)
	T4	Confluence of erythema ≥ 80 % body surface area
Node	N0	No clinically abnormal peripheral lymph nodes; biopsy not required[l]
	N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation[m] and organ involved should be specified)
Blood	B0	Absence of significant blood involvement: ≤ 5 % of peripheral blood lymphocytes are atypical (Sezary) cells[n]
	B1	Low blood tumor burden: > 5 % of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2
	B2	High blood tumor burden: ≥ 1000/mcL Sezary cells[m]

[g] Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.

[h] Sezary syndrome (B2) is defined as a clonal rearrangement of the TCR in the blood (clones should be relevant to clone in the skin) and either 1000/mcL or increased CD4 or CD3 cells with CD4/CD8 of 10 or more or increase in CD4 cells with an abnormal phenotype (40% CD4/CD7 or 30% CD4/CD26).

[i] Patch = Any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting and/or poikiloderma should be noted.

[j] Plaque = Any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting and/or poikiloderma should be noted. Histological features such as folliculotropism or large cell transformation (≥ 25 % large cells), CD30+ or CD30- and clinical features such as ulceration are important to document.

[k] Tumor = at least one > 1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histological evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

[l] Abnormal peripheral lymph node(s) = any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or ≥ 1.5 cm in diameter. Node groups examined on physical examination = cervical, supraclavicular, epitrochlear, axillary and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.

[m] Spleen and liver may be diagnosed by imaging criteria.

[n] Sezary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sezary cells are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead. (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio ≥ 10, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26.

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Clinical Staging/Classification of MF and SS[g]

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1-2	1,2	0	0,1
IIB	3	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

[g] Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the Staging and Classification of Mycosis Fungoides and Sezary Syndrome: A Proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-1722.

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STAGE (MFSS-2)

PRIMARY TREATMENT[p]

Stage IA →

Skin-directed therapies (may be alone or in combination with other skin-directed therapies):
See Suggested Treatment Regimens "Skin-directed therapies (skin-limited/local)" (MFSS-A)

If B1 blood involvement, consider primary treatment for Stage III, B1 MFSS-7 (category 2B)

CR/PR[q] **or inadequate response** → **Relapse with or persistent T1 skin disease**

Refractory disease[r] **or progression to > stage IA on skin-directed therapies** →
Systemic therapy ± skin-directed therapy (see Stage IB on page MFSS-5)
or
Total skin electron beam therapy (TSEBT)
or
Clinical trial

Histologic evidence of folliculotropic or large cell transformed MF[o] → **See Primary Treatment for Stage IIB on page MFSS-6**

[o] Folliculotropic, large cell transformed MF, or B1 involvement has been associated with worse outcome, thus, may be managed as "tumor (IIB)" disease (MFSS-6) or stage III with B1 involvement (MFSS-7), respectively.

[p] It is preferred that treatment occur at centers with expertise in the management of the disease.

[q] Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[r] Refractory or intolerant to multiple previous therapies.

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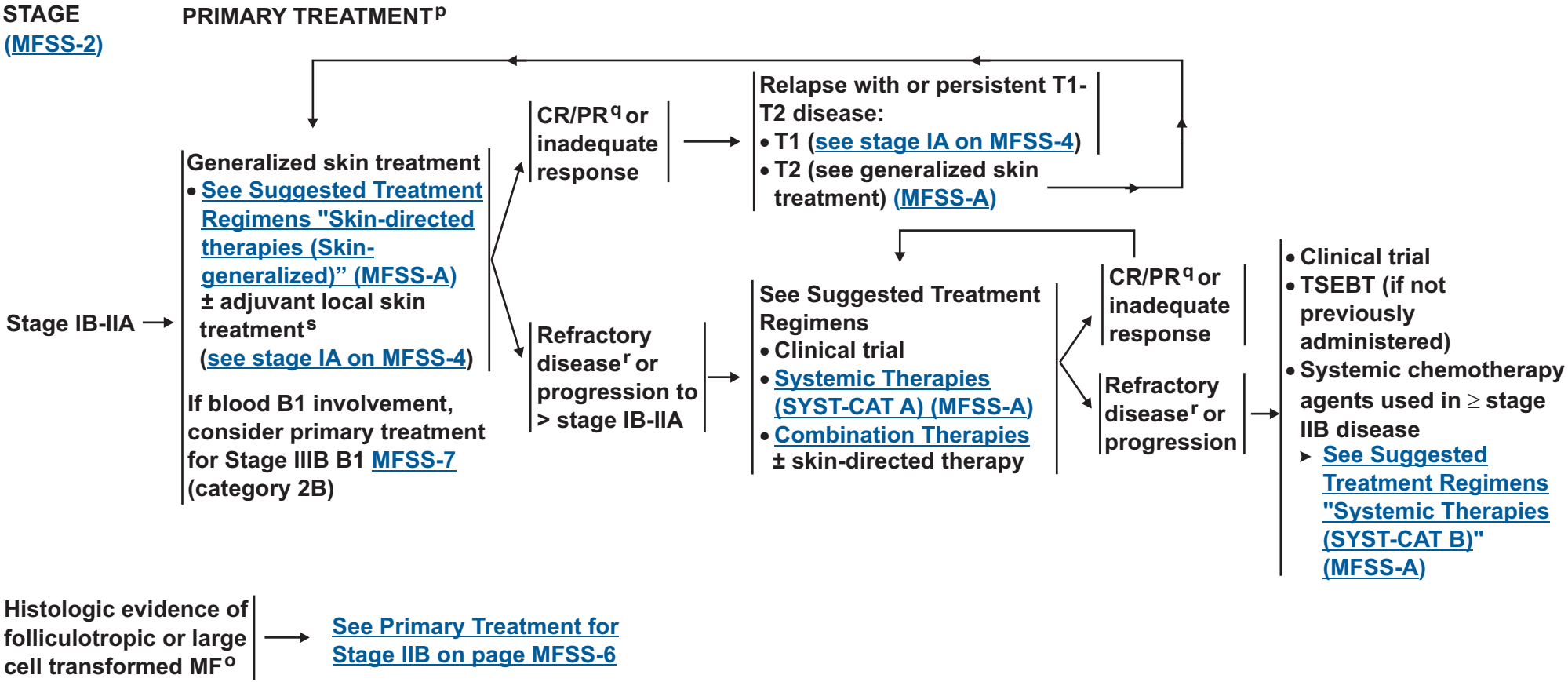

[o]Folliculotropic, large cell transformed MF, or B1 involvement has been associated with worse outcome, thus, may be managed as "tumor (IIB)" disease (MFSS-6) or stage III with B1 involvement (MFSS-7), respectively.

[p]It is preferred that treatment occur at centers with expertise in the management of the disease.

[q]Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[r]Refractory or intolerant to multiple previous therapies.

[s]For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.

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Discussion

STAGE
(MFSS-2)

PRIMARY TREATMENT[p]

Stage IIB[t] and/or histologic evidence of folliculotropic or large cell transformation (LCT)

Limited extent tumor disease ± patch/plaque disease

- **Local RT for limited extent tumor, transformed, and/or folliculotrophic disease[w]**
- **Systemic Therapies (SYST-CAT A) (MFSS-A) ± skin-directed therapies[x] ± RT**

CR/PR[q] or inadequate response → **Relapse with or persistent T1-T3 limited:**
- **T1-2 (see stage IA on MFSS-4 or stage IB-IIA on MFSS-5)**
- **T3 limited extent**

Refractory disease[r] or progression

Generalized extent tumor, transformed, and/or folliculotropic disease[u,v]

- **TSEBT[y]**
- **See Suggested Treatment Regimens[u,v]**
  - ▸ **Systemic Therapies (SYST-CAT A) (MFSS-A)**
  - ▸ **Systemic Therapies (SYST-CAT B) (MFSS-A)**
  - ▸ **Systemic Therapies (SYST-CAT C) (MFSS-A)**
  - ▸ **Combination Therapies**

± skin-directed therapy

CR/PR[q] or inadequate response → **Relapse with or persistent T1-T3:**
- **T1-2 (see stage IA on MFSS-4 or stage IB-IIA on MFSS-5)**
- **T3**

Refractory disease[r] or progression →
- **Multi-agent chemotherapy[z]**
- **Consider allogeneic transplant[aa]**
- **Clinical trial**

[p] It is preferred that treatment occur at centers with expertise in the management of the disease.

[q] Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[r] Refractory or intolerant to multiple previous therapies.

[t] Rebiopsy if suspect large cell transformation.

[u] Histologic evidence of LCT often, but not always corresponds to a more aggressive growth rate. If there is no evidence of more aggressive growth, choosing systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[v] Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should first be considered for therapies under SYST-CAT A before resorting to treatments listed in SYST CAT B or SYST CAT C.

[w] For non-radiated sites, see Stage I-IIA. After patient is rendered disease free by RT, may consider adjuvant systemic biologic therapy (SYST-CAT A) after RT to improve response duration.

[x] Skin-directed therapies are for patch or plaque lesions and not for tumor lesions.

[y] May consider adjuvant systemic biologic therapy (SYST-CAT A) after TSEBT to improve response duration.

[z] Most patients are treated with multiple SYST-CAT A/B or Combination therapies before receiving multiagent chemotherapy.

[aa] The role of allogeneic HSCT is controversial. See discussion for further details.

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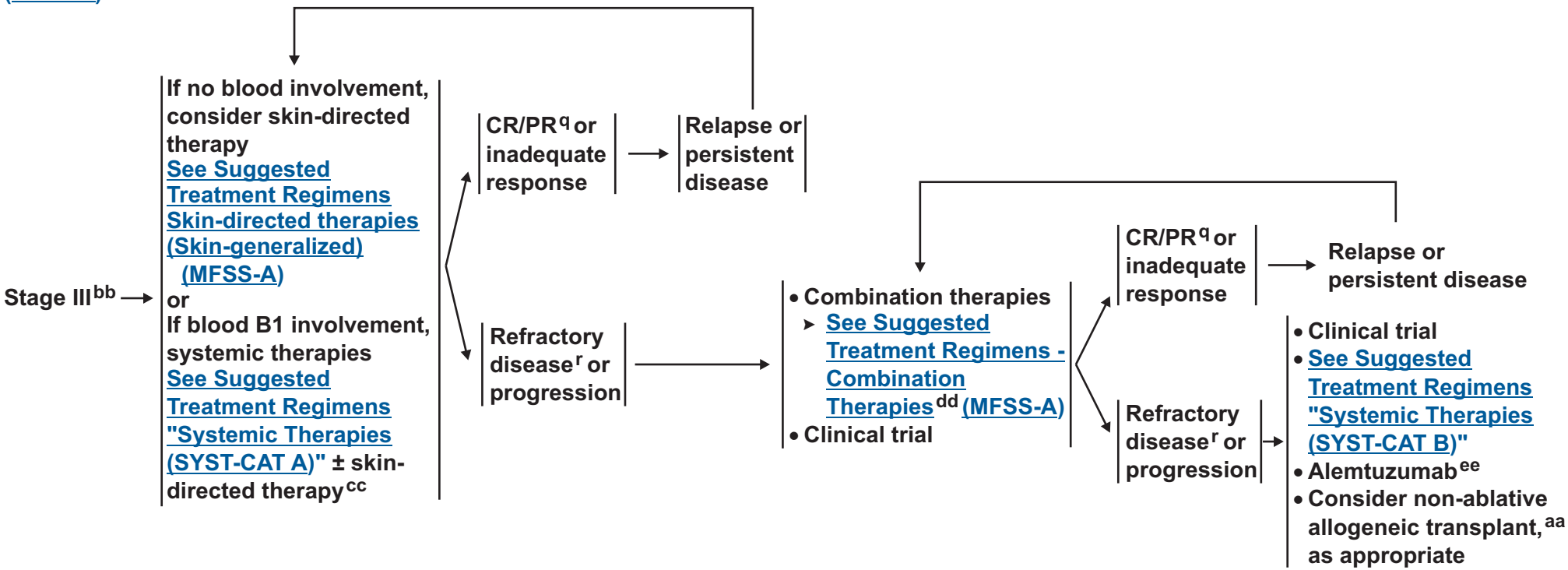
STAGE (MFSS-2)

PRIMARY TREATMENT[p]



[p] It is preferred that treatment occur at centers with expertise in the management of the disease.

[q] Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[r] Refractory or intolerant to multiple previous therapies.

[aa] The role of allogeneic HSCT is controversial. See discussion for further details.

[bb] Generalized skin-directed therapies (other than topical steroids) may not be well-tolerated in stage III and should be used with caution. Phototherapy (PUVA or UVB) or TSEBT can be used successfully.

[cc] Mid-potency topical steroids should be included (± occlusive modality) with any of the primary treatment modalities to reduce skin symptoms. Erythrodermic patients are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered.

[dd] Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.

[ee] Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

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STAGE (MFSS-2)

PRIMARY TREATMENT[p]

Stage IV

Sezary syndrome →
- See Suggested Treatment Regimens
  - Systemic Therapies (SYST-CAT A) (MFSS-A)
  - Combination Therapies

→ CR/PR[q] or inadequate response → **Relapse or persistent disease**
- Consider allogeneic transplant,[aa] as appropriate

→ Refractory disease[r] or progression →
- See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT B) (MFSS-A)
- Alemtuzumab[ee]
- Clinical trial

Non Sezary or Visceral disease (solid organ) →

See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT B) or (SYST-CAT C)[ff] or multi-agent chemotherapy ± RT for local control[gg]

→ CR/PR[q] or inadequate response → **Relapse or persistent disease**
- Consider allogeneic transplant,[aa] as appropriate

→ Refractory disease[r] or progression → **Clinical trial**

[p] It is preferred that treatment occur at centers with expertise in the management of the disease.

[q] Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[r] Refractory or intolerant to multiple previous therapies.

[aa] The role of allogeneic HSCT is controversial. See discussion for further details.

[ee] Lower doses of alemtuzumab administered subcutaneously has shown lower incidence of infectious complications.

[ff] Patients with stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. If there is no evidence of more aggressive growth, systemic therapies from SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[gg] Consider adjuvant systemic biologic therapy (SYST-CAT A) after chemotherapy to improve response duration.

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SUGGESTED TREATMENT REGIMENS[a]

SKIN-DIRECTED THERAPIES

For limited/localized skin involvement (Skin-Limited/Local)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Local radiation (12-36 Gy)
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, nbUVB for patch/thin plaques; PUVA for thicker plaques)[c]
- Topical imiquimod

For generalized skin involvement (Skin-Generalized)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)[c]
- Total skin electron beam therapy (30-36 Gy)[d] (reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies)

SYSTEMIC THERAPIES

Category A (SYST-CAT A)
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)[e]
- Extracorporeal photopheresis[f]
- Denileukin diftitox
- Methotrexate (≤ 100 mg q week)

Category B (SYST-CAT B)
- First-line therapies
  - Liposomal doxorubicin
  - Gemcitabine
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Bortezomib
  - Low dose pralatrexate

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C)[g]
- Liposomal doxorubicin
- Gemcitabine
- Denileukin diftitox
- Romidepsin
- Low or standard dose pralatrexate
- See regimens listed on TCEL-B[h]

COMBINATION THERAPIES

Skin-directed + Systemic
- Phototherapy + retinoid[e]
- Phototherapy + IFN
- Phototherapy + photopheresis[f]
- Total skin electron beam + photopheresis[f]

Systemic + Systemic
- Retinoid + IFN
- Bexarotene + denileukin diftitox
- Photopheresis[f] + retinoid
- Photopheresis[f] + IFN
- Photopheresis[f] + retinoid + IFN

[a] See references for regimens MFSS-A 2 of 4, MFSS-A 3 of 4, and MFSS-A 4 of 4

[b] Long-term use of topical steroid may be associated with skin atrophy and/or striae formation. This risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption.

[c] Cumulative dose of UV is associated with increased risk of UV-associated skin neoplasms; thus, phototherapy may not be appropriate in patients with history of extensive squamoproliferative skin neoplasms or basal cell carcinomas or who have had melanoma.

[d] It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response.

[e] Safety of combining TSEBT with systemic retinoids or HDAC-inhibitors, such as vorinostat or romidepsin or combining phototherapy with vorinostat or romidepsin is unknown.

[f] Photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).

[g] Patients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.

[h] Combination regimens are generally reserved for patients with relapsed/refratory or extracutaneous disease.

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SUGGESTED TREATMENT REGIMENS
References

Skin-directed therapies

Topical corticosteroids

Zackheim HS, Kashani Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol 1998;134(8):949-954.

Zackheim HS. Treatment of patch stage mycosis fungoides with topical corticosteroids. Dermatol Ther 2003;16:283- 287.

Carmustine

Zackheim HS. Topical carmustine (carmustine) in the treatment of mycosis fungoides. Dermatol Ther 2003;16:299-302.

Nitrogen mustard (mechlorethamine hydrochloride)

Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: Update of the Stanford experience. Arch Dermatol 2003;139:165-173.

Local radiation

Wilson LD, Kacinski BM, Jones GW. Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (Mycosis Fungoides). Int J Radiat Oncol Biol Phys 1998;40:109-115.

Topical bexarotene

Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial of bexarotene gel for skin directed treatment of patients with cutaneous T cell lymphoma. Arch Dermatol 2002;138:325-332.

Heald P, Mehlmauer M, Martin AG, et al. Topical bexarotene therapy for patients with refractory or persistent early stage cutaneous T cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol 2003;49:801-815.

Tazarotene Gel

Apisarnthanarax N, Talpur R, Ward S, Ni X, Kim HW, Duvic M. Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am Acad Dermatol 2004;50:600-607.

Topical imiquimod

Deeths MJ, Chapman JT, Dellavalle RP, Zeng C, Aeling JL. Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. J Am Acad Dermatol 2005;52:275-280.

Phototherapy (UVB and PUVA)

Gathers RC, Scherschun L, Malick F, Fivenson DP, Lim HW. Narrowband UVB phototherapy for early stage mycosis fungoides. J Am Acad Dermatol 2002;47:191-197.

Querfeld C, Rosen ST, Kuzel TM, et al. Long term follow up of patients with early stage cutaneous T cell lymphoma who achieved complete remission with psoralen plus UV A monotherapy. Arch Dermatol 2005;141:305-311.

Total skin electron beam therapy (TSEBT)

Chinn DM, Chow S, Kim YH, Hoppe RT. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. Int J Radiat Oncol Biol Phys 1999;43:951-958.

Ysebaert L, Truc G, Dalac S et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides. Int J Radiat Oncol Biol Phys 2004;58:1128-1134.

Systemic therapies

Alemtuzumab for Sezary Syndrome ± lymph node disease

Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003;101:4267-4272.

Bernengo MG, Quaglino P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007;92:784-794.

Gautschi O, Blumenthal N, Streit M, et al. Successful treatment of chemotherapy-refractory Sezary syndrome with alemtuzumab (Campath-1H). Eur J Haematol 2004;72:61-63.

Retinoids

Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. Dermatol Ther 2006;19:264-271.

Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001;137:581-593.

Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001;19:2456-2471.

Interferon

Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 2003;16:311-321.

Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:208-212.

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SUGGESTED TREATMENT REGIMENS
References

Systemic therapies continued

Vorinostat

Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007;109:31-39.

Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109-3115.

Duvic M, Olsen EA, Breneman D, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9:412-416.

Romidepsin

Piekarz RL, Frye R, Turner M, et al. Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma. J Clin Oncol 2009;27:5410-5417.

Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010; 28:4485-4491.

Extracorporeal photopheresis (ECP)

Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med 1987;316:297-303.

Zic JA, Stricklin GP, Greer JP, et al. Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. J Am Acad Dermatol 1996;35:935-945.

Denileukin diftitox

Olsen E, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J Clin Oncol 2001;19:376-388.

Prince HM, Duvic M, Martin A, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. J Clin Oncol 2010;28:1870-1877.

Talpur R, Jones DM, Alencar AJ, et al. CD25 expression is correlated with histological grade and response to denileukin diftitox in cutaneous T-cell lymphoma. J Invest Dermatol 2006;126:575-583.

Methotrexate

Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. J Am Acad Dermatol 1996;34:626-631.

Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. J Am Acad Dermatol 2003;49:873-878.

Liposomal doxorubicin

Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. Cancer 2003;98:993-1001.

Quereux G, Marques S, Nguyen J-M, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. Arch Dermatol 2008;144:727-733.

Gemcitabine

Duvic M, Talpur R, Wen S, Kurzrock R, David CL, Apisarnthanarax N. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2006;7(1):51-58.

Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. Cancer 2005;104:2437-2441.

Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. J Clin Oncol 2000;18:2603-2606.

Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 2010;21:860-863.

Awar O, Duvic M. Treatment of transformed mycosis fungoides with intermittent low-dose gemcitabine. Oncology 2007;73:130-135.

Pentostatin

Cummings FJ, Kim K, Neiman RS, et al. Phase II trial of pentostatin in refractory lymphomas and cutaneous T-cell disease. J Clin Oncol 1991;9:565-571.

Temozolomide

Tani M, Fina M, Alinari L, Stefoni V, Baccarani M, Zinzani PL. Phase II trial of temozolomide in patients with pretreated cutaneous T-cell lymphoma. Haematologica 2005;90(9):1283-1284.

Querfeld C, Rosen ST, Guitart J, et al. Multicenter phase II trial of temozolomide in mycosis fungoides/sezary syndrome: correlation with O^6-methylguanine-DNA methyltransferase and mismatch repair proteins. Clin Cancer Res 2011;17:5748-5754.

Bortezomib

Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293-4297.

Low dose Pralatrexate

Horwitz SM, Duvic M, Kim Y, et al. Pralatrexate is active in cutaneous T-cell lymphoma (CTCL): Results of a multicenter, dose-finding trial [abstract]. Blood 2009;114:Abstract 910.

Pralatrexate

O'Connor O, Pro B, Pinter-Brown L, et al. PROPEL: Results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) [abstract]. J Clin Oncol 2009;27:Abstract 8561.

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SUGGESTED TREATMENT REGIMENS
References

Combination therapies

Skin-directed + Systemic

Rupoli S, Goteri G, Pulini S, et al. Long term experience with low dose interferon alpha and PUVA in the management of early mycosis fungoides. Eur J Haematol 2005;75:136-145.

Kuzel TM, Roenigk HH Jr, Samuelson E, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sézary syndrome. J Clin Oncol 1995;13:257-263.

McGinnis KS, Shapiro M, Vittorio CC, et al. Psoralen plus long wave UV A (PUVA) and bexarotene therapy: An effective and synergistic combined adjunct to therapy for patients with advanced cutaneous T cell lymphoma. Arch Dermatol 2003;139:771-775.

Wilson LD, Jones GW, Kim D, et al. Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides. J Am Acad Dermatol 2000;43:54-60.

Stadler R, Otte H-G, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon alpha -2a plus acitretin versus interferon alpha -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 1998;92:3578-3581.

Systemic + Systemic

Foss F, Demierre MF, DiVenuti G. A phase 1 trial of bexarotene and denileukin diftitox in patients with relapsed or refractory cutaneous T cell lymphoma. Blood 2005;106:454-457.

Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa 2b (Intron A) for patients with cutaneous T cell lymphoma. Cancer 2007;109:1799-1803.

Talpur R, Ward S, Apisarnthanarax N, Breuer Mcham J, Duvic M. Optimizing bexarotene therapy for cutaneous T cell lymphoma. J Am Acad Dermatol 2002;47:672-684.

Suchin KR, Cucchiara AJ, Gottleib SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Arch Dermatol. 2002;138:1054-1060.

Richardson SK, Lin JH, Vittorio CC, et al. High clinical response rate with multimodality immunomodulatory therapy for Sezary syndrome. Clin Lymphoma Myeloma 2006;7:226-232.

Allogeneic stem cell transplant

Duarte RF, Canals C, Onida F, et al. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: A retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010;28:4492-4499.

Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transplant 2008;41:597-604.

Duvic M, Donato M, Dabaja B, et al. Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. J Clin Oncol 2010;28:2365-2372.

Molina A, Zain J, Arber DA, et al. Durable clinical, cytogenetic, and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sezary syndrome and mycosis fungoides. J Clin Oncol 2005;23:6163-6171.

Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transplant 2009;15:982-990.

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Adult T-cell Leukemia/Lymphoma

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DIAGNOSIS

ESSENTIAL:[a]
- HTLV-1 serology: ELISA and confirmatory Western Blot if ELISA is positive
- Peripheral blood smear analysis for atypical cells[b]
- Flow cytometry on peripheral blood[c]

USEFUL IN CERTAIN CIRCUMSTANCES:
- Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy[d] is required if:
  - Diagnosis is not established on peripheral blood, or
  - Ruling out an underlying infection (tuberculosis, histoplasmosis, toxoplasmosis, etc.)
  - If biopsy performed, the recommended panel for paraffin section immunohistochemistry:[e,f] CD3, CD4, CD7, CD8, and CD25

→

WORKUP

ESSENTIAL:
- Complete history and physical examination-including complete skin exam
- CBC and blood smear: lymphocytosis (ALC > 4000/μL in adults) in acute and chronic subtypes
- Electrolytes, BUN, creatinine, serum calcium, serum LDH
- Chest/abdominal/pelvic/neck CT scan
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- Upper gastrointestinal endoscopy
- Skeletal survey in symptomatic patients
- Stool examination for parasites (strongyloides is most likely)
- PET-CT scan
- Central nervous system evaluation: CT scan, MRI and/or lumbar puncture in all patients with acute or lymphoma subtypes or in patients with neurologic manifestations

DIAGNOSTIC CATEGORY

see ATLL-A

See Primary Therapy Chronic/ Smoldering (ATLL-2)

See Primary Therapy Acute (ATLL-3)

See Primary Therapy Lymphoma (ATLL-3)

[a] The diagnosis of ATLL requires histopathology and immunophenotyping of tumor lesion, *or* morphology and immunophenotying of peripheral blood, *and/or* HTLV serology.

[b] Typical ATL cells ("flower cells") have distinctly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli and agranular and basophilic cytoplasm but multiple morphological variations can be encountered. Presence of ≥ 5% atypical cells by morphology in peripheral blood is required for diagnosis in the absence of other criteria.

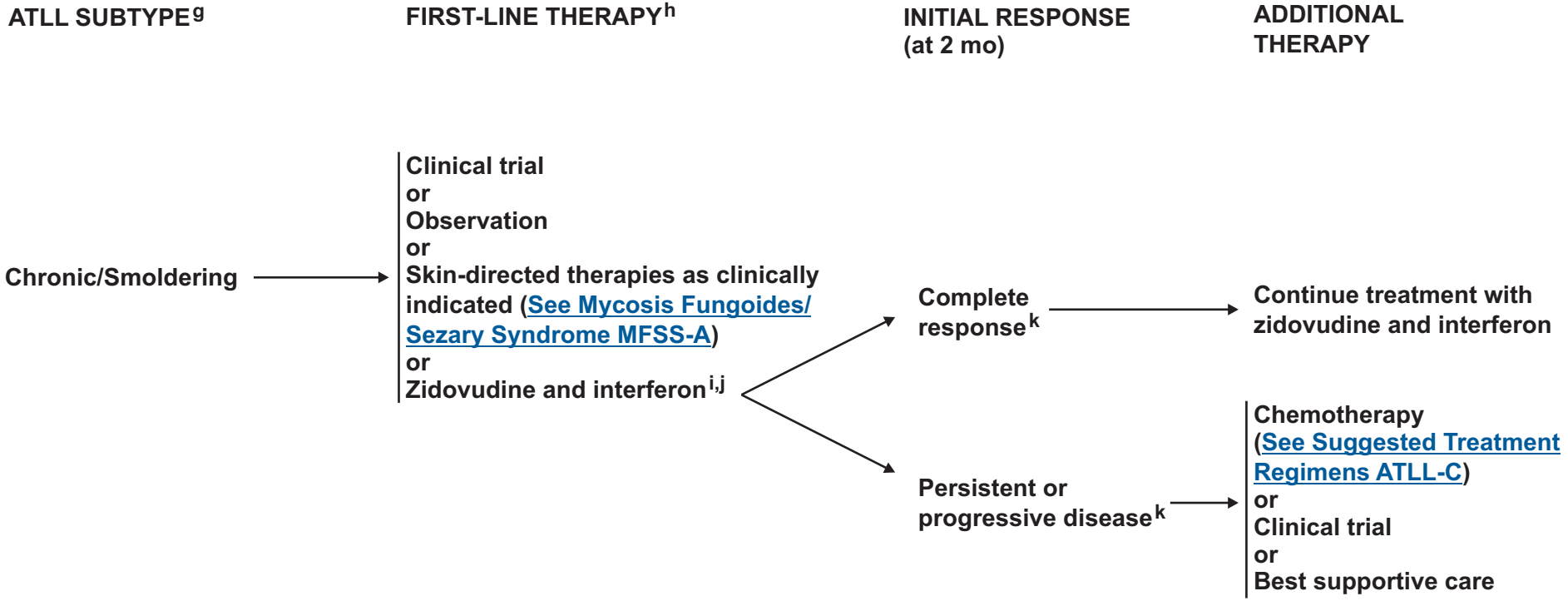
[c] Presence of ≥ 5% T-lymphocytes with an abnormal immunophenotype in peripheral blood is required for diagnosis.

[d] Bone marrow involvement is an independent poor prognostic factor.

[e] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[f] Usually CD4+ T-cells with expression of CD2, CD5, CD25, CD45RO, CD29, T-cell receptor αβ and HLA-DR. Most cases are CD7 - and CD26 - with low CD3 expression. Rare cases are CD8 + or CD4/CD8 double positive or double negative.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[g] See Diagnostic Criteria for Clinical Subtype of ATLL (ATLL-A).

[h] Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis prophylaxis is recommended.

[i] Outside of a clinical trial, if a patient is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life threatening manifestations, treatment can be discontinued before the two months period.

[j] See references for zidovudine and interferon (ATLL-D).

[k] See Response Criteria for ATLL (ATLL-B).

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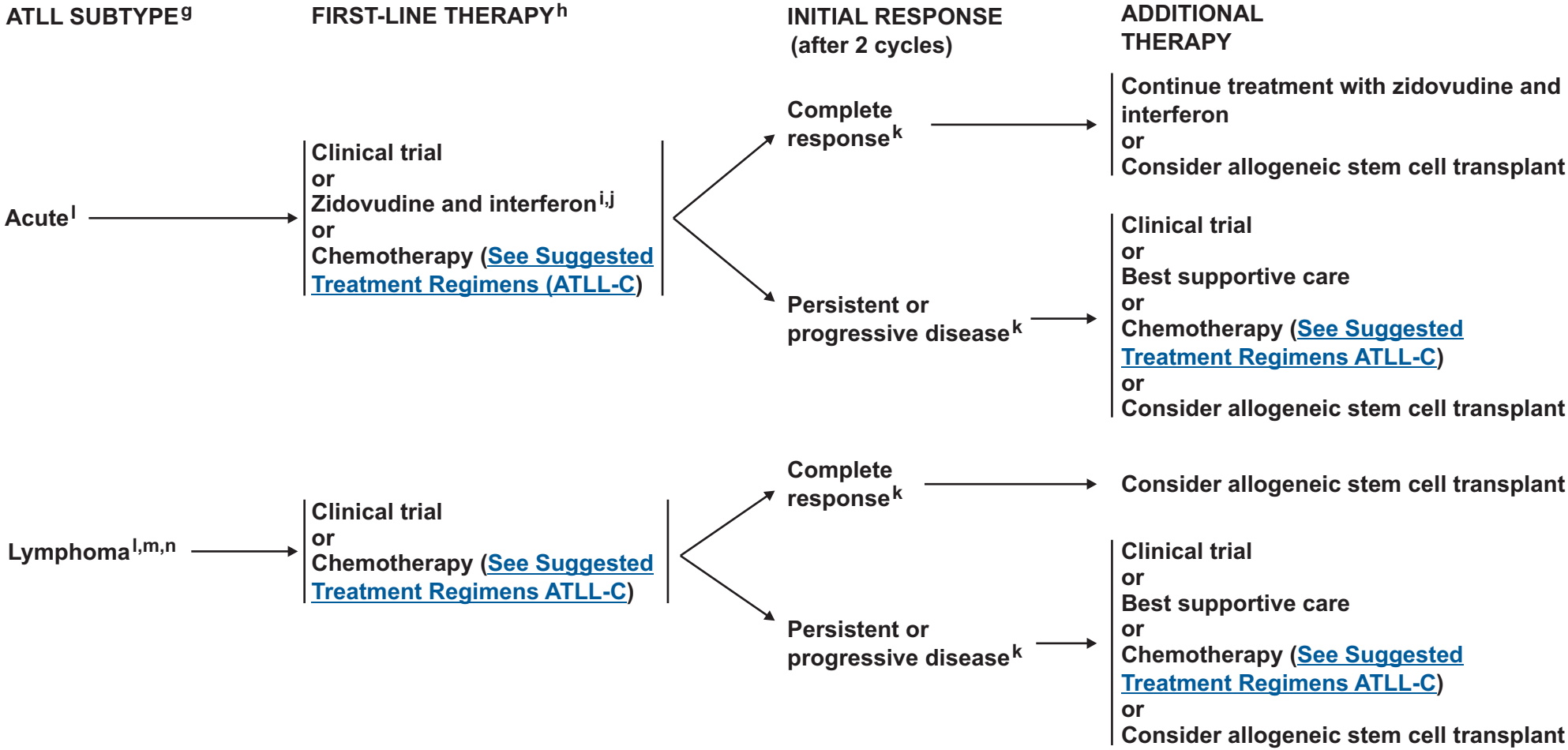

[g] See Diagnostic Criteria for Clinical Subtype of ATLL (ATLL-A).

[h] Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis prophylaxis is recommended.

[i] Outside of a clinical trial, if a patient is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life threatening manifestations, treatment can be discontinued before the two months period.

[j] See References for zidovudine and interferon (ATLL-D).

[k] See Response Criteria for ATLL (ATLL-B).

[l] Efficacy of long term treatment is limited. There are small series where transplant is beneficial. There is no defined treatment.

[m] Antiviral therapy is not effective.

[n] CNS prophylaxis: intrathecal chemotherapy is recommended (methotrexate and cytarabine and corticosteroids).

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DIAGNOSTIC CRITERIA AND CLASSIFICATION OF CLINICAL SUBTYPES OF ATLL[a]

	Healthy carrier	Smoldering ATL	Chronic ATL	Acute ATL	ATL Lymphoma
Anti-HTLV-1 serology	+	+	+	+	+
Clonal intergration of provirus	- (blood)	+ (blood)	+ (blood)	+ (blood)	+ (lymph nodes)
Lymphocyte count	Normal	Normal	Elevated	Elevated	Elevated
Abnormal cells (%)	< 5%	> 5%	> 5%	> 5%	< 1%
Hypercalcemia	-	-	-	+	+
LDH	Normal	≤ 1.5 N	≤ 2 N	> 2 N	> 2 N
Skin and lung involvement	-	+	+	+	+
Bone marrow or spleen involvement	-	-	+	+	+
Bone, GI or CNS involvement	-	-	-	+	+

[a] Modified from Shimoyama M and members of The Lymphoma Study Group. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RESPONSE CRITERIA FOR ATLL[a]

Response	Definition	Lymph Nodes	Extranodal Masses	Spleen, Liver	Skin	Peripheral Blood	Bone Marrow
Complete remission*	Disappearance of all disease	Normal	Normal	Normal	Normal	Normal†	Normal
Uncertified complete remission*	Stable residual mass in bulky lesion	≥ 75% decrease‡	≥ 75% decrease‡	Normal	Normal	Normal†	Normal
Partial remission*	Regression of disease	≥ 50% decrease‡	≥ 50% decrease‡	No increase	≥ 50% decrease	≥ 50% decrease	Irrelevant
Stable disease*	Failure to attain complete/partial remission and no progressive disease	No change in size	No change in size	No change in size	No change in size	No change	No change
Relapsed disease or progressive disease	New or increased lesions	New or ≥ 50% increase§	New or ≥ 50% increase§	New or ≥ 50% increase	≥ 50% increase	New or ≥ 50% increase#	Reappearance

*Required that each criterion to be present for a period of at least 4 weeks.

†Provided that < 5% of flower cells remain, complete remission is judged to have been attained if the absolute lymphocyte count, including flower cells, is < 4 x 10^9/L.

‡Calculated by the sum of the products of the greatest diameters of measurable disease.

§Defined by ≥ 50% increase from nadir in the sum of the products of measurable disease.

#Defined by ≥ 50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of > 4 x10^9/L.

[a]Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: A proposal from an international consensus meeting. J Clin Oncol 2009;27:453-459.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS

- **Chemotherapy**[a]
  - **CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)**
  - **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)**
  - **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine**

[a]There is not published data regarding the use of these regimens, however, they are used at NCCN member institutions for the treatment of ATLL.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

REFERENCES FOR ZIDOVUDINE AND INTERFERON

Zidovudine and interferon

Bazarbachi A, Hermine O. Treatment with a combination of zidovudine and alpha-interferon in naive and pretreated adult T-cell leukemia/lymphoma patients. J Acquir Immune Defic Syndr Hum Retrovirol 1996;13 Suppl 1:S186-190.

Bazarbachi A, Plumelle Y, Carlos Ramos J, et al. Meta-analysis on the use of zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. J Clin Oncol 2010;28:4177-4183.

Hermine O, Allard I, Levy V, Arnulf B, Gessain A, Bazarbachi A. A prospective phase II clinical trial with the use of zidovudine and interferon-alpha in the acute and lymphoma forms of adult T-cell leukemia/lymphoma. Hematol J 2002;3:276-282.

Hodson A, Crichton S, Montoto S, et al. Use of zidovudine and interferon alfa with chemotherapy improves survival in both acute and lymphoma subtypes of adult T-cell leukemia/lymphoma. J Clin Oncol 2011;29:4696-4701.

White JD, Wharfe G, Stewart DM, et al. The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell leukemia/lymphoma. Leuk Lymphoma 2001;40:287-294.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Guidelines Version 2.2012
Extranodal NK/T-cell Lymphoma, nasal type

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DIAGNOSIS[a]

ESSENTIAL:

- **Hematopathology review of all slides with a least one paraffiin block representative of the tumor. Rebiopsy if consult material is non-diagnostic.**
- **A FNA or core needle biopsy alone is not suitable for the initial diagnosis of lymphoma.[b]**
- **In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for antigen receptor rearrangements and FISH for major translocations) may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[c,d]**
  - **IHC panel: B cell: CD20; T lineage antigens: CD2, CD7, CD8, CD4, CD5, cCD3ε; NK lineage markers: CD56; Ki-67 (nuclear antigen marker)**
  - **EBER-ISH[e]**

Useful under certain circumstances

- **Molecular analysis for TCR gene rearrangements**

SUBTYPES

Subtypes included:

- **Extranodal NK/T-cell, nasal type**

Subtypes *not* included:

- **NK-cell leukemias**
- **Precursor NK-cell neoplasm**

WORKUP

ESSENTIAL:

- **Physical exam; attention to complete ENT evaluation nasopharynx involvement (including Waldeyer's ring), testicles and skin**
- **Performance status**
- **B symptoms**
- **CBC, differential platelets**
- **LDH**
- **Comprehensive metabolic panel**
- **Uric acid**
- **Bone marrow biopsy + aspirate[f]**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality or PET-CT scan with diagnostic quality CT**
- **Dedicated CT of the nasal cavity, hard palate, anterior fossa or MRI nasopharynx**
- **Calculation of NK/T-cell PI[g]**
- **MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenediones**
- **EBV viral load[h]**

USEFUL IN SELECTED CASES:

- **Pregnancy testing in women of child-bearing age**
- **Discussion of fertility and sperm banking**
- **HIV**

→ **See Induction Therapy (NKTL-2)**

[a] It is preferred that treatment occur at centers with expertise in the management of this disease.

[b] Necrosis is very common in diagnostic biopsies and may delay diagnosis significantly. Biopsy should include the edges of lesions, to increase the odds of having viable tissue. Useful to perform multiple nasopharyngeal biopsies even in areas not clearly involved.

[c] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[d] Typical NK/T-cell immunophenotype: CD20-, CD2+, cCD3ε+ (surface CD3-), CD7+, CD8+ CD45RO+, CD43+, CD56+, T-cell receptor (TCR)αβ-, TCR-, TCRγδ, TCR and Ig genes are usually germline (NK lineage) EBV- EBER+.

[e] Negative result should prompt pathology review for alternative diagnosis.

[f] BM aspirate - lymphoid aggregates rare, considered involved if EBER-1 positive, hemophagoctosis may be present.

[g] See NK/T-cell Lymphoma Prognostic Index (NKTL-A).

[h] EBV viral load is important in diagnosis and possibly in monitoring of disease. A positive result is consistent with NK/T-cell, nasal type. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2012
Extranodal NK/T-cell Lymphoma, nasal type

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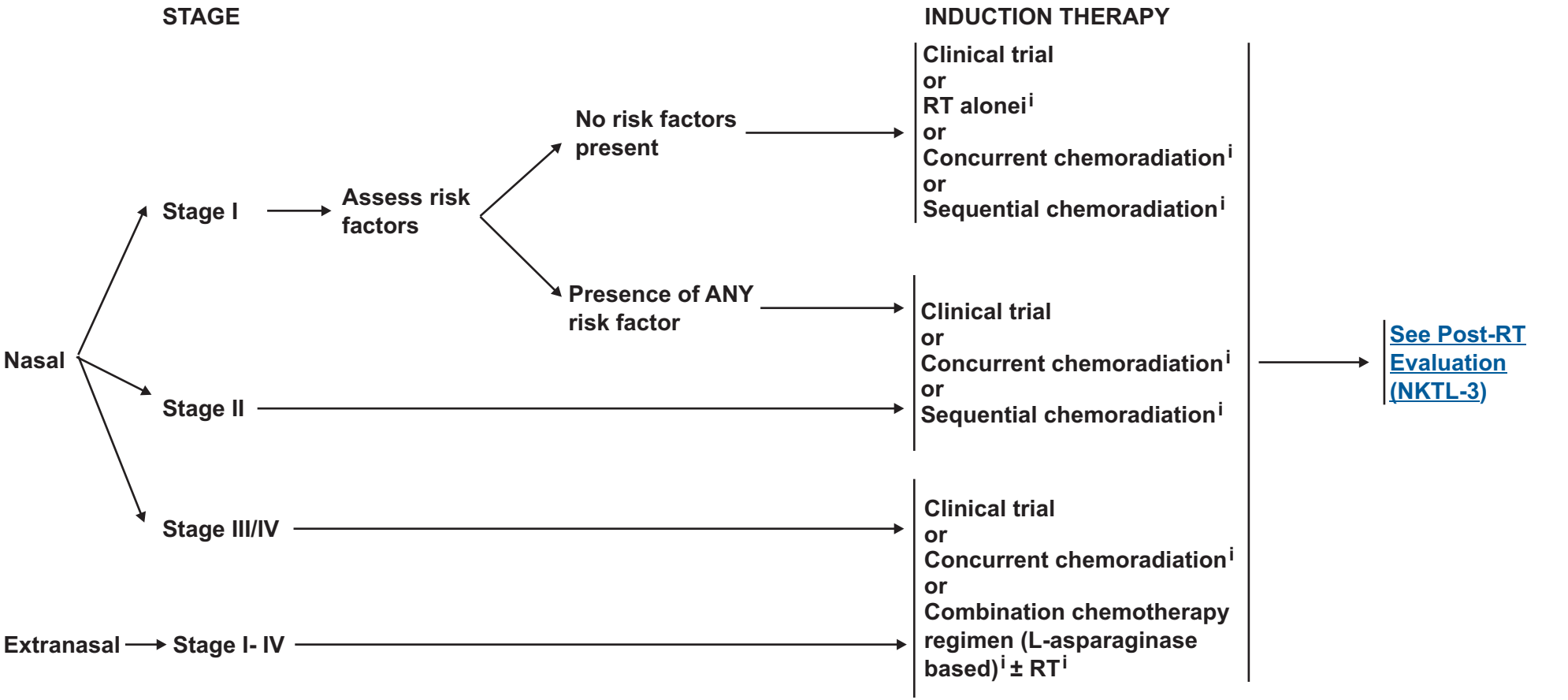

Risk factors
(includes elements of NK/T-cell Lymphoma PI on NKTL-A)

- Age > 60 y
- B symptoms
- ECOG PS ≥ 2
- Elevated LDH
- Regional node involvement
- Local tumor invasion (LTI); bone or skin
- Histological evidence of high Ki-67 staining
- EBV DNA titer ≥ 6.1×10^7 copies/ml

Adapted with permission from Kohrt H, Lee M, Advani R. Risk stratification in extranodal natural killer/T-cell lymphoma. Expert Rev Anticancer Ther 2010;10:1395-1405.

[i] See Suggested Treatment Regimens (NKTL-B).

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Extranodal NK/T-cell Lymphoma, nasal type

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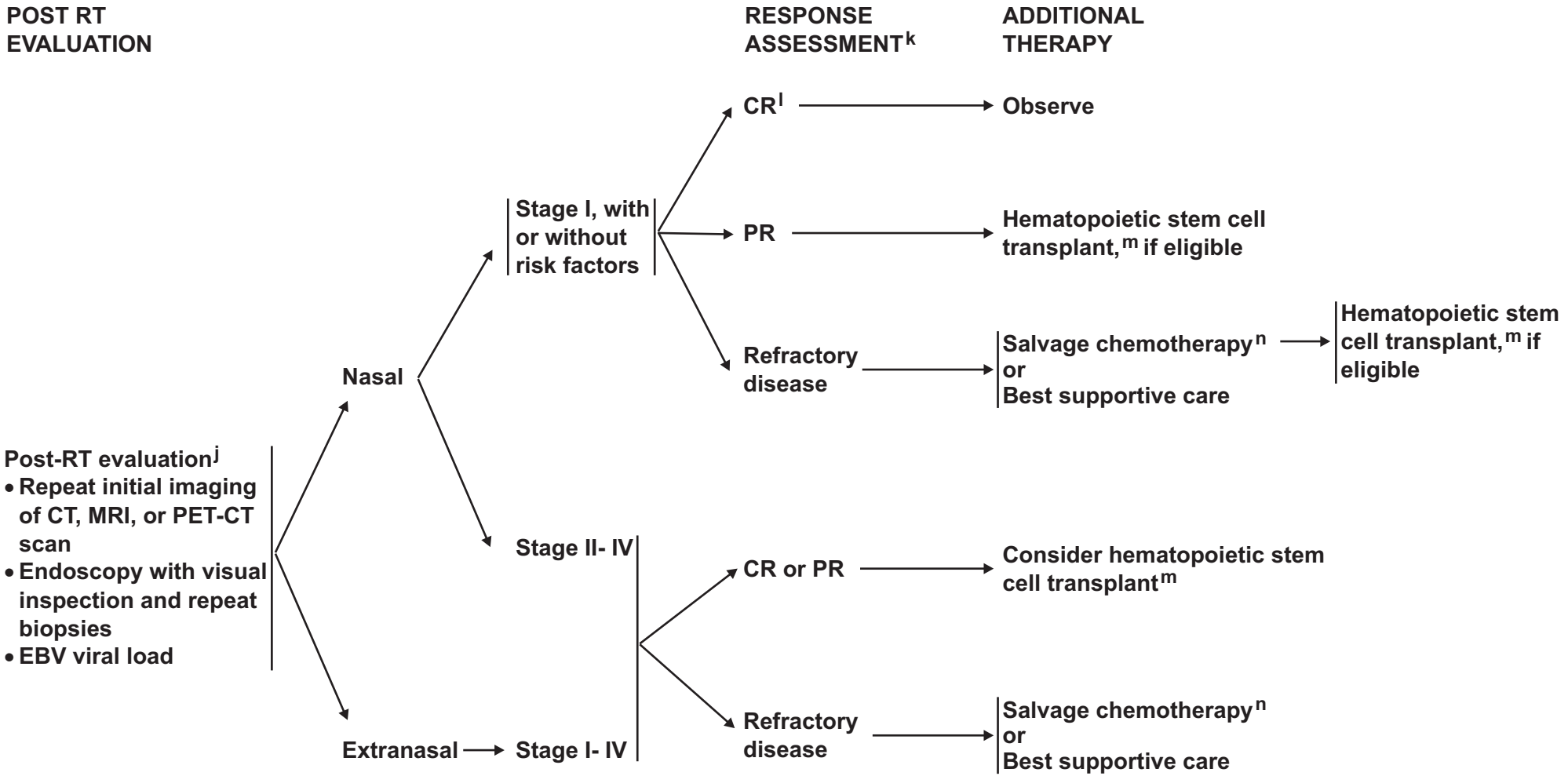

[j] The role of PET scan in this disease is not well established.
[k] See Response Criteria for Lymphoma (NHODG-C).
[l] Includes a negative ENT evaluation.
[m] Allogeneic preferred, if matched donor available.
[n] Combination chemotherapy regimen (L-asparaginase based) See Suggested Treatment Regimens (NKTL-B).

Adapted with permission from Kohrt H, Lee M, Advani R. Risk stratification in extranodal natural killer/T-cell lymphoma. Expert Rev Anticancer Ther 2010;10:1395-1405.

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NK/T CELL LYMPHOMA PROGNOSTIC INDEX[a]

ALL PATIENTS

Serum LDH > normal
B symptoms
Lymph nodes, N1 to N3, not M1
Ann Arbor Stage III

	Number of risk factors
Low	**0**
Low intermediate	**1**
High intermediate	**2**
High	**3 or 4**

[a]Lee J, Suh C, Park YH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: A prognostic model from a retrospective multicenter study. J Clin Oncol 2006;24:612-618.

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

Combination chemotherapy regimen (L-asparaginase based)
- AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) (Reported as a second line regimen.)
- SMILE (steroid [dexamethasone], methotrexate, ifosfamide, L-asparaginase, and etoposide)

Concurrent chemoradiation (CCRT)
- CCRT (radiation 50 Gy and 3 courses of DeVIC [dexamethasone, etoposide, ifosfamide, and carboplatin])
- CCRT (radiation 40 to 52.8 Gy and cisplatin) followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)

Sequential chemoradiation
- SMILE followed by RT 45-50.4 Gy
- VIPD followed by RT 45-50.4 Gy

Radiotherapy alone
- Recommended tumor dose is ≥ 50 Gy
  - Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract.
  - Up-front RT may yield more benefits on survival in patients with stage I disease.

[a] See references for regimens NKTL-B 2 of 2.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS

References

Combination chemotherapy regimen (L-asparaginase based)

Jaccard A GN, Coppo P, Morschhauser F, et al. A prospective phase II trial of an L-asparaginase containing regimen in patients with refractory or relapsing extra nodal NK/T-cell lymphoma [abstract]. Blood 2008;112:Abstract 79.

Yamaguchi M, Suzuki R, Kwong YL, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci 2008;99:1016-1020.

Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: The NK-Cell Tumor Study Group Study. J Clin Oncol 2011;29:4410-4416.

Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood 2011;117:1834-1839.

Concurrent chemoradiotherapy

Yamaguchi M TK, Oguchi M, Isobe Y, et al, Japan Clinical Oncology Group Lymphoma Study Group (JCOG-LSG). Phase I/II study of concurrent chemoradiotherapy for localized nasal NK/T-cell lymphoma: Final results of JCOG0211 [abstract]. J Clin Oncol 2009;27:Abstract 8549.

Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-cell lymphoma: Consortium for Improving Survival of Lymphoma study. J Clin Oncol 2009;27:6027-6032.

Radiotherapy alone

Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2008;70:166-174.

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Post-Transplant Lymphoproliferative Disorder

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DIAGNOSIS

ESSENTIAL:

- **Histopathology and adequate immunophenotype to establish diagnosis. Rebiopsy if consult material is nondiagnostic.**
  - **IHC panel: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, Ki67, kappa, lambda**
  - **Cell surface marker analysis by flow cytometry: CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, Kappa, lambda**
- **Epstein-Barr virus evaluation by EBV-LMP1 or EBER-ISH (if EBV-LMP1 negative, EBER-ISH is recommended)**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **IHC panel: CD15, CD30, CD45, CD7, CD4, CD8, ALK, TIA-1, Granzyme B, CD57, CD56, CD138**
- **Cell surface marker analysis by flow cytometry: CD138, cytoplasmic Kappa and lambda, CD30, CD57, CD56, CD16, CD25, CD52.**
- **Molecular analysis-to detect: IgH gene rearrangements**
- **BCL6 gene mutation analysis[a]**
- **EBV by southern blot**

WORKUP

ESSENTIAL:

- **Performance status**
- **Albumin**
- **Immunosuppressive regimen**
- **LDH, electrolytes, BUN, creatinine**
- **CBC, differential**
- **Hepatitis B testing[b]**
- **Chest/abdomen/pelvis CT**

USEFUL IN SELECTED CASES:

- **MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenediones**
- **Bone marrow evaluation**
- **PET-CT scan**
- **Brain MRI**
- **EBV PCR**
- **CMV PCR**
- **EBV serology for primary versus reactivation**

→ **Early lesions** → **See Primary Treatment (PTLD-2)**

→ **Polymorphic** → **See Primary Treatment (PTLD-2)**

→ **Monomorphic** → **See Primary Treatment (PTLD-2)**

→ **Classic Hodgkin lymphoma** → **See Primary Treatment (PTLD-2)**

[a] BCL6 gene mutation positivity has been associated with a poor response to reduction in immunosuppressive therapy.

[b] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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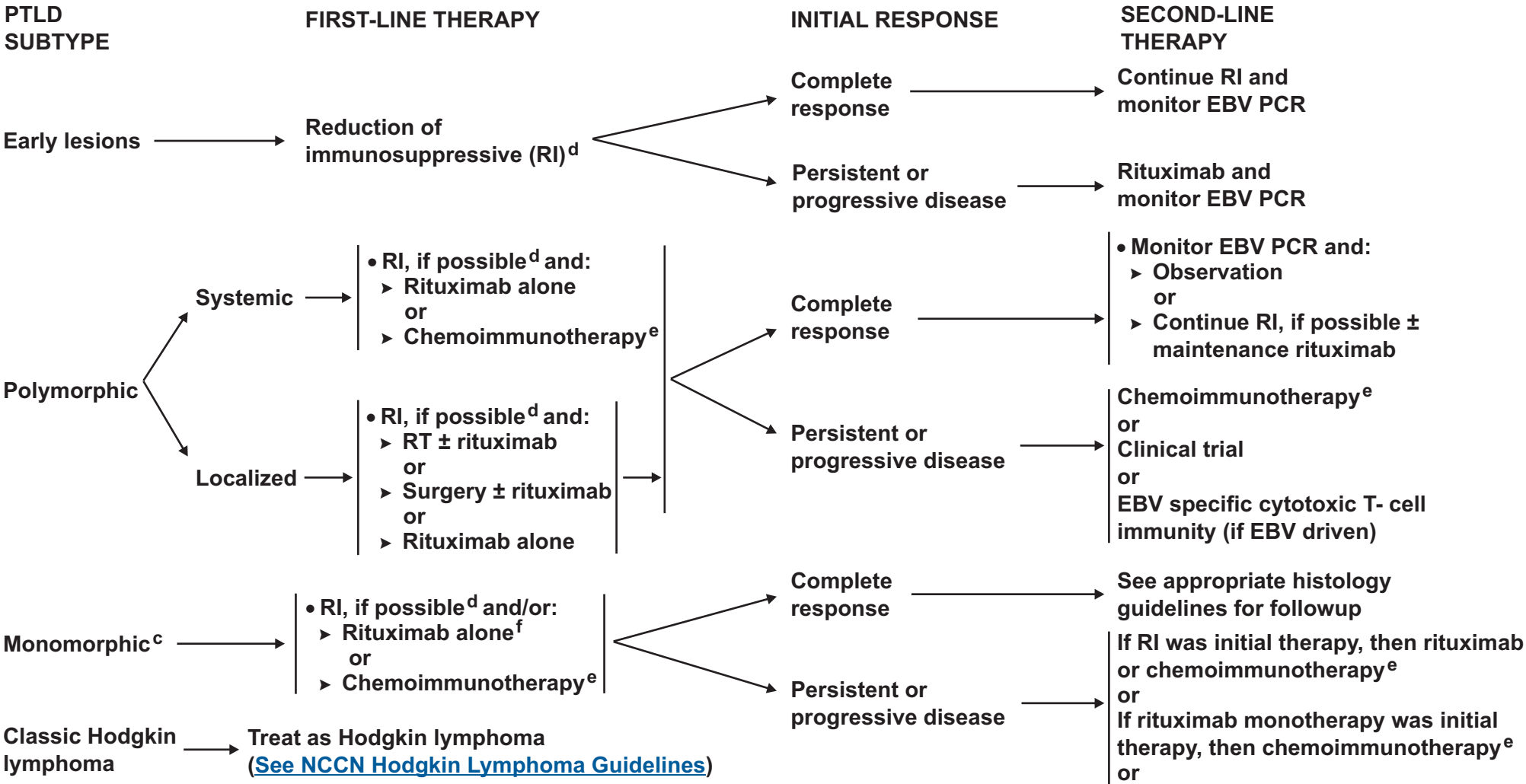

[c] Treatment is based on the unique histology.

[d] Response to RI therapy is variable and patients need to be closely monitored; RI should be coordinated with the transplant team.

[e] Concurrent or sequential chemoimmunotherapy, See Suggested Treatment Regimens PTLD-A.

[f] As part of a step-wise approach in patients who are not highly symptomatic or cannot tolerate chemotherapy secondary to co-morbidity.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

Concurrent chemoimmunotherapy

- **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)**
- **RCHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide)**
- **RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (for frail patients who cannot tolerate anthracycline)**

Sequential chemoimmunotherapy

- **Rituximab 375 mg/m^2 weekly x 4 weeks followed by CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone) starting Day 1 of week 9 x 4 cycles**

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

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NCCN Guidelines Version 2.2012
T-cell Prolymphocytic Leukemia

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DIAGNOSIS

ESSENTIAL:
- Tissue histology not essential for diagnosis
- Peripheral blood smear analysis for morphology
- Adequate immunophenotype to establish diagnosis[a]
  - IHC panel: CD1a, TdT, CD2, CD3, CD5, TCL-1
  - Cell surface marker analysis by flow cytometry: TdT, CD 1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, TCRα/β
- Cytogenetics: inv(14)(q11;q32); t(14;14)(q11;q32); t(X;14)(q28;q11); trisomy 8

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: TCR-β, TCR-γ gene rearrangement; ATM mutation; TCL-1 overexpression; MTCP-1 gene rearrangement

→

WORKUP

ESSENTIAL
- Complete history and physical examination-including complete skin exam, and evaluation of lymph nodes, spleen and liver.
- Performance status
- LDH, electrolytes, BUN, creatinine
- CBC, differential
- Chest/abdomen/pelvis CT

USEFUL IN SELECTED CASES:
- MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenediones
- Bone marrow evaluation
- PET-CT scan
- HTLV-1 serology: ELISA and confirmatory Western blot if ELISA positive
- Consider screening for active infections and CMV serology if therapy with alemtuzumab is contemplated

→

Asymptomatic[b] → Observe until progression or symptomatic

Symptomatic disease → See TPLL-2

[a] Typical immunophenotype: CD1a-, TdT-, CD2+, sCD3+/-, cCD3+/-, CD5+, CD7++, CD52++, TCRαβ+, CD4+/CD8- (65%), CD4+/CD8+ (21%), CD4-/CD8+ (13%).

[b] In a minority of patients, the disease may be asymptomatic and can follow an indolent course of variable duration. In these selected cases expectant observation is a reasonable option.

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NCCN Guidelines Version 2.2012
T-cell Prolymphocytic Leukemia

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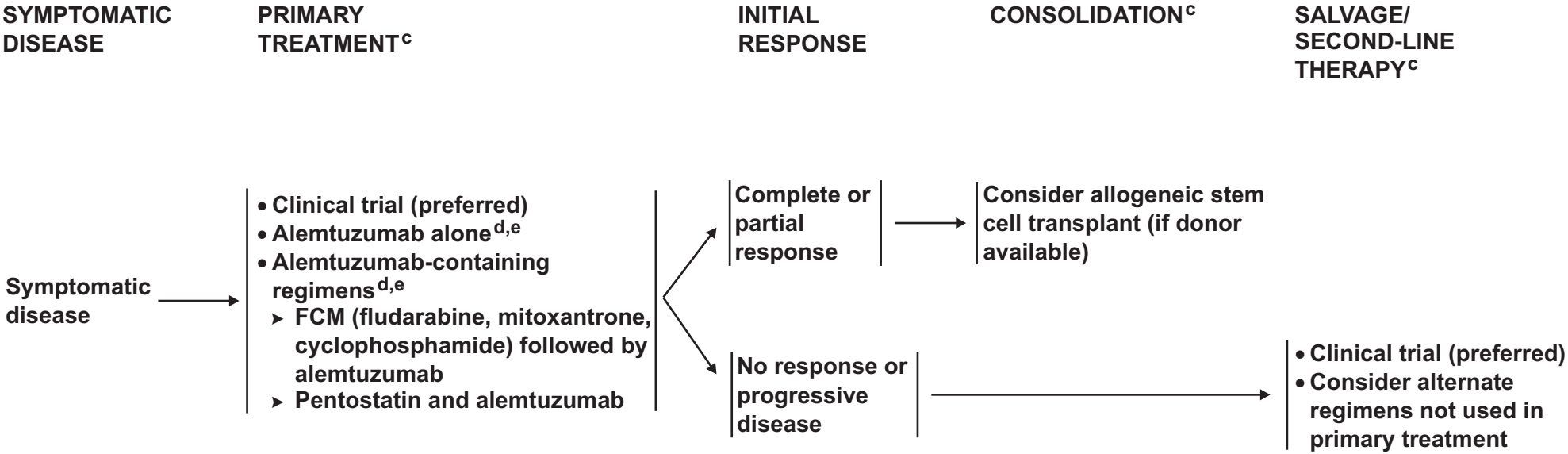

[c] See Treatment References (TPLL-A).

[d] IV alemtuzumab is preferred over SC based on data showing inferior activity with SC delivery in patients with T-PLL (Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukaemia: Comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood 2011;118:5799-5802).

[e] Monitor for CMV reactivation; antiinfective prophylaxis for herpes virus and PCP recommended when treating with alemtuzumab ± purine analogs.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT REFERENCES

Alemtuzumab
Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. Blood 2001;98:1721-1726.
Keating MJ, Cazin B, Coutre S, et al. Campath-1H treatment of T-cell prolymphocytic leukemia in patients for whom at least one prior chemotherapy regimen has failed. J Clin Oncol 2002;20:205-213.
Khot AtS, Matutes E, Kaczmarek PA, et al. Alemtuzumab administered by subcutaneous route is less effective than intravenous route for first line therapy of T-cell prolymphocytic leukaemia: Results of a pilot study (UKCLL05) [abstract]. Blood 2008;112:Abstract 4204.
Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukaemia: Comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood 2011;118:5799-5802.

Alemtuzumab combined with pentostatin
Ravandi F, Aribi A, O'Brien S, et al. Phase II study of alemtuzumab in combination with pentostatin in patients with T-cell neoplasms. J Clin Oncol 2009;27:5425-5430.

FMC (fludarabine, mitoxantrone, cyclophosphamide) followed by alemtuzumab
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Castagna L, Nozza A, Bertuzzi A, Siracusano L, Timofeeva I, Santoro A. Allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning in primary refractory prolymphocytic leukemia: graft-versus-leukemia effect without graft-versus-host disease. Bone Marrow Transplant 2001;28:1155-1156.
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Murase K, Matsunaga T, Sato T, et al. Allogeneic bone marrow transplantation in a patient with T-prolymphocytic leukemia with small-intestinal involvement. Int J Clin Oncol 2003;8:391-394.
Wiktor-Jedrzejczak W, Dearden C, de Wreede L, et al. Hematopoietic stem cell transplantation in T-prolymphocytic leukemia: A retrospective study from the European Group for Blood and Marrow Transplantation and the Royal Marsden Consortium. Leukemia 2011 [e-pub].

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Hairy Cell Leukemia

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DIAGNOSIS[a]

ESSENTIAL:

- **Presence of characteristic hairy cells upon morphological examination of peripheral blood and characteristic infiltrate with increased reticulin in bone marrow biopsy samples. Dry tap is frequent.**
- **IHC and flow cytometry are essential for establishing the diagnosis and for distinguishing between hairy cell leukemia and hairy cell variant.[b]**
- **Adequate immunophenotyping to establish diagnosis[c,d]**
  - **IHC panel: CD20, CD25, CD123, cyclin D1**
    or
  - **Cell surface marker analysis by flow cytometry: CD3, CD5, CD10, CD11c, CD19, CD20, CD22, CD25, CD103**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: IGHV mutational status**
- **Sequencing for BRAF V600E mutation**

WORKUP

ESSENTIAL:

- **Physical exam: Presence of enlarged spleen and/or liver; presence of peripheral lymphadenopathy (uncommon)**
- **Performance status**
- **Peripheral blood examination**
- **CBC, differential, platelets**
- **Comprehensive metabolic panel with particular attention to renal function**
- **LDH**
- **Bone marrow biopsy ± aspirate**
- **Hepatitis B testing[e] if rituximab contemplated**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL UNDER CERTAIN CIRCUMSTANCES

- **Chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **PET-CT scan**
- **Discussion of fertility issues and sperm banking**

See Primary Treatment (HCL-2)

[a] This GL applies to hairy cell leukemia, not hairy cell variant. There is not sufficient data on treatment of hairy cell variant.

[b] Hairy cell variant is characteristically CD25- CD123-, Annexin A1-. This helps to distinguish the variant form from classical HCL.

[c] Typical immunophenotype: CD5-, CD10-, CD11c+, CD20+ (bright), CD22+, CD25+, CD103+, CD123+, cyclin D1+, Annexin A1+. Monocytopenia is characteristic.

[d] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[e] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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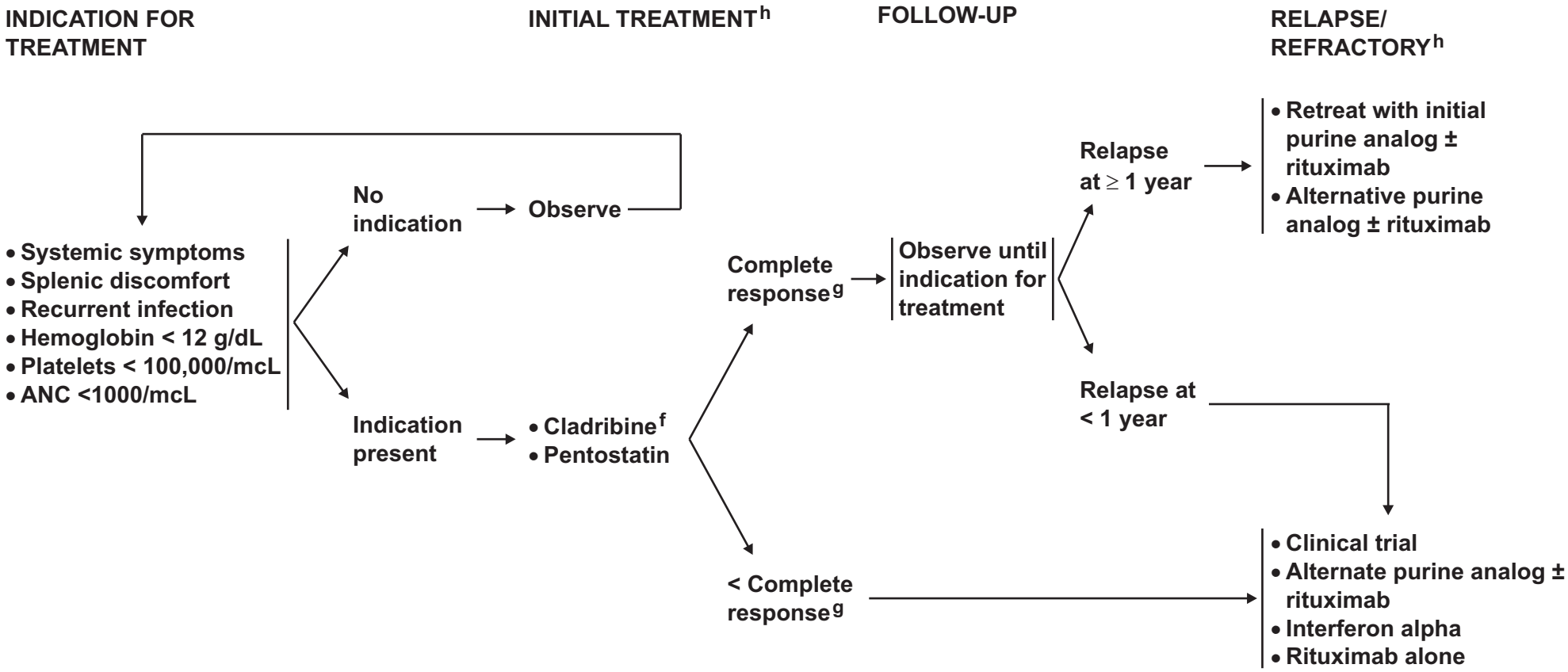

Adapted from: Grever MR. How I treat hairy cell leukemia. Blood 2010;115:21-28.

[f]Cladribine should not be administered to patients with active life-threatening or chronic infection.

[g]Complete response defined as: recovery of blood counts (Hgb >12 g/dL, ANC >1500/mcL, Platelet >100,000/mcL), absence of HCL cells by morphological examination of bone marrow biopsy or peripheral blood samples, resolution of organomegaly by physical exam, absence of disease symptoms. Eradication of minimal residual disease (as determined by flow cytometry, immunohistochemistry, or molecular analysis) is of unproven value at this point.

[h]See Treatment References (HCL-A).

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT REFERENCES

Single-agent purine analogs

Flinn IW, Kopecky KJ, Foucar MK, et al. Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. Blood 2000;96:2981-2986.

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Rituximab

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Thomas DA, O'Brien S, Bueso-Ramos C, et al. Rituximab in relapsed or refractory hairy cell leukemia. Blood 2003;102:3906-3911.

Purine analogs with rituximab

Else M, Osuji N, Forconi F, et al. The role of rituximab in combination with pentostatin or cladribine for the treatment of recurrent/refractory hairy cell leukemia. Cancer 2007;110:2240-2247.

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Ravandi F, O'Brien S, Jorgensen J, et al. Phase 2 study of cladribine followed by rituximab in patients with hairy cell leukemia. Blood 2011;118:3818-3823.

Interferon-alpha

Damasio EE, Clavio M, Masoudi B, et al. Alpha-interferon as induction and maintenance therapy in hairy cell leukemia: a long-term follow-up analysis. Eur J Haematol 2000;64:47-52.

Benz R, Siciliano RD, Stussi G, Fehr J. Long-term follow-up of interferon-alpha induction and low-dose maintenance therapy in hairy cell leukemia. Eur J Haematol 2009;82:194-200.

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USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND T/NK-CELL NEOPLASMS[a]
(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

GENERAL PRINCIPLES

- Morphology ± clinical features drive both the choice and the interpretation of special studies.
- Differential diagnosis is based on morphology ± clinical setting.
- Begin with a broad but limited panel of antibodies, based on the differential diagnosis.
  - Avoid "shotgun" panels of unnecessary antibodies unless a clinically urgent situation warrants.
- Add antigens in additional panels, based on initial results.
- Follow with genetic studies as needed.
- Return to clinical picture if immunophenotype + morphology are not specific.

B-cell antigens positive

- Morphology
  - Small cells
  - Medium-sized cells
  - Large cells
- Immunophenotype/Genetics
  - Naïve B cells: CD5, CD23
  - GCB cells: CD10, BCL6, FDC (CD21, 23)
  - Post-GC cells: IRF4/MUM1, CD138
  - Immunoglobulin heavy and light chains (s, c, class switch, light chain type)
  - Oncogenes/products: BCL2,cyclin D1, MYC, BCL6, ALK
  - Viruses: EBV, HHV8
- Clinical features
  - Age
  - Location (nodal, extranodal, specific site)

T-cell antigens positive

- Morphologic features
  - Anaplastic vs non-anaplastic
  - Epidermotropic
- Immunophenotype
  - CD30, ALK*, CD56, βF1, cytotoxic granule proteins,
  - CD4, CD8, CD5, CD7
  - Follicular T-cells: CD10, BCL6, CD279(PD1)
  - EBV-EBER
- Clinical: Location
  - Cutaneous
  - Extranodal non-cutaneous (specific site)
  - Nodal

*Always do ALK if CD30+

See Initial Morphologic, Clinical and Immunophenotypic Analysis (NHODG-A 2 of 10)

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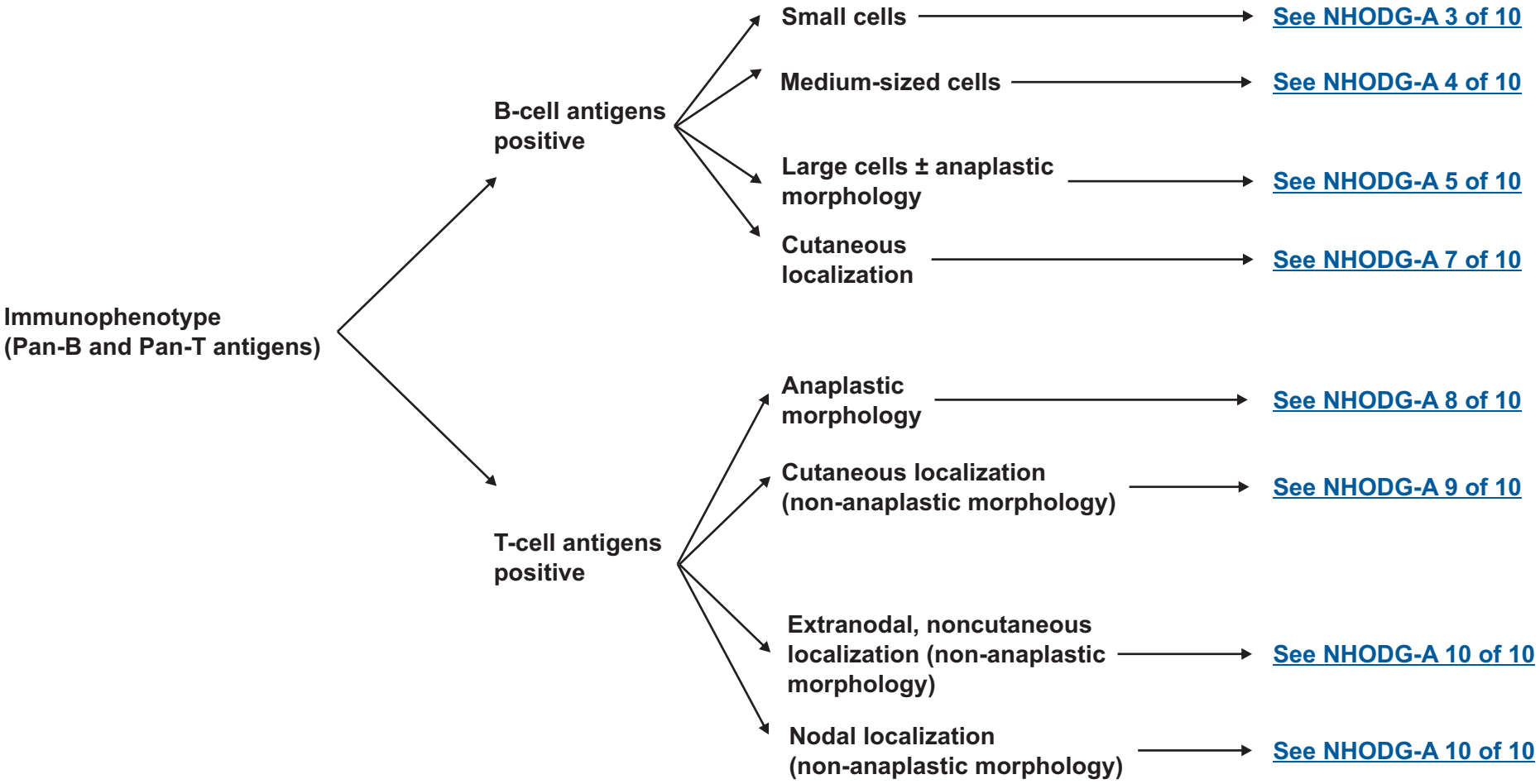
INITIAL MORPHOLOGIC, CLINICAL AND IMMUNOPHENOTYPIC ANALYSIS



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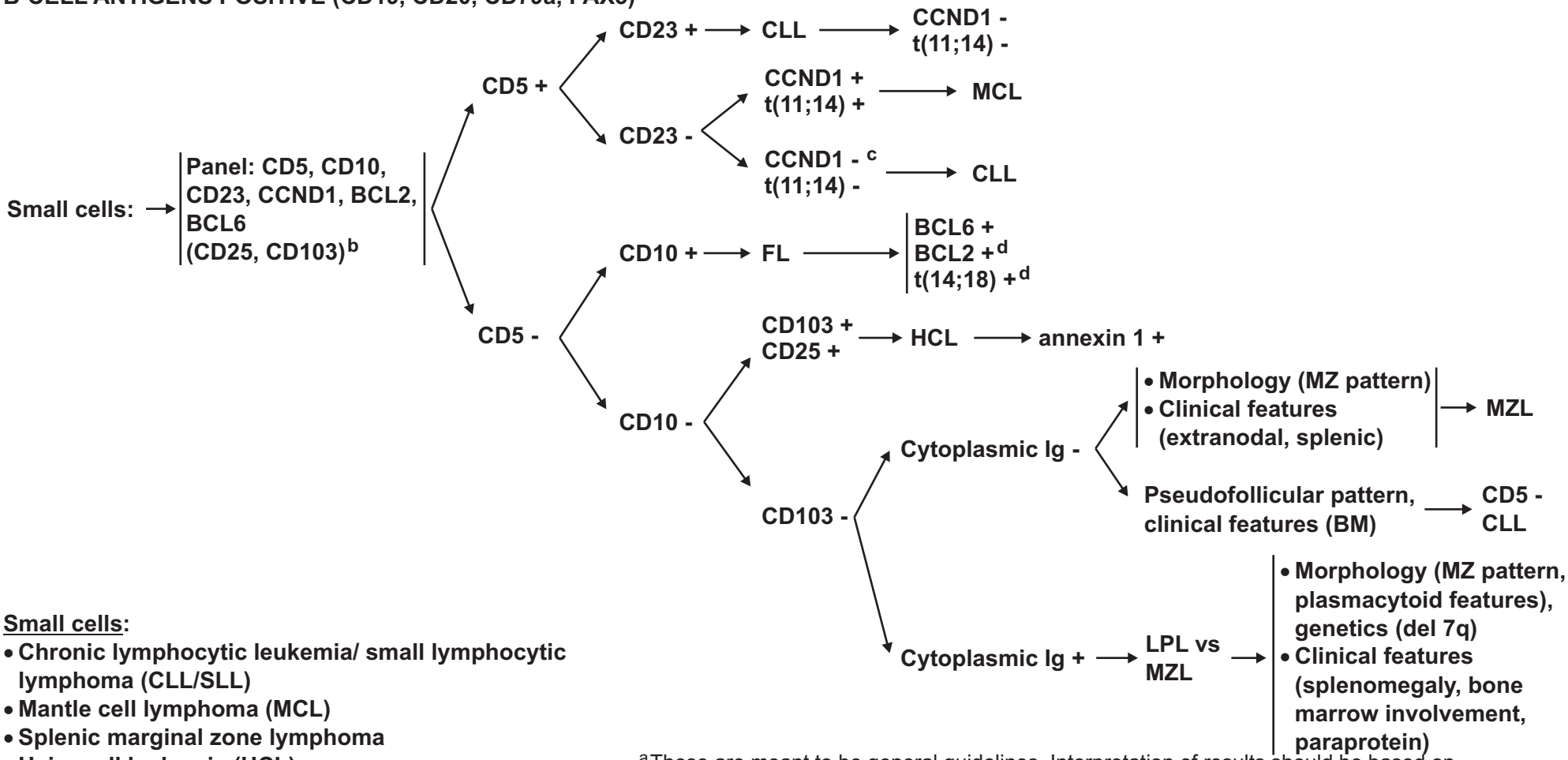
(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)



Small cells:

- Chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL)
- Mantle cell lymphoma (MCL)
- Splenic marginal zone lymphoma
- Hairy cell leukemia (HCL)
- Lymphoplasmacytic lymphoma (LPL)
- Extranodal marginal zone lymphoma (MALT lymphoma)
- Nodal marginal zone lymphoma
- Follicular lymphoma (FL)

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[b] Flow cytometry, blood or bone marrow, if HCL is in differential diagnosis.
[c] Rare cases of both CCND1 and t(11;14) negative MCL have been reported. This diagnosis should be made with extreme caution and with expert consultation.
[d] 85% of Follicular Lymphoma will be BCL2 + or t(14;18) +.

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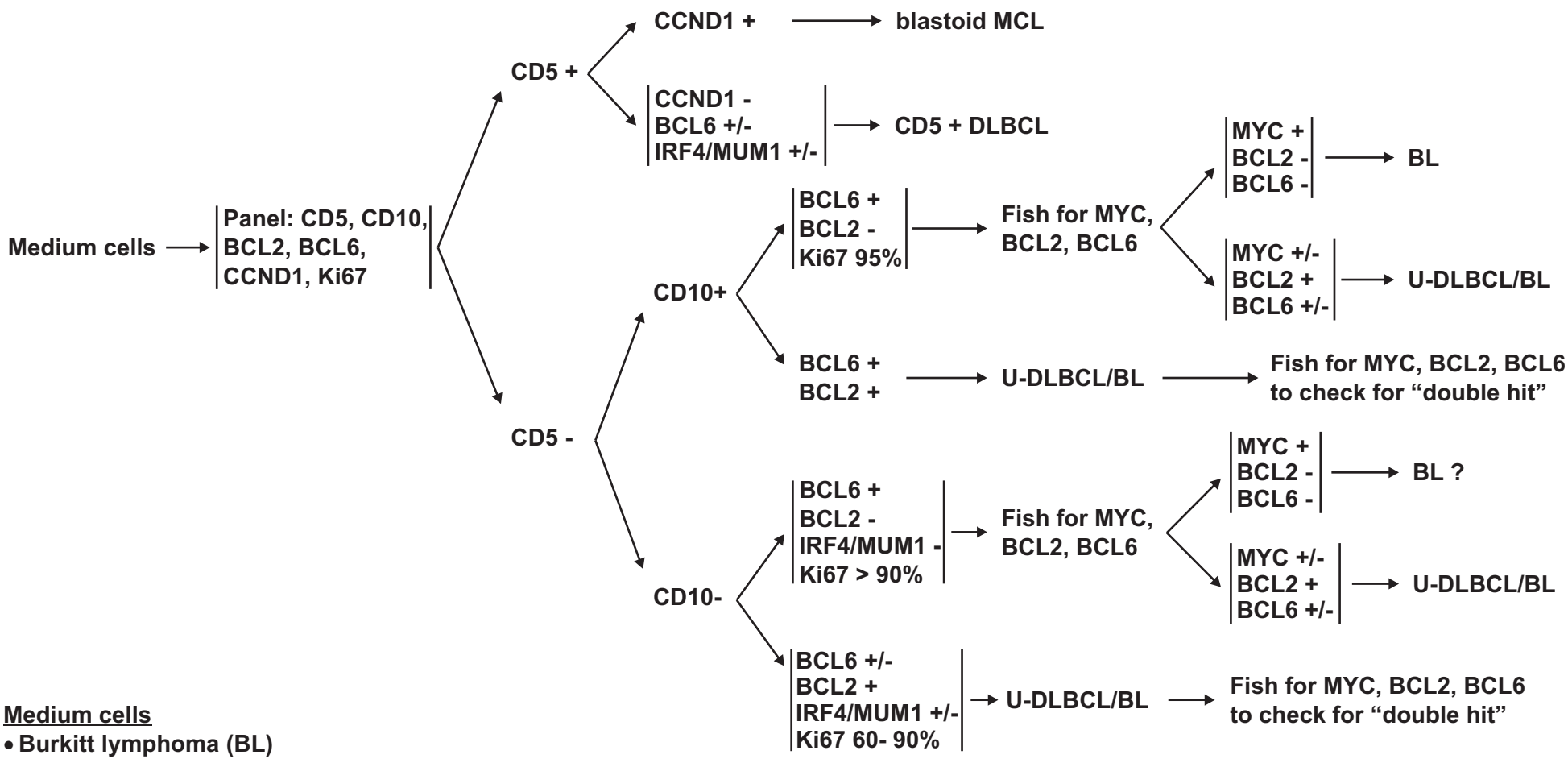
B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)



Medium cells

- **Burkitt lymphoma (BL)**
- **Diffuse large B-cell lymphoma (DLBCL)**
- **Mantle cell lymphoma (MCL), blastoid variant**
- **B-cell lymphoma (BCL), unclassifiable, intermediate between DLBCL and BL (U-DLBCL/BL)**

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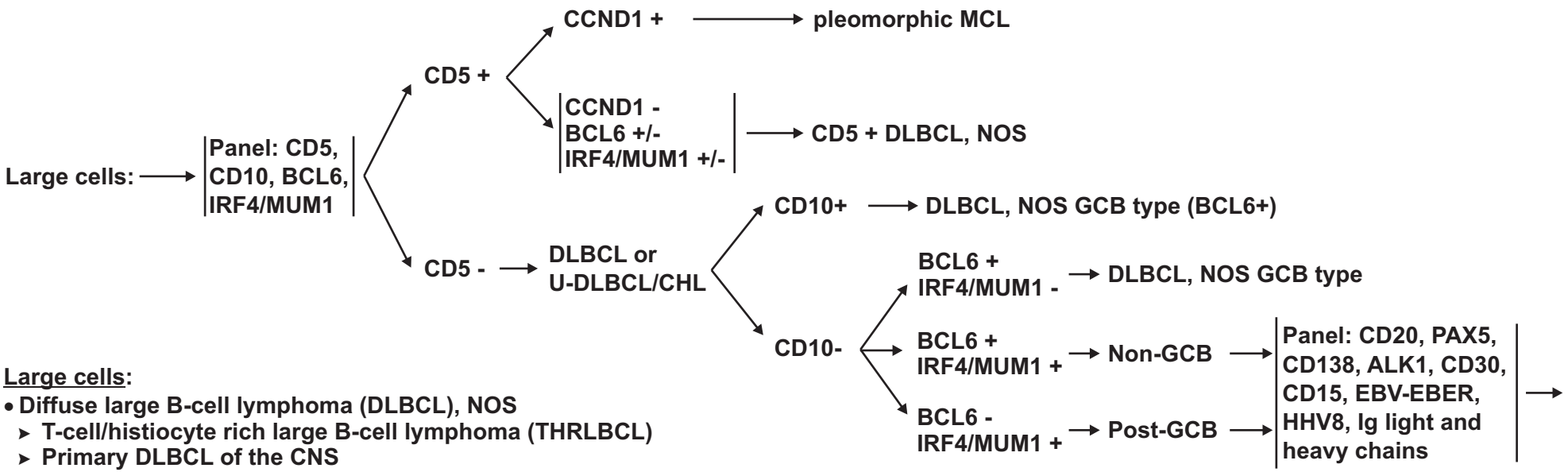
B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)



Large cells:

- **Diffuse large B-cell lymphoma (DLBCL), NOS**
  - **T-cell/histiocyte rich large B-cell lymphoma (THRLBCL)**
  - **Primary DLBCL of the CNS**
  - **Primary cutaneous DLBCL, leg type**
  - **EBV positive DLBCL of the elderly (EBV + DLBCL)**
- **DLBCL associated with chronic inflammation**
- **Lymphomatoid granulomatosis**
- **Primary mediastinal (thymic) large B-cell lymphoma (PMBL)**
- **Intravascular large B-cell lymphoma**
- **ALK positive large B-cell lymphoma**
- **Plasmablastic lymphoma**
- **Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease (LBCL in HHV8 + MCD)**
- **Primary effusion lymphoma**
- **B-cell lymphoma, unclassifiable, intermediate between DLBCL (U-DLBCL) and classical Hodgkin lymphoma (CHL)**
- **Mantle cell lymphoma (MCL), pleomorphic variant**

Continued on next page

GCB= Germinal center B-cell like

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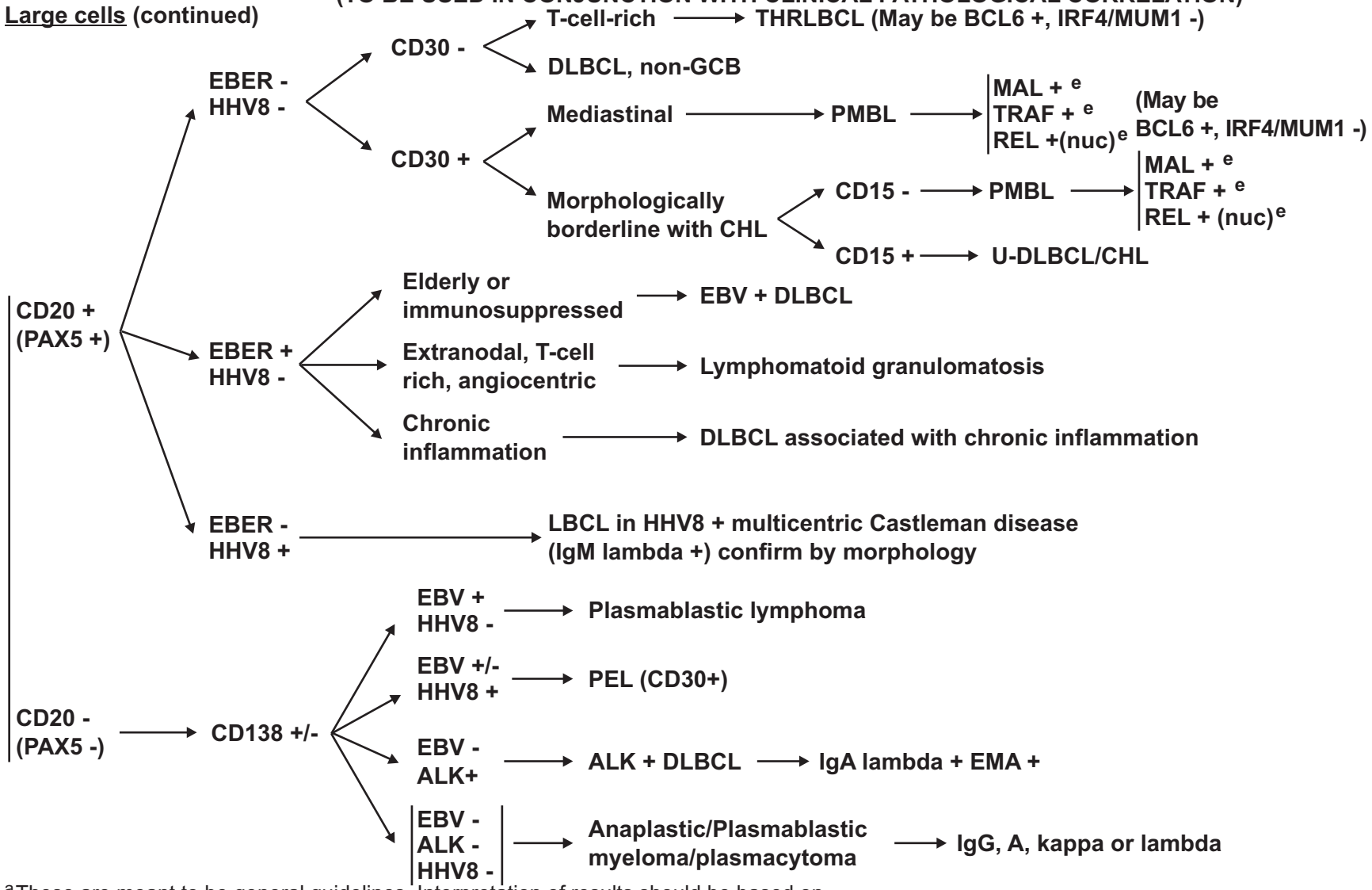

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[e] These stains/studies are not routinely available.

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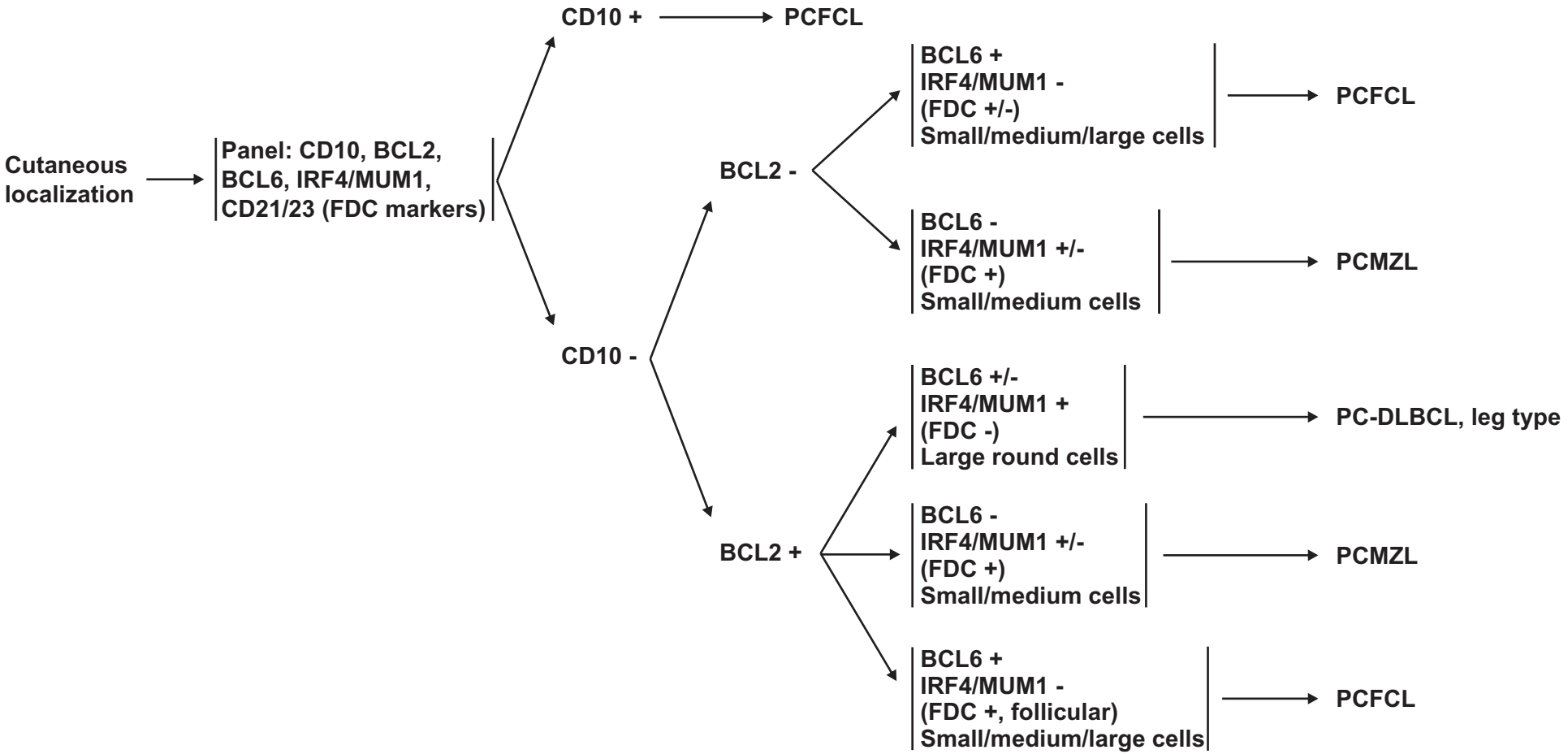
B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)



- **Primary cutaneous marginal zone lymphoma (PCMZL)**
- **Primary cutaneous follicle center lymphoma (PCFCL)**
- **Primary cutaneous DLBCL, leg type (PC-DLBCL, leg type)**

FDC = Follicular dendritic cells

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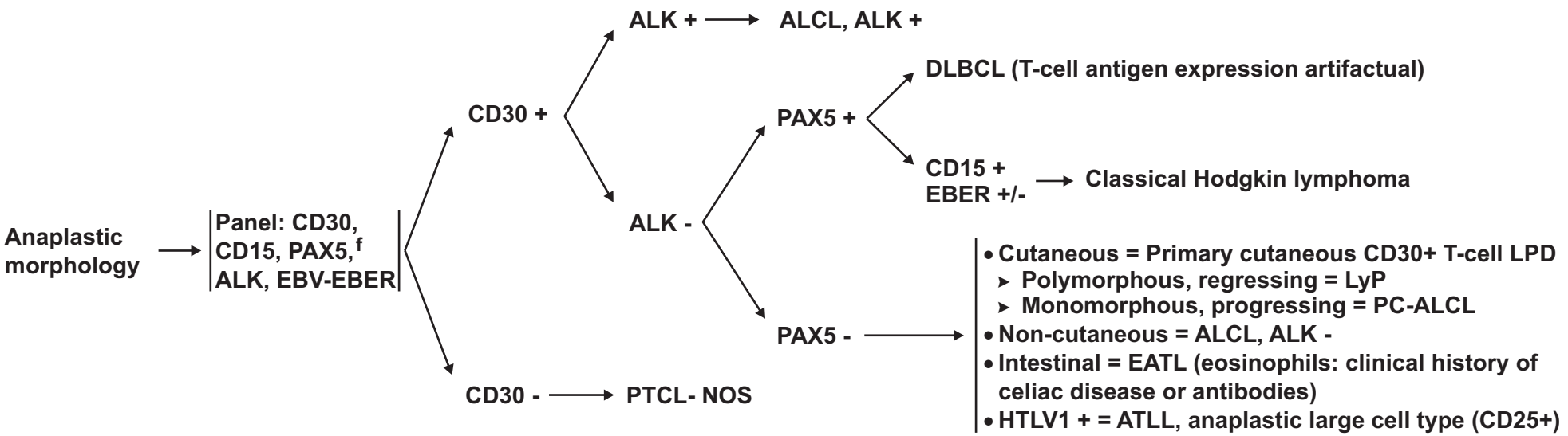
(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

T-CELL ANTIGENS POSITIVE (CD2, CD3, CD5, CD7) [and B-cell antigens negative]



Anaplastic morphology

- Anaplastic large cell lymphoma (ALCL), ALK positive
- Anaplastic large cell lymphoma (ALCL), ALK negative
- Adult T-cell leukemia/lymphoma (ATLL), anaplastic large cell type
- Enteropathy associated T-cell lymphoma (EATL)
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis (LyP)
  - Primary cutaneous anaplastic large cell lymphoma (PC-ALCL)

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[f] Rare T-cell lymphomas may be PAX5+. PCR analysis may be required to determine lineage in such cases.

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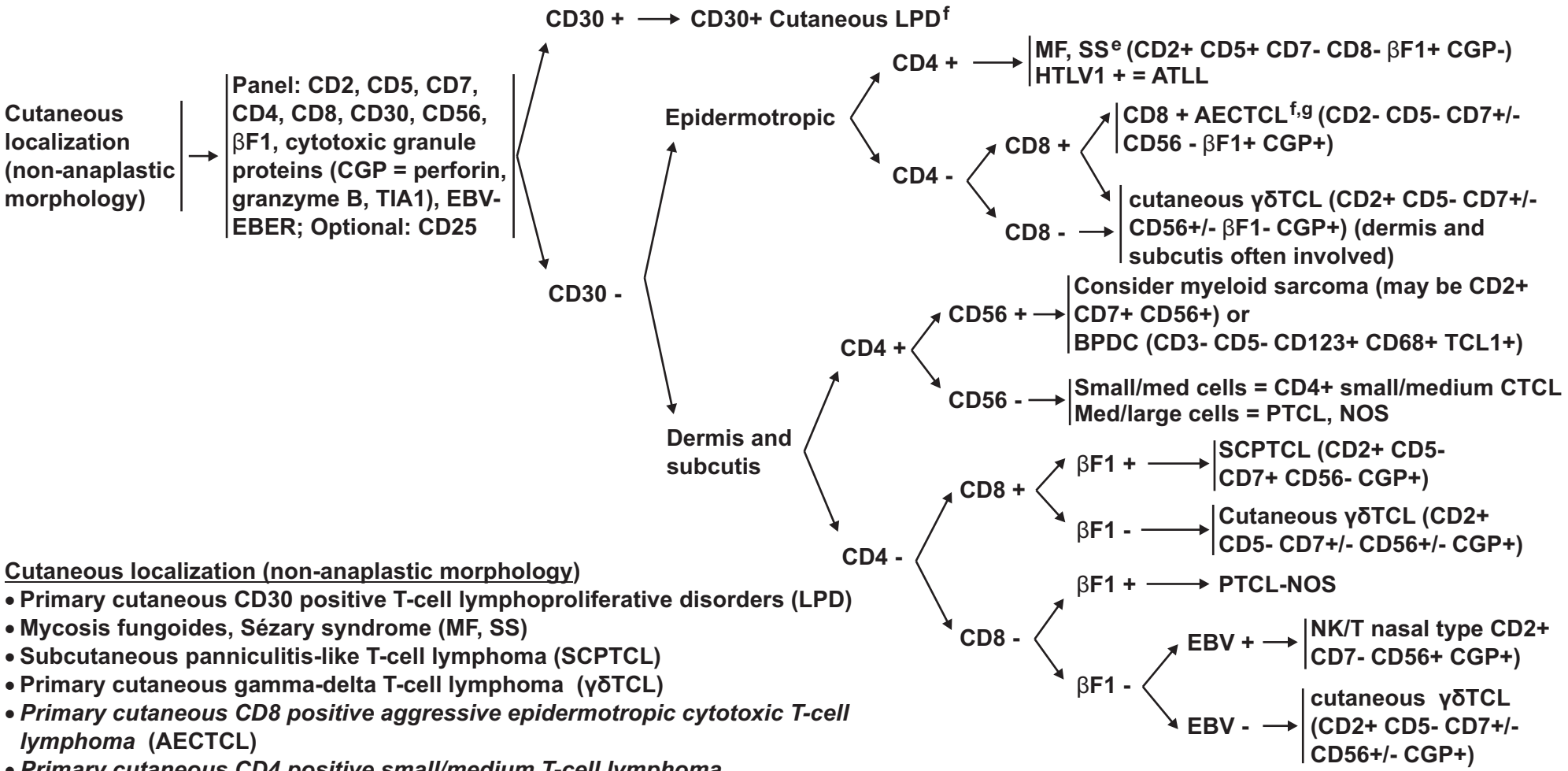
(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

T-CELL ANTIGENS POSITIVE (CD2, CD3, CD5, CD7) [and B-cell antigens negative (Pax5)]



<u>Cutaneous localization (non-anaplastic morphology)</u>

- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders (LPD)
- Mycosis fungoides, Sézary syndrome (MF, SS)
- Subcutaneous panniculitis-like T-cell lymphoma (SCPTCL)
- Primary cutaneous gamma-delta T-cell lymphoma (γδTCL)
- *Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma* (AECTCL)
- *Primary cutaneous CD4 positive small/medium T-cell lymphoma*
- Extranodal NK/T-cell lymphoma, nasal type
- Peripheral T-cell lymphoma, NOS
- Blastic plasmacytoid dendritic cell neoplasm (BPDC)

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[f] A minority of MF cases can be CD30+, CD4 - and either CD8 +/-, TIA1 +.
[g] AECTCL has distinctive morphology and clinical presentation.

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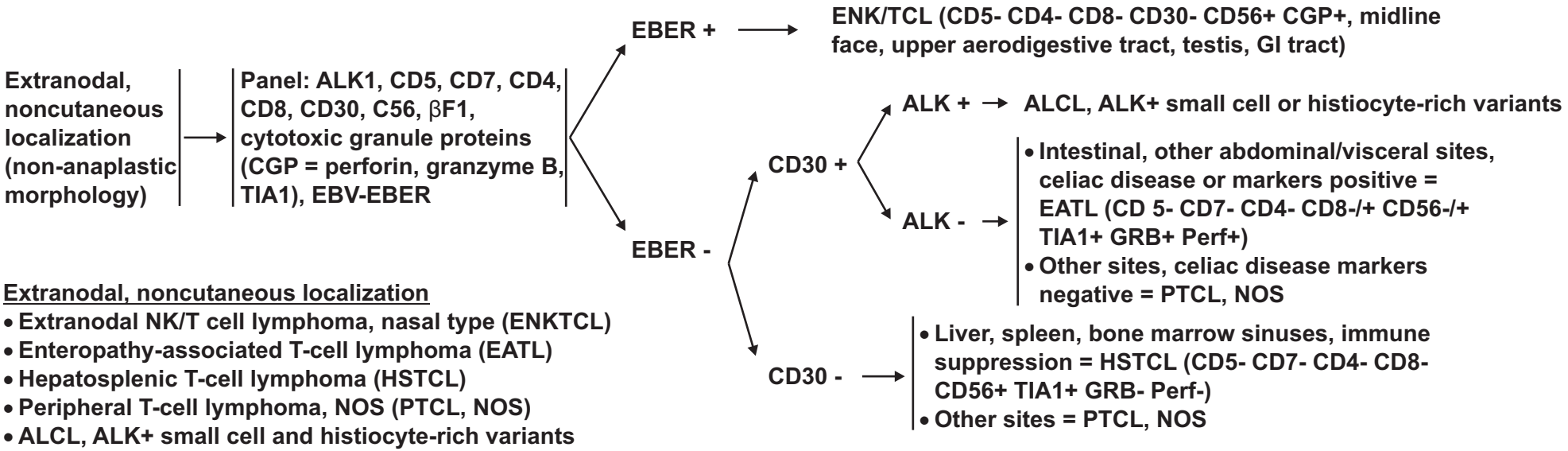
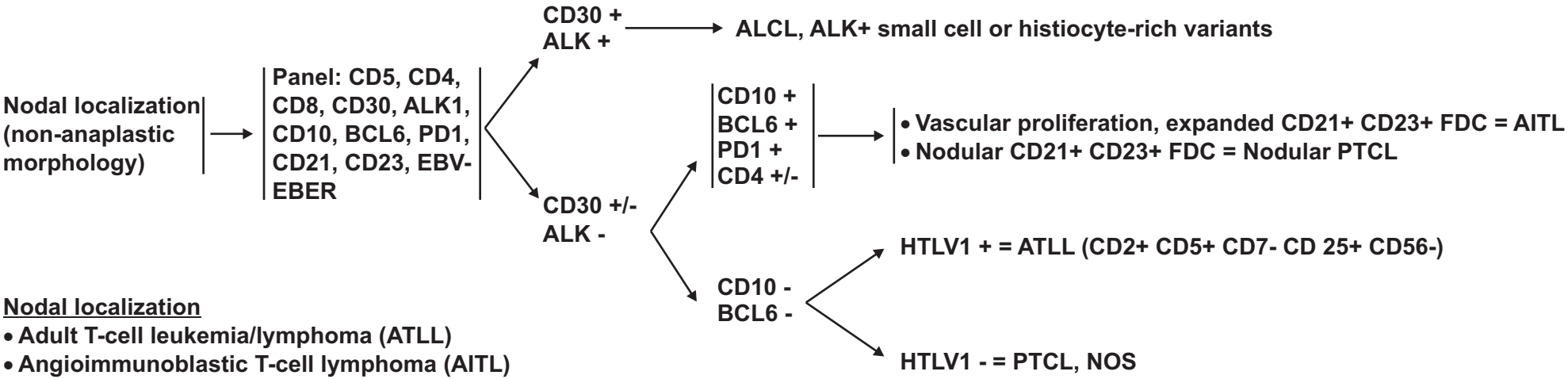


Extranodal, noncutaneous localization

- Extranodal NK/T cell lymphoma, nasal type (ENKTCL)
- Enteropathy-associated T-cell lymphoma (EATL)
- Hepatosplenic T-cell lymphoma (HSTCL)
- Peripheral T-cell lymphoma, NOS (PTCL, NOS)
- ALCL, ALK+ small cell and histiocyte-rich variants



Nodal localization

- Adult T-cell leukemia/lymphoma (ATLL)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Peripheral T-cell lymphoma, NOS (PTCL, NOS)
- ALCL, ALK+ small cell and histiocyte-rich variants

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TUMOR LYSIS SYNDROME

Laboratory hallmarks of TLS:
- High potassium
- High uric acid
- High phosphorous
- Low calcium

Symptoms of TLS:
- Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.

High risk features
- Histologies of Burkitt Lymphoma and Lymphoblastic Lymphoma; occasionally patients with DLBCL and CLL
- Spontaneous TLS
- Elevated WBC
- Bone marrow involvement
- Pre-existing elevated uric acid
- Ineffectiveness of allopurinol
- Renal disease or renal involvement by tumor

Treatment of TLS:
- TLS is best managed if anticipated and treatment started prior to chemotherapy.
- Centerpiece of treatment includes
  - ➤ Rigorous hydration
  - ➤ Management of hyperuricemia
  - ➤ Frequent monitoring of electrolytes and aggressive correction is essential
- First-line and at retreatment
  - ➤ Allopurinol beginning 2-3 days prior to chemotherapy and continued for 10-14 days
    or
    Rasburicase is indicated for patients with any of the following risk factors:
    - ◊ presence of any high risk feature
    - ◊ urgent need to initiate therapy in a high-bulk patient
    - ◊ situations where adequate hydration may be difficult or impossible
    - ◊ Acute renal failure
  - ➤ One dose of rasburicase is frequently adequate. Redosing should be individualized.

- If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

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RESPONSE CRITERIA FOR LYMPHOMA
(not including PET)

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu (unconfirmed)	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/ Progression	Enlarging liver/spleen, new sites	New or increased	New or increased	Reappearance

Source: Table 2 from Cheson BD, Horning SJ, Coiffier B et al: Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma. J Clin Oncol 1999; 17:1244. Reprinted with permission from the American Society of Clinical Oncology.

See Response Designations and PET findings NHODG-C 2 of 2

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

REVISED RESPONSE CRITERIA FOR LYMPHOMA (including PET)[a]

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules(for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Source: Table 2 from Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579-586. Reprinted with permission from the American Society of Clinical Oncology.

[a]Recommended for use with Diffuse Large B-Cell Lymphoma and Hodgkin Disease/Lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MONOCLONAL ANTIBODY DIRECTED AT CD20 AND VIRAL REACTIVATION

- **Hepatitis B surface antigen (HBSAg) and Hepatitis B core antibody (HBCAb) testing for all patients receiving rituximab**
  - **Quantitative hepatitis B viral load by PCR only if one of the screening tests positive**
  - **In areas with high prevalence/ population or prevalence is HBV not known, recommend testing all patients receiving immunotherapy, chemotherapy, or chemoimmunotherapy**

Note: Patients receiving IV immunoglobin may be HBCAb positive as a consequence of IVIG therapy.

- **Empiric antiviral therapy with oncologic treatment for any patient who is HBSAg or HBCAb positive**
  - **Monitor hepatitis B viral load with PCR monthly through treatment and every 3 months thereafter**
    - **If viral load is consistently undetectable, treatment is considered prophylactic**
    - **If viral load fails to drop, consult hepatologist**
  - **Maintain prophylaxis for at least 6 months after oncologic treatment ends**
    - **Consult with hepatologist for duration of therapy in patient with active hepatitis B virus**

Progressive multifocal leukoencephalopathy (PML)

- **Caused by the JC virus and is usually fatal**
  - **Diagnosis made by PCR of CSF and in some cases brain biopsy**
- **No known effective treatments**
- **Check for changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF RADIATION THERAPY[a]

Field:

Options: Involved-Field or Reduced Involved-Field

For extra nodal sites:

- **Organ involvement: The field includes the involved organ alone (example: Gastric MALT- the whole stomach; Parotid- the total unilateral parotid gland).**
- **Bone/spine involvement: Only the involved part of the organ is irradiated (with margins). No radiation is required to uninvolved adjacent lymph nodes.**

For nodal sites:

- **Field: In most cases an involved-field is appropriate. Regional fields or extended-field are not recommended unless there is significant concern that adjacent nodes are involved.**
  - **In DLBCL, RT consolidation following chemotherapy, RT may be limited to the originally involved lymph node(s). In the mediastinum, abdomen and pelvis treating only the post-chemotherapy volume in the transverse diameter is recommended.**
  - **When RT is the primary treatment, involved-field or reduced-IFRT (involved nodal radiation therapy) is recommended.**
  - **Margins are influenced by the quality of imaging and clinical information.**

Dose:

- **RT for follicular lymphoma: 24-30 Gy (36 only if bulky)**
- **RT for MALT lymphoma: Stomach- 30 Gy. Other organs 24-30 Gy**
- **RT for early stage mantle cell lymphoma: 30-36 Gy**
- **Consolidation dose in DLBCL following CR to chemotherapy: 30-36 Gy**
  - **RT dose for residual disease (PR) after chemotherapy: 40-50 Gy.**
- **Mini-RT for palliation of advanced-stage low-grade lymphomas (FL, SLL, MZL, MCL): 2 GyX2 (may be repeated)**

[a] References:

Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol 2004;22:3032-3038.

Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-26.

Haas RL, Poortmans P, de Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas, J Clin Oncol 2003;21: 2474-2480.

Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. Cancer 2010;116:3797-3806.

Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. Radiother Oncol 2011;100:86-92.

Goda JS, Gospodarowicz M, Pintilie M, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy Cancer 2010;116:3815-3824.

Phan J, Mazloom A, Medeiros LJ, et al: The benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. J Clin Oncol 2010;28:4170-4176.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Classification

Table 1

WHO Classification of the mature B-cell, T-cell, and NK-cell neoplasms (2008)

Mature B-Cell Neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic lymphoma/leukemia, unclassifiable**
  - *Splenic diffuse red pulp small B-cell lymphoma**
  - *Hairy cell leukemia-variant**
- Lymphoplasmacytic lymphoma
  - Waldenström's macroglobinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT type)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma**
- Follicular lymphoma
  - *Pediatric follicular lymphoma**
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma

Diffuse large B-cell lymphoma (DLBCL), NOS

- T-cell/histiocyte rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- *EBV positive DLBCL of the elderly**
- DLBCL associated with chronic inflammation
- Lymphamatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Continued on next page

*The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

Classification

Table 1 continued

Mature T-Cell and NK-Cell Neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
  - *Chronic lymphoproliferative disorder of NK-cells**
- Aggressive NK cell leukemia
- Systemic EBV positive T-cell lymphoproliferative disorder of childhood
- Hydroa vaccineforme-like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma**
- *Primary cutaneous CD4 positive small/medium T-cell lymphoma**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell lymphoma, ALK positive
- *Anaplastic large-cell lymphoma, ALK negative**

Hodgkin Lymphoma

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

Post-Tranplant Lymphoproliferative Disorders (PTLD)

- Early lesions
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)#
- Classical Hodgkin lymphoma type PTLD#

From Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds): World Health Organization Classification of Tumours of the Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2008.

*The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

#These lesions are classified according to the leukemic or lymphoma to which they correspond.

Staging

Table 2

Cotswolds Modification of Ann Arbor Staging System

Stage	Area of Involvement
I	Single lymph node group
II	Multiple lymph node groups on same side of diaphragm
III	Multiple lymph node groups on both sides of diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease
X	Bulk > 10 cm
E	Extranodal extension or single isolated site of extranodal disease
A/B	B symptoms: weight loss > 10%, fever, drenching night sweats

From: Lister TA, Crowther D, Sutcliffe SB, et al.: Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J of Clin Onc* 1989;7(11): 1630-1636.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells. In the United States, B-cell lymphomas represent 80-85% of the cases with 15-20% being T-cell lymphomas. NK-cell lymphomas are very rare. In 2012, 70,130 new cases of NHL and 18,940 deaths due to the disease are estimated.[1] NHL is the seventh leading site of new cancer cases among men and women, accounting for 4% of new cancer cases and 3% of cancer-related deaths.[1]

The incidence of NHL has increased dramatically between 1970 and 1995; the increase has moderated since the mid-90s. This increase has been attributed partly to the human immunodeficiency virus (HIV) epidemic and the development of AIDS-related NHL. However, much of the increase in incidence has been observed in patients in their sixth and seventh decades; a large part of this increase incidence has paralleled a major decrease in mortality from other causes. The median age of individuals with NHL has risen in the last two decades.[2] As a result, patients with NHL may also have significant comorbid conditions, which complicate treatment options.

The National Comprehensive Cancer Network (NCCN) Guidelines for NHL (the NCCN Guidelines®) were developed as a result of meetings convened by a multidisciplinary panel of NHL experts, with the aim to provide recommendations on the standard diagnostic and treatment approaches based on the current evidence. The NCCN Guidelines and the following discussions focus on the classification of the various subtypes of NHL, immunophenotyping, supportive care considerations, and importantly, the recommendations for diagnostic workup, treatment, and surveillance strategies according to each of the lymphoma subtypes covered in the NCCN Guidelines.

Classification

In 1956, Rappaport et al. proposed a lymphoma classification that was based on the pattern of cell growth (nodular or diffuse), and size and shape of the tumor cells.[3, 4] This classification, though widely used in the Unites states, quickly became outdated with the discovery and the existence of distinct types of lymphocytes (B, T and NK). The Kiel classification became the first and most significant classification that applied this new information to the classification of lymphomas.[5-7] According to the Kiel classification, the lymphomas were divided into low-grade and high-grade based on the histological features. This classification was widely used in Europe. The use of different classification systems in clinical studies made it difficult to compare results from clinical studies. Hence, the International Working

Formulation (IWF) for NHLs was developed to standardize the classification of lymphomas.

International Working Formulation Classification

The IWF classified NHL into three major categories as low, intermediate and high grade, based on the morphology and natural history.[8] This classification divided diffuse large B-cell lymphoma (DLBCL) into intermediate and high grade groups. However, these distinctions were not reproducible. Since this classification did not include immunophenotyping, the categories were not reproducible.[9] In addition, after this classification was published many new diseases were described that were not included in the IWF classification.

Revised European American Classification

In 1994, the International Lymphoma Study Group (ILSG) developed the REAL classification, which classified lymphomas based on the cell of origin (B, T, or NK) and included morphology, immunophenotype, genetic and clinical features to define diseases.[10] In 1997, the International Lymphoma Classification Project performed a clinical evaluation of the Revised European American Classification (REAL) classification in a cohort of 1,403 cases of NHL.[11, 12] The diagnosis of NHL was confirmed in 1,378 (98.2%) of the cases. This study identified the thirteen most common histological types, comprising about 90% of the cases of NHL in the United States. The findings were as follows: DLBCL, 31%; follicular lymphoma (FL), 22%; small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 6%; mantle cell lymphoma (MCL), 6%; peripheral T-cell lymphoma (PTCL), 6%; and mucosa associated lymphoid tissue (MALT) lymphoma, 5%. The remaining subtypes each occurred in less than 2% of cases. Importantly, in the United States more than 50% of cases of lymphoma are either DLBCL or FL. The study investigators concluded that the REAL classification can be readily applied and identifies clinically distinctive types of NHL.

World Health Organization Classification

In 2001, the World Health Organization (WHO) updated the classification of hematopoietic and lymphoid neoplasms.[13, 14] The 2001 WHO classification applied the principles of REAL classification and represented the first international consensus on classification of hematologic malignancies. The REAL/WHO classification of NHL includes many entities not recognized by the IWF.[13, 14] After consideration of cell of origin (B, T, or NK), the classification subdivides lymphomas into those derived from precursor lymphocytes versus those derived from mature lymphocytes. The classification is further refined based on immunophenotype, genetic, and clinical features. These considerations have aided in defining active treatment for specific subtypes of lymphoma.

In 2008, the International T-cell lymphoma Project evaluated the WHO classification of T-cell lymphoma in a cohort of 1,314 cases of PTCL and natural killer/T-cell lymphomas (NKTCL). The diagnosis of PTCL or NKTCL was confirmed in 1,1,53 cases (88%). The most common subtypes were PTCL-not otherwise specified (NOS; 25.9%), angioimmunoblastic lymphoma (18.5%), NKTCL (10.4%), adult T-cell leukemia/lymphoma (ATLL; 9.6%), anaplastic large cell lymphoma (ALCL), ALK-positive (6.6%) and ALCL, ALK-negative (5.5%).[15] The findings of this study validated the utility of the WHO classification for defining subtypes of T-cell lymphomas.

The WHO classification was updated again in September 2008 to add new diseases and subtypes that have been recognized in the past decade, and to better define some of the heterogeneous and ambiguous categories based on the recent advances.[16, 17] Genetic

features, detected by cytogenetics or fluorescence in-situ hybridization (FISH) are increasingly important in defining specific NHL subtypes. In addition, detection of viruses, particularly Epstein-Barr virus, HHV8 and HTLV1, is often necessary to establish a specific diagnosis.

2008 WHO Classification of Mature B-cell Lymphomas

CLL/SLL

The updated classification includes the definition issued by the International Working Group on CLL (IWCLL).[18] The diagnosis of CLL requires the presence of at least 5,000 clonal B lymphocytes/mcL in the peripheral blood. The presence of fewer than 5,000 B-lymphocytes/mcL in the absence of lymphadenopathy, organomegaly or other clinical features is defined as monoclonal B-lymphocytosis (MBL). CLL requiring treatment develops in individuals with CLL-phenotype MBL and with lymphocytosis at the rate of 1.1% per year.[19]

Follicular lymphoma

In FL, pathological grading according to the number of centroblasts is considered to be a clinical predictor of outcome. In the 2001 WHO classification, 3 grades were recommended: FL1, FL2, and FL3; FL3 could be optionally stratified into 3A (centrocytes still present) or 3B (sheets of centroblasts). However, clinical outcomes for patients with FL1 and FL2 do not differ and classification is unreliable. Therefore, in the updated 2008 WHO classification these are grouped into one grade (FL1-2). Hans et al reported that there was no difference in survival between Grade 3A and 3B, whereas patients with FL3 with more than 50% diffuse component have an inferior survival that is similar to the survival of those with DLBCL.[20] FL3B with cytogenetic abnormalities of BCL6 (at 3q27) are thought to be genetically more akin to germinal center type DLBCL than FL1-3A and has a more aggressive clinical course. Patients with FL3B with BCL2 translocation appear to have similar clinical behavior to patients with FL1-3A.[21] Since FL3B is rare, in most studies clinical behavior of FL3 is based mainly on FL 3A cases. The 2008 WHO classification mandates stratifying FL3 into either 3A or 3B. FL is thus still divided into three grades (FL1-2, FL3A and FL3B) based on the number of centroblasts. Any diffuse areas in FL should be given a separate diagnosis of DLBCL, if it meets the criteria for FL3A or 3B.

Pediatric FL, primary intestinal FL, other extranodal FLs and intrafollicular neoplasia ("in situ" FL) are the other variants that are included under FL.

Pediatric follicular lymphoma: Children with FL typically have early stage disease, lack BCL2 expression and the t(14;18). Pediatric FL has a better prognosis than adult FL and is often cured with minimal therapy.

Primary Intestinal follicular lymphoma: FL of the gastrointestinal tract is a recently described entity which is common in the small intestine, with the vast majority occurring in the duodenum. The morphology, immunophenotype, and genetic features are similar to those of nodal follicular lymphoma. However, most patients have clinically indolent and localized disease. Survival appears to be excellent even without treatment.

Other Extranodal Follicular Lymphoma: In many of the other extranodal sites, the morphology, immunophenotype, and genetic features are similar to those of nodal FL. Patients usually have localized disease and systemic relapses are rare.

Intrafollicular Neoplasia or "In situ" Follicular Lymphoma: This is defined as a morphologically normal lymph node or other lymphoid tissues with a few follicles that are BCL2-positive. Some of these

patients are found to have either a history of FL or FL elsewhere in the body and some have no evidence of FL.[22] Intrafollicular neoplasia may represent the nodal equivalent of circulating clonal B-cells that have BCL2 rearrangement, but lack the other genetic abnormalities required for the development of a progressive lymphoma. In some cases, this may represent the earliest evidence of a true FL that will progress to an overt lymphoma. A diagnosis of lymphoma should not be made in such cases, and careful staging and follow-up are recommended; patients should not be treated for lymphoma based on this finding.

Primary cutaneous follicle center lymphoma (PC-FCL)

This is a new category in the 2008 classification and is defined as a tumor of neoplastic follicle center cells, including centrocytes and variable numbers of centroblasts, with a follicular, follicular and diffuse or a diffuse growth pattern. PC-FCL is the most common B-cell lymphoma of the skin and it is classified as a distinct entity in the EORTC classification of cutaneous lymphomas.[23] Gene expression profiling studies have also provided evidence in support of this classification.[24] PC-FCL presents as a solitary or localized skin lesion on the scalp, forehead or the trunk. It is characterized by an indolent course and rarely disseminates to extracutaneous sites. PC-FCL is consistently BCL6-positive, may be CD10-positive in cases with a follicular growth pattern. BCL2 is either negative or dim (predominantly seen in cases with a follicular growth pattern). PC-FCL has an excellent prognosis with a 5-year survival rate of 95%. PC-FCL must be distinguished from primary cutaneous diffuse large B-cell lymphoma, leg type, which is typically IRF4/MUM1+ and strongly BCL2+ and has a more unfavorable prognosis.[25, 26]

Diffuse large B-cell lymphomas (DLBCL)

Some of the new categories of DLBCL are defined by extranodal primary sites and the association with viruses such as EBV or HHV8. Two borderline categories have also been included to incorporate cases in which it is not possible distinguish between adult Burkitt lymphoma (BL) and DLBCL, and primary mediastinal large B-cell lymphoma (PBML) and nodular sclerosis classical Hodgkin lymphoma (NSCHL). The ALK-positive DLBCL, plasmablastic lymphoma and primary effusion lymphoma are considered as distinct entities. The 2008 classification also has new category of large B-cell lymphoma arising in HHV8-associated multicentric Castleman's disease.

DLBCL, not otherwise specified (NOS)

The 2008 classification has included DLBCL, NOS as a new category to include GCB and ABC subtypes as well as other DLBCL cases that do not belong to any of the four specific subtypes (T-cell/histiocyte rich large B-cell lymphoma, primary CNS DLBCL, primary cutaneous DLBCL ("leg type") or EBV+ DLBCL of the elderly).

Gene expression profiling (GEP) has been used to identify distinct subtypes of DLBCL: germinal center B-cell (GCB) subtype, activated B-cell (ABC) subtype, primary mediastinal B-cell lymphoma (PMBL), and type 3 which includes cases that cannot be classified as GCB, ABC, or PMBL subtypes.[27] GEP is not yet recommended for routine clinical use. Immunostaining algorithms have been developed to differentiate between GCB and ABC subtypes using a combination of CD10, BCL6, IRF4/MUM1, GCET1 and FOXP1,[28, 29] and outcome appears improved in GCB patients, though subtype does not impact choice of therapy at the present time.[30-32]

B-cell lymphoma, intermediate between BL and DLBCL

BL is characterized by t(8;14), which results in the juxtaposition of *MYC* gene from chromosome 8 with the immunoglobulin heavy chain variable (IGHV) region on chromosome14 and variant translocations involving *MYC* and the immunoglobulin light chain genes.[33]

Nevertheless, *MYC* translocations also occur in DLBCL. GEP studies have confirmed that the distinction between BL and DLBCL is not reliably reproducible with the use of the current criteria of morphology, immunophenotype, and genetic abnormalities.[34, 35] Mature aggressive B-cell lymphomas without a molecular BL signatures (non-mBL) with *MYC* rearrangements[35] as well as those with both t(8;14) and t(14;18) translocations are associated with a poor prognosis.[36]

This provisional category replaces the "Atypical Burkitt Lymphoma" that was included in the 2001 WHO classification. The new category includes lymphomas with features of both DLBCL and BL, but or biological and clinical reasons should not be diagnosed as DLBCL or BL. Lymphomas in this provisional category include those that are morphologically intermediate between BL and DLBCL with immunophenotype suggestive of BL (CD10-positive, BCL6-positive, BCL2-negative and IRF4/MUM1-negative or weakly positive), lymphomas that are morphologically similar to BL but are strongly BCL2-positive and those with both *MYC* and *BCL2* rearrangements ("double hit") and complex karyotypes.

B-cell lymphoma intermediate between PMBL and NSCHL

PMBL has been recognized as a subtype of DLBCL based on its distinctive clinical and morphological features. NSCHL is the most common form of HL. Both tumors occur in the mediastinum and affect adolescents and young adults. GEP studies strongly support a relationship between PMBL and CHL. About a third of the genes that were more highly expressed in PMBL were also characteristically expressed in CHL cells.[37] Traverse-Glehen, et al., reported borderline cases with biologic and morphologic features of both CHL and B-cell NHL, known as "mediastinal gray zone lymphomas" (MGZL)''.[38]

This provisional category includes lymphomas with overlapping features between CHL and DLBCL, especially PBML. Those cases that morphologically resemble NSCHL have a strong expression of CD20 and other B-cell associated markers. Those cases that resemble PBML may have dim or no expression of CD20, strong expression of CD30 and CD15. These lymphomas have a more aggressive course and poorer outcome than either CHL or PBML.

2008 WHO Classification of Mature T-cell and NK-cell Lymphomas

The 2008 WHO classification has adapted the EOTRC classification for cutaneous T-cell lymphomas.[23] The new categories include primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous aggressive epidermotropic CD9-positive cytotoxic T-cell lymphoma and primary cutaneous small/medium CDE4-positive T-cell lymphoma. Anaplastic large cell lymphoma (ALCL), ALK-negative is now separated out from PTCL-NOS as a provisional entity.

ALCL

ALCL accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: ALCL, ALK-positive, ALCL, ALK-negative and primary cutaneous ALCL. Primary cutaneous ALCL is a distinct subtype of mature T-cell lymphoma. ALK-positive ALCL is most common in children and young adults. It is characterized by the over expression of anaplastic lymphoma kinase (ALK1) protein, resulting from t(2;5) in 40-60% of patients.[39, 40] Although clinically aggressive, it is highly curable with CHOP chemotherapy. The distinction between ALK-positive and ALK-negative ALCL was not required in the 2001 WHO classification. It is now clear that ALK-positive ALCL is a well-defined clinicopathologic entity. The International Peripheral T-Cell Lymphoma

Project reported that patients with ALK-positive ALCL had a superior outcome compared with those with ALK-negative ALCL [5-year failure-free survival (FFS): 60% vs. 36%; and 5-year overall survival (OS): 70% vs. 49%].[41] Contrary to prior reports, ALK-negative ALCL was associated with a better outcome than PTCL-NOS. The 5-year FFS (36% vs. 20%) and OS (49% vs. 32%) were superior compared with PTCL-NOS. A recent analysis from the GELA found that age and beta-2 microglobulin, not ALK1 expression, was the most significant variable in the outcome of ALCL; however, age was very closely associated with ALK1 expression.[42] Patients with primary cutaneous ALCL had a very favorable 5-year OS (90%) despite being negative for ALK1; the 5-year FFS rate was 55%. The findings of this study confirmed that ALK-negative ALCL should be separated from both ALK-positive ALCL and PTCL-NOS.

Based on the recent findings, the 2008 WHO classification has included a provisional category for ALK-negative ALCL. It is morphologically identical to ALK-positive ALCL, with a strong and diffuse expression of CD30, no expression of B-cell antigens and absence of ALK1. The prognosis is intermediate between that of ALK-positive ALCL and PTCL-NOS.

Response Criteria

The International Working Group (IWG) published the guidelines for response criteria for lymphoma in 1999. These response criteria are based on the reduction in the size of the enlarged lymph node as measured by CT scan and the extent of bone marrow involvement that is determined by bone marrow aspirate and biopsy.[43] These guidelines were revised in 2007 by the International Harmonization Project to incorporate IHC, flow cytometry and 18flourodeoxyglucose (FDG)-positron emission tomography (PET) scans in the definition of response for lymphoma.[44] In the revised guidelines, the response category of complete response uncertain (CRu) was essentially eliminated because residual masses were defined as a partial response (PR) or a complete response (CR) based on the result of a PET scan. Using the revised system, response is categorized as CR, PR, stable disease (SD) and relapsed disease or progressive disease (PD). However, the application of PET to responses is limited to histologies where there is reliable FDG uptake in active tumor. However, the revised response criteria have thus far only been validated for DLBCL and Hodgkin lymphoma. The application of the revised response criteria to other histologies requires validation and the original IWG guidelines should be used.

Diagnosis

In all cases, the most important first step is to make an accurate pathologic diagnosis. The basic pathological evaluation is the same in each guideline though some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathological evaluation of the individual guideline.

An incisional or excisional lymph node biopsy is recommended to establish the diagnosis of NHL. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue. Fine needle aspiration (FNA) biopsy is widely used in the diagnosis of malignant neoplasms, but its role in the diagnosis of lymphoma is still controversial.[45, 46] Since the revised REAL/WHO classification is based on both morphology and immunophenotyping, FNA alone is not acceptable as a reliable diagnostic tool for NHL. However, its use in combination with ancillary techniques may provide precise diagnosis thereby obviating the need for a more invasive biopsy in highly selected circumstances. Recent

studies have shown that the diagnostic accuracy of FNA improves significantly when it is used in combination with IHC and flow cytometry.[47-49]

In the NCCN Guidelines, FNA alone is not suitable for an initial diagnosis of NHL, though it may be sufficient to establish relapse. However, in certain circumstances, when a lymph node is not easily accessible, a combination of core biopsy and FNA in conjunction with appropriate ancillary techniques [PCR for *IGHV* and/or T-cell receptor (*TCR*) gene rearrangements; FISH for major translocations; immunophenotypic analysis] may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL. In other entities presenting in leukemic phase, such as FL or MCL, a biopsy is still preferred to clarify histological subtype.

Immunophenotypic analysis is essential for the differentiation of various subtypes of NHL to establish the proper diagnosis. It can be performed by flow cytometry and/or IHC; the choice depends on the antigens as well as the expertise and resources available to the hematopathologist. In some cases flow cytometry and IHC are complementary diagnostic tools.[50] Cytogenetic or molecular genetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of some NHL subtypes or to establish clonality.

Immunophenotyping/Genetic Testing Algorithm

After the publication of the 2008 WHO Classification, the NHL Guidelines panel developed a series of algorithms for the use of immunophenotyping in the diagnosis of mature lymphoid neoplasms. These algorithms should be used in conjunction with clinical and pathological correlation. They were developed to provide guidance for surgical pathologists as well as an aid to the clinician in the interpretation of pathology reports.

The initial assessment begins with morphologic, clinical, and immunophenotypic analysis. Morphologic assessment involves determining the cell size (small cells, medium-sized cells, or large cells), with or without anaplastic morphology. Clinical features include patient's age and the location (nodal, extranodal, and among extranodal sites skin vs. other specific sites). The initial immunophenotyping panel should include Pan-B and Pan-T-cell antigens. Based on the morphologic and clinical features, some of the B-cell and T-cell subset antigens may also be added in the initial panel.

B-cell Lymphomas (expression of one or more B-cell antigens (CD20, Pax5, CD79a, CD19, CD22)

Small cells

In the differential diagnosis of small cell lymphomas [CLL/SLL, mantle cell lymphoma (MCL), hairy cell leukemia (HCL), splenic marginal zone lymphoma, extra- nodal marginal zone lymphoma, nodal marginal zone lymphoma and follicular lymphoma], the panel for immunophenotyping includes CD5, CD10, CD23, cyclin D1, BCL6, BCL2, and may include CD25 and CD103 if HCL is suspected.

Both CLL and MCL are CD5+ B-cell lymphomas. CLL is usually CD5+, CD23+ and cyclin D1-. However, some cases of CLL have an atypical immunophenotype (CD 23 dim or negative). Dysregulated expression of cyclin D1, a cell cycle protein that results from the chromosomal translocation, t(11;14) is seen in the vast majority of cases of MCL.[51, 52] This translocation is not seen in other NHLs though it can be seen in multiple myeloma.

The initial stratification is based on the expression of CD5. If CD5 is positive, confirmatory studies should be done with CD23 and cyclin D1 to differentiate between CLL and MCL. CD23 is often helpful but cyclin D1 expression is the most reliable marker for differentiating between CLL and MCL. Thus, immunophenotypic analysis of cyclin D1 or cytogenetic analysis of t(11;14) using FISH is helpful in confirming the diagnosis of MCL. Rare cases of both cyclin D1 and t(11;14) negative MCL have been reported.[53] This diagnosis should be made with extreme caution and with expert consultation.

If CD5 is negative, then the next stratification is based on CD10. CD10 positivity (which must be confirmed by morphology to be on tumor cells and not on residual reactive or colonized follicles) indicates follicular lymphoma, and this diagnosis can be confirmed further by staining for BCL6, BCL2 and detection of t(14;18) by FISH or PCR, since BCL2 resulting from t(14;18) is over-expressed in 90% of cases of FL.[54] FL is also CD20+, CD5- and cyclin D1-, and nodular aggregates of CD21+ or CD23+ FDC will usually be found. When CD10 is negative, the differential diagnosis includes MZLs, LPL, and HCL; immunophenotypic analysis of CD103 and CD25 can be used to identify HCL. If both are positive, the suggested diagnosis would be HCL, which can be confirmed by the staining of annexin-1 since HCL is characterized by a strong expression of annexin-1.

CD103-negative small B-cell neoplasms can be further stratified by staining for cytoplasmic immunoglobulin light chains. If cytoplasmic light chains are negative the most likely diagnosis is one of the MZLs, which are further classified by a combination of morphological and clinical features (extranodal, nodal, and splenic). If cytoplasmic immunoglobulin is positive, the differential diagnosis includes MZL or lymphoplasmacytic lymphoma (LPL). This distinction is based on a combination of morphology, clinical and laboratory (monoclonal gammopathy) features and may be aided by cytogenetics (deletion 7q in splenic MZL, t(11;18) in some extranodal MZL, vs. deletion 6q in LPL).

Medium-sized cells

For medium-sized cell lymphomas [BL, DLBCL, blastoid variant of MCL, B-cell lymphoma, intermediate between BLBCL and BL (U-DLBCL/BL)], the immunophenotyping panel includes CD5, CD10, BCL2, BCL6, cyclin D1 and Ki-67.

As with small cell lymphomas, the initial stratification is based on CD5. If CD5 is positive, the differential diagnosis is MCL vs. DLBCL and it can be confirmed based on the analysis of cyclin D1, BCL6 and IRF4/MUM1. BCL6 rearrangements associated with various chromosomal translocations involving chromosome 3q27 are observed in about 28-35% of DLBCL.[55] IRF4/MUM1 is an oncogene associated with myeloma, activated as a result of chromosomal translocation, t(6;14) and it is observed in 73% of DLBCLs.[56] Cyclin D1 positivity confirms the diagnosis of blastoid MCL. If cyclin D1 is negative, the diagnosis is confirmed as CD5+ DLBCL, irrespective of the expression of BCL6 and IRF4/MUM1.

If CD5 is negative, the stratification is based on the expression of CD10. If CD10 is positive, the differential diagnosis includes BL vs. U-DLBCL/BL. These can be further stratified by Ki-67, BCL2 and BCL6. BCL6+, BCL2- and Ki-67 (95% or greater) would support the diagnosis of BL especially in pediatric cases. In adults, when BL is suspected, FISH for MYC, BCL2 and possibly BCL6 should be done to confirm the presence of MYC rearrangement and assess for the presence of a dual rearrangement of MYC and BCL2 (double hit), particularly if BCL2 is expressed.[54] If MYC is positive and BCL2 and BCL6 are not rearranged, one may make a diagnosis of BL. If BCL2

or BCL6 is rearranged, with or without MYC, the diagnosis could be U-DLBCL/BL. CD10-negative medium-sized B-cell neoplasms generally fall into the category of U-DLBCL/BL. If both BCL2 and BCL6 are positive by IHC, FISH for MYC, BCL2 and BCL6 should be done to check for double hit U-DLBCL/BL, which have a poor prognosis.

Large cells

DLBCL-NOS and the newly described subtypes of DLBCL as well as the pleomorphic variant of MCL are characterized by large cells. The immunophenotyping panel for large cell lymphomas includes CD5, CD10, BCL6, and IRF4/MUM1 The first stratification is based on the expression of CD5. If CD5 is positive, cyclin D1 expression should be assessed to distinguish between pleomorphic MCL and CD5+ DLBCL, NOS, which has a variable expression of BCL6 and IRF4/MUM1. If CD5 is negative, the differential diagnosis is DLBCL which can be stratified again based on the expression of CD10. CD10 positivity confirms the diagnosis of DLBCL, NOS (GCB subtype). If CD10 is negative, confirmatory studies can be done with BCL6 and IRF4/MUM1 to differentiate GCB subtype (BCL6+ and IRF4/MUM1-) from non-GCB subtypes. For clinical purposes, it is not necessary to distinguish between GCB and non-GCB subtypes. Recently described DLBCL subtypes (EBV+ DLBCL of the elderly, DLBCL associated with chronic inflammation, ALK1+ DLBCL, plasmablastic lymphoma) often have immunophenotypic profiles consistent with non-GCB origin; therefore, non-GCB immunophenotype should prompt further analysis to detect these subtypes in the appropriate clinical setting.

Additional markers (CD20, PAX5, CD30, ALK1, CD138 and cytoplasmic immunoglobulin, as well as detection of HHV8 and EBV) may be useful for the further classification of large B-cell lymphomas. In a tumor that is positive for both CD20 and PAX5, CD30 positivity supports the diagnosis of PMBL. If CD30 is positive and the morphology overlaps with CHL, CD15 may be helpful: if it is positive, this supports either U-DLBCL/CHL or CHL, depending on the morphologic features. Absence of CD15 would support PMBL. Absence of both CD20 and PAX5 and expression of IRF4/MUM1 and CD138 suggest terminal B-cell differentiation, and the differential diagnosis would include ALK-positive DLBCL, plasmablastic lymphoma and primary effusion lymphoma. ALK-positive DLBCL is characterized by the expression of ALK protein and absence of CD30. It has an aggressive clinical course and poor outcome.[57] If ALK is negative, the stratification is now based on the staining for EBV and HHV. EBV+ and HHV8- indicate plasmablastic lymphoma. Primary effusion lymphoma is HHV8+ with or without EBV and is CD30+. DLBCL associated with HHV8+ multicentric Castleman's disease is CD20+/-, HHV8+ and has characteristic morphologic features. Many of these DBLCL subtypes have plasmacytic differentiation, and will have detectable cytoplasmic immunoglobulin.

Cutaneous B-cell lymphomas

In the WHO classification, three main types of primary cutaneous B-cell lymphomas are recognized: PC-FCL, PC-DLBCL, leg type, and primary cutaneous MZL (PC-MZL). PC-MZL express CD20 and BCL2 but are negative for CD5, CD10 and BCL6.[58] PC-FCL, which is an indolent disease, has a germinal center phenotype; whereas, most PC-DLBCL, leg type which is an aggressive tumor, have an activated B cell phenotype.[59]

The immunophenotyping panel includes CD10, BCL2, BCL6, IRF4/MUM1 and follicular dendritic cell (FDC) markers (CD21 or CD23) to detect neoplastic follicles or colonized germinal centers. Initial stratification is based on CD10. CD10 positivity on the neoplastic cells indicates PC-FCL; however, many cases of PC-FCL

are CD10-. If CD10 is negative, the differential diagnosis is based on the expression of BCL2. BCL-2 is usually negative in PC-FCL but strongly expressed in PC-DLBCL. When BCL2 is negative, immunophenotypic analysis of BCL6 and IRF4/MUM1 is necessary to distinguish between PC-FCL and PC-MZL. PC-FCL is consistently BCL6-positve and IRF4/MUM1-negative, whereas PC-MZL is BCL6-negative and IRF4/MUM1 can be either positive or negative. If BCL2 is positive, IRF4/MUM1 is helpful to differentiate between PC-FCL and PC-DLBCL, leg type, since PC-FCL is usually IRF4/MUM1-negative while PC-DLBCL, leg type is usually IRF4/MUM1-positive.

T-cell Lymphomas (expression of one or more pan-T antigens (CD2, CD3, CD5, CD7, CD43, CD45RO)

T-cell lymphomas (anaplastic morphology)

In cases with anaplastic morphology, the immunophenotyping panel includes CD30, CD15, PAX5, ALK, EBV-EBER. ALCL has a strong, diffuse expression of CD30. If CD30 is positive, evaluation of ALK1 status is used to identify ALK-positive ALCL. If ALK1 is negative, analysis of CD15 and PAX5 are essential in the differential diagnosis of non-cutaneous ALK-negative ALCL and CHL. ALK-negative ALCL is PAX5-negative whereas CHL typically shows expression of CD15 as well as dim expression of PAX5.

Cutaneous T-cell lymphomas (non-anaplastic morphology)

Mycosis fungoides (MF) and Sezary syndrome (SS) are the most common types of cutaneous T-cell lymphomas (CTCLs) lacking anaplastic morphology. Primary CTCLs are very rare. In the WHO classification, three rare provisional entities are included under primary CTCL- primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (AECTCL) and primary cutaneous CD4-positive small/medium T-cell lymphoma.

The immunophenotyping panel for the diagnosis of cutaneous T-cell lymphomas includes CD2, CD5, CD7,CD4, CD8, CD30, CD56, βF1, cytotoxic granule proteins (CGP). Initial stratification can be based on CD30. Strong and uniform CD30 positivity favors primary cutaneous CD30-positive T-cell lymphoproliferative disorders (LPD), even if the morphology is not obviously anaplastic; however some CD30+ cells can be seen in MF and ATLL. In an epidermotropic cutaneous T-cell lymphoma, if CD30 is negative, then the differential diagnosis is based on the expression of CD4 and CD8. If CD4 is positive, then the differential diagnosis is MF/SS vs. adult T-cell leukemia and lymphoma (ATLL). ATLL and MF/SS both lack CGP. ATLL is CD25+ while MF/SS is CD25-; it is suggested by epidemiologic factors and can be confirmed by serologic testing for HTLV1. If CD4 is negative and CD8 is positive, then the diagnosis is more likely AECTCL which has an aggressive clinical course.[60] Since a minority of MF cases can be CD30+, CD4 - and CD8 +/-, AECTCL should be confirmed further by its characteristic immunophenotype (CD4-, CD3+, CD8+, CD5- and CD45RO-). Cutaneous gamma-delta T-cell lymphoma may be epidermotropic, but typically also involves dermis and subcutis; is typically CD4- CD8- CD5- CD56+, but may express CD8. Staining for βF1 is negative, and CGP are strongly expressed. Subcutaneous panniculitis-like T-cell lymphoma is typically CD3+ CD7+ CD8+ βF1+ and expresses CGP.

Nodal localization (non-anaplastic morphology)

Angioimmunoblastic T-cell lymphoma (AITL), ATLL and PTCL-NOS are included in this category, as well as small cell variants of ALCL. The immunophenotypic panel includes CD5, CD4, CD8, CD30, ALK1, CD10, BCL6, PD1, CD21, CD23 and EBV-EBER. Follicular helper T

cell markers CD10, BCL6, PD1, and CD4 are helpful to differentiate between AITL and PTCL-NOS and ATLL. The initial stratification is based on ALK and CD30 expression. If CD30 and ALK are negative and CD10, BCL6, PD1 and CD4 are positive, the likely diagnosis is AITL; this can be confirmed by detection of FDCs expressing CD21 and CD23, and typically some EBV+ large B cells. If follicular helper T cell markers are absent, the differential diagnosis includes ATLL and PTCL-NOS; expression of CD25, clinical features and assessment for HTLV1 antibodies can confirm the diagnosis of ATLL.

Extranodal non-cutaneous localization (non-anaplastic morphology)

Extranodal NK T-cell lymphoma (ENKTCL), nasal type, enteropathy-associated T-cell lymphoma (EATL), hepatosplenic T-cell lymphoma (HSTCL), extranodal involvement by PTCL-NOS and ALCL, ALK+ small-cell histiocyte-rich variants are included in this category. The differential diagnosis will be affected by the specific clinical presentation. Initial stratification may be based on the EBV EBER status. If EBER is positive, ENKTCL is suggested and can be confirmed by CD56 expression. If EBER is negative, the differential diagnosis may include EATL, HSTCL, ALCL, ALK+ small-cell histiocyte-rich variants and extranodal PTCL-NOS, depending on the clinical features. The stratification can then be based on the expression of CD30 and ALK1. If ALK is negative, expression of βF1, CD4, CD5, CD8, and CD30 may be useful in further classification: EATL is βF1+ CD30+ CD56-/+, while HSTCL is usually βF1-, CD30-, and is CD56+.

Workup

Essential workup procedures include a complete physical exam with particular attention to node bearing areas and the size of liver and spleen, symptoms present, performance status, laboratory studies including CBC, serum lactate dehydrogenase (LDH), hepatitis B virus testing (see below), comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless co-existent renal insufficiency). MUGA scan or echocardiograms are recommended when anthracyclines and anthracenedione containing regimens are used. Bone marrow biopsy with or without aspirate is essential in all cases where treatment is considered; however, there are circumstances where it may be deferred (see below). Due the risk of hepatitis B reactivation, the panel has included hepatitis B testing (hepatitis B surface antigen and hepatitis B core antibody) as part of essential workup prior to initiation of treatment in all patients who will receive anti CD20 monoclonal antibody-based regimens. Furthermore, hepatitis B reactivation has been reported with chemotherapy alone and testing should be considered in anyone with a risk factor (e.g. blood transfusion, IV drug abuse) or if from a region with a non-negligible prevalence of hepatitis B infection (see Discussion section on "Hepatitis B Reactivation" in the Supportive Care section below). Hepatitis C testing is needed in high-risk patients and patients with splenic marginal zone lymphoma.

Optional procedures (depending on specific lymphoma type) include beta-2-microglobulin, CT or PET-CT scans, endoscopic ultrasound (gastric MALT lymphoma), head CT or brain MRI and lumbar puncture to analyze cerebrospinal fluid (MCL and DLBCL). Discussion of fertility issues and sperm banking should be addressed in the appropriate circumstances.[61]

Bone marrow biopsy is usually included in the workup for all patients with NHL with the exception of SLL/CLL when there is a clonal lymphocytosis identified by flow cytometry. Bone marrow involvement occurs in 39% of low-grade, 36% of intermediate grade and 18% of high-grade lymphomas. Bone marrow involvement was associated

with significantly shorter survivals in patients with intermediate or high-grade lymphomas.[62] In a recent retrospective analysis, the incidence of bone marrow involvement and the parameters predicting bone marrow involvement were analyzed in 192 patients with stage I and II in DLBCL. Overall incidence of BM involvement was 3.6%. The authors concluded that bone marrow biopsy may be safely omitted in selected patients with early stage DLBCL.[63] In cutaneous B-cell lymphomas, bone marrow biopsy is essential for PC-DLBCL, leg type since this is an aggressive lymphoma that will probably require systemic treatment, whereas the role of bone marrow biopsy in the PC-FCL and PC-MZL is less clear. Recent studies have indicated that bone marrow biopsy is an essential component of staging in patients with PC-FCL first presenting in the skin, whereas it appears to have limited value in patients with MZL presenting in the skin, and may be considered only in selected cases.[64, 65]

In the NCCN Guidelines, bone marrow biopsy with or without aspirate is included as part of essential workup for all lymphomas. However, in patients with low bulk indolent disease with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if observation is recommended as it will not change the clinical recommendations. However, in the evaluation of potentially early stage indolent lymphoma (stage I or II), bone marrow biopsy is essential; some panel members advocate bilateral core biopsies in this situation.[66] Bilateral cores are recommended if radioimmunotherapy is considered.

FDG-PET scan has been used for initial staging, restaging and follow-up of patients with NHL.[67] In a recent meta-analysis, PET showed a high positivity and specificity when used for the staging and restaging of patients with lymphoma.[68] FDG-PET is nearly universally positive at diagnosis in Hodgkin lymphoma, DLBCL, and follicular lymphoma,[69] about 90% in T-cell lymphoma[70] and nodal MZL but less sensitive for extra-nodal MZL.[71] However, a number of benign conditions including sarcoid, infection, and inflammation can result in false-positive PET scans complicating the interpretation. Lesions smaller than 1 cm are not reliably visualized with PET scans. PET scan is now part of pre-treatment evaluation in Hodgkin lymphoma and DLBCL and may be useful in selected cases in other histologies. The pre-treatment PET is particularly important to aid in the interpretation of post-treatment response evaluation according to new response criteria (see above). Although PET scans may detect additional disease sites at diagnosis, the clinical stage is modified only in 15-20% of patients and a change in treatment in only 8% of patients. PET scan has generally been used in conjunction with diagnostic CT scans.

Integrated PET-CT as a largely replaced the dedicated CT scans in the United States. This diagnostic study has distinct advantages in both staging and restaging compared to full dose diagnostic CT or PET alone.[72, 73] In a retrospective study, PET-CT performed with low-dose non-enhanced CT was found to be more sensitive and specific than the routine contrast-enhanced CT in the evaluation of lymph node and organ involvement in patients with Hodgkin disease or high-grade NHL.[73] Preliminary results of another recent prospective study (47 patients; patients who had undergone prior diagnostic CT were excluded) showed a good correlation between low-dose unenhanced PET-CT and full-dose enhanced PET-CT in the evaluation of lymph nodes and extranodal disease in lymphomas.[72] However, the lack of intravenous contrast and the diminished resolution can make it difficult in some cases to interpret the anatomical localization and significance of FDG-avid sites. Further studies are needed to determine if PET-CT scans can replace diagnostic CT scans in the initial staging and response evaluation of

lymphomas. The panel has included PET-CT scan as an optional workup procedure for selected patients.

Supportive Care

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation has been reported to occur in patients treated with chemotherapy with or without anti-CD20 monoclonal antibody; treatment with rituximab alone is also a risk for hepatitis B reactivation.[74] HBV reactivation may result in a fulminant hepatitis, hepatic failure, and death. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab (See rituximab package insert at www.fda.gov).

Testing of patients at risk for hepatitis B reactivation should include: hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). In a prospective study of all patients receiving immunosuppressive (chemotherapy, antibody therapy, high dose dexamethasone) therapy at MSKCC, 1% of patients were HBsAg positive and 9% were HBcAb positive.[75] A retrospective study conducted by MDACC also reported similar findings (HBsAg and HBcAb were positive in 2% and 8% of patients, respectively).[76] Patients positive for HBsAg are at a greater risk for HBV reactivation than those positive for HBcAb.[74] In a prospective study of 100 Chinese patients receiving chemotherapy for lymphoma, hepatitis developed in 67% of HBsAg positive patients and 14% HBsAg negative patients during cytotoxic therapy.[77] Other risk factors for reactivation include young age, male gender, elevated pretreatment viral load and prolonged immunosuppression.[78, 79] The use of rituximab in HBcAb positive patients has been reported to cause fatal HBV-related liver disease. A retrospective study of Italian HBcAb positive patients with lymphoma found that 2.7% of patients treated with rituximab and chemotherapy developed HBV-related liver disease compared to 0.8% of patients treated with chemotherapy alone. HBV-related liver disease was not seen in patients who were observed or received other therapy (radiation, antibiotics, interferon).[80]

Anti-viral prophylaxis has been effective in the prevention of hepatitis B reactivation during chemoimmunotherapy in HBsAg positive patients.[81-83] The results of a systematic review of 14 studies involving HBsAg positive patients receiving chemotherapy showed that lamivudine prophylaxis for HBsAg positive patients undergoing chemotherapy reduced the risk for HBV reactivation by ≥79%; HBV-associated hepatic failure and death may also be reduced.[81] None of the patients in the preventive lamivudine group developed HBV-related hepatic failure compared to 21 of 162 patients in the control group, and only 4 deaths were attributable to HBV in the preventive lamivudine group compared to 27 deaths in the control group. Lamivudine was well tolerated with no adverse effects. In a small randomized study, Lau et al demonstrated that pre-emptive antiviral treatment with lamivudine was superior to deferred treatment.[84] This study randomized 30 HBsAg positive lymphoma patients to receive lamivudine before chemotherapy or to receive lamivudine for the treatment of increased viral load based on HBV DNA PCR levels. HBV reactivation was observed in 53% of monitored patients and none in the prophylaxis group. Interestingly, clinical cancer-related outcomes were also significantly better in the prophylaxis group than the treatment group.

The NCCN Guidelines recommend HBsAg and HBcAb testing for all patients planned for treatment with rituximab-containing regimens. In patients for who one or both of these tests are positive, a baseline hepatitis B viral load should be determined by quantitative PCR. However, a negative baseline PCR does not preclude the possibility

of activation. In patients from areas with high prevalence (Asia, Africa, Eastern Europe, and portions of South America) or regions where the prevalence of HBV is not known, all patients receiving immunotherapy, chemotherapy, or chemoimmunotherapy should be tested for HBsAg and HBcAb. Patients receiving intravenous immunoglobulin (IVIG) may be HBcAb positive as a consequence of IVIG therapy. Empiric antiviral therapy with oncologic treatment is recommended for any patient who is either HBsAg or HBcAb positive. During the treatment period, viral load should be monitored monthly with PCR and 3 months thereafter. Patients receiving chemotherapy alone should receive prophylaxis if they have a measurable viral load independent of the viral serology. If viral load is consistently undetectable, prophylaxis should be given to HBsAg positive patients and may be considered in patients who are HBcAb positive. If viral load fails to drop, consultation with a hepatologist is recommended. However, because of the potential emergence of resistance to lamivudine, it is not the optimal drug for prophylaxis. There are a number of appropriate anti-viral agents for prophylactic measures; the optimal choice will be driven by institutional standard or recommendation from the consultant. The appropriate duration of prophylaxis remains undefined, but the NCCN Guidelines panel recommended it should be maintained for at least 6 months after the completion of oncologic treatment.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a serious and usually fatal CNS infection caused by JC polyoma virus. In a recent report of 57 cases from the Research on Adverse Drug Events and Reports project, 52 patients with lymphoproliferative disorders developed PML after treatment with rituximab and other treatments which included hematopoietic stem cell transplantation or chemotherapy with purine analogs or alkylating agents.[85] Median time from last rituximab dose to PML diagnosis was 5.5 months. Median time to death after PML diagnosis was 2.0 months. The case fatality rate was 90%.

PML is usually diagnosed with PCR of cerebrospinal fluid (CSF) or sometimes brain biopsy. There is no effective treatment for PML. Patients need to be carefully monitored for the development of any neurological symptoms. There is currently no pretreatment evaluation that can be undertaken to predict for the subsequent development of PML.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by metabolic abnormalities caused by the abrupt release of intracellular contents into the blood resulting from cellular disintegration induced by chemotherapy. It is usually observed within 12 to 72 hrs after start of chemotherapy.[86] Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and death.

Cairo and Bishop have recently classified TLS into laboratory TLS and clinical TLS. Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels.[87] Clinical TLS refers to laboratory TLS with clinical toxicity that requires intervention. Clinical complications may include renal insufficiency, cardiac arrhythmia, or seizures. The four primary electrolyte abnormalities of TLS are hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Symptoms associated with TLS may include nausea and vomiting, diarrhea, seizures, shortness of breath, or cardiac arrhythmias.

TLS is best managed if anticipated and treatment started prior to chemotherapy. The cornerstone of the management of TLS is hydration and the control of hyperuricemia. Allopurinol should be administered prior to the initiation of chemotherapy. In cases where the uric acid level remains elevated despite treatment with allopurinol or there is renal insufficiency treatment with rasburicase is indicated. Electrolytes and renal function should be monitored every 6-8 hours with appropriate interventions for hyperkalemia and hyperphosphatemia. Careful clinical monitoring will help to preempt complications and in many cases admission to ICU is appropriate. Cardiac monitoring or serial ECG may be beneficial to identify early electrolyte related cardiac abnormalities. Dialysis may be necessary in cases of anuric acute renal failure.

Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase thereby blocking conversion of purine metabolites to uric acid. Allopurinol will decrease the formation of uric acid production and has been shown to reduce and reduce the incidence of uric-acid uropathy.[88] Since the drug inhibits new uric acid formation rather than to reduce existing uric acid, it can take several days for elevated levels of uric acid to normalized after the initiation of treatment thereby delaying the start of chemotherapy. Furthermore, allopurinol may lead to the accumulation of xanthine crystals in renal tubules leading to acute obstructive uropathy. Allopurinol will also reduce clearance of 6-mercaptopurine and high-dose methotrexate.

Rasburicase is recombinant urate oxidase which catalyzes the oxidation of uric acid to a highly soluble non-toxic metabolite that is readily excreted. It has been shown to be safe and highly effective in the prevention and treatment of chemotherapy-induced hyperuricemia in both children and adults.[89] The GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte) trial on rasburicase activity in adult patients with lymphoma evaluated the efficacy and safety of rasburicase for the prevention and treatment of hyperuricemia in patients with NHL during induction chemotherapy.[90] Uric acid levels decreased within 4 hours after the first injection of the drug. Creatinine levels and other metabolites were also controlled with the administration of rasburicase.

Cortes et al recently reported the results of a prospective, randomized controlled trial which compared the efficacy of rasburicase and allopurinol in adult patients with hematological malignancies at high or potential risk for TLS.[91] The plasma uric acid response rate was 87% for rasburicase, 78% for rasburicase plus allopurinol arm and 66% for allopurinol. Rasburicase was superior to allopurinol in the overall study population as well as in patients at high risk TLS (89% vs. 68%) and in patients with baseline hyperuricemia (90% vs. 53%). The time to control serum uric acid in hyperuricemic patients was 4 h for rasburicase and 27 h for allopurinol. However, rasburicase can induce anaphylactic reactions. Other adverse reactions include methemoglobinemia and severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The risk factors for TLS include bone marrow involvement, bulky tumors that are chemosensitive, rapidly proliferative or aggressive hematologic malignancies, an elevated leukocyte count or pretreatment lactate dehydrogenase (LDH), pre-existing elevated uric acid, renal disease or renal involvement of tumor. Patients diagnosed with lymphoblastic lymphoma or Burkitt lymphoma are at a higher risk of developing TLS. Occasionally, patients with bulky presentation of DLBCL and patients with CLL and high white blood cell count may experience TLS at a moderately high frequency.

The NCCN Guidelines recommend that allopurinol be started 2−3 days prior to chemotherapy and continued for 10−14 days. Rasburicase is recommended for patients with any of the following risk factors: presence of any high risk feature; bulky disease requiring immediate therapy; patients in whom adequate hydration is not possible; allopurinol is ineffective; or acute renal failure. One dose is adequate in most cases; repeat dosing should be individualized.

The NCCN Guidelines®

The National Comprehensive Cancer Network (NCCN) Guidelines for NHL (the NCCN Guidelines) were developed for the most common subtypes of NHL:

- **Mature B-cell lymphomas**
  - Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
  - Hairy cell leukemia (HCL)
  - Diffuse large B-cell lymphoma (DLBCL)
  - Burkitt lymphoma (BL)
  - AIDS-related B-cell lymphoma
  - Primary Cutaneous B-cell Lymphomas
  - Follicular lymphoma (FL)
  - Marginal Zone lymphomas (MZL)
    - Extranodal MZL of mucosa associated lymphoid tissue (MALT lymphoma)
      - Gastric MALT lymphoma
      - Non-gastric MALT lymphoma
    - Nodal MZL
    - Splenic MZL
  - Mantle cell lymphoma (MCL)
- **Precursor B-cell/T-cell lymphomas**
  - Lymphoblastic lymphoma
- **Mature T-cell and NK-cell lymphomas**
  - Peripheral T-cell lymphoma (PTCL)
  - Mycosis fungoides (MF) and Sezary syndrome(SS)
  - Adult T-cell leukemia/lymphoma (ATLL)
  - Extranodal NK/T-cell lymphomas, nasal type (ENKL)
  - T-cell prolymphocytic leukemia (T-PLL)
- **Post-transplant lymphoproliferative disorders (PTLD)**

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

CLL/SLL comprises approximately 7% of newly diagnosed cases of NHL.[11] CLL remains the most common adult leukemia in Western countries whereas it is considered rare in areas such as East Asia. In the U.S. alone, 14,570 new cases of CLL and 4,380 deaths were estimated in 2011.[92] Morphologically, the leukemic cells appear as small, mature lymphocytes that may be found admixed with larger or atypical cells, cleaved cells, or prolymphocytes.[18] CLL is characterized by progressive accumulation of these leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. CLL and SLL are different manifestations of the same disease and are managed in much the same way.[93] The major difference is that in CLL, a significant number of the abnormal lymphocytes are also found in the bone marrow and blood, while in SLL the abnormal lymphocytes are predominantly found in the lymph nodes.

Diagnosis

The diagnosis of CLL requires the presence of at least 5000 clonal B-cells/mcL in the peripheral blood.[18] The presence of fewer B-cells in the absence of lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder is defined as monoclonal B-lymphocytosis (MBL). MBL is a relatively recent diagnostic category describing individuals who present with an abnormal B-cell population but do not meet the diagnostic criteria for CLL.[94] Most cases of MBL have the immunophenotype of CLL (see below). Favorable molecular lesions, mutated immunoglobulin heavy-chain variable region gene (*IGHV*) and chromosomal abnormality del(13q), are commonly seen in patients with MBL.[19] The estimated rate of progression of MBL to CLL requiring treatment was 1.1% per year. To distinguish MBL from SLL, evaluation with CT scan is essential. The CLL/SLL guideline now includes an initial stratification between CLL/SLL and MBL (absolute B-lymphocyte count of less than 5000/mcL, lymph nodes less than 1.5 cm, no anemia or thrombocytopenia). Observation is recommended for all patients diagnosed with MBL. The diagnosis of SLL requires the presence of no more than 5000 B-lymphocytes/mcL in the peripheral blood, and the presence of lymphadenopathy and/or splenomegaly.[18]

Adequate immunophenotyping using flow cytometry of peripheral blood or paraffin-section immunohistochemistry is required to confirm the diagnosis of CLL/SLL. Recommended panel for immunohistochemistry include CD3, CD5, CD10, CD20, CD23 and cyclin D1. These can be useful, particularly for diagnosing CLL/ SLL type without circulating cells. Cell surface markers for flow cytometric studies include kappa/lambda, CD19, CD20, CD5, CD23 and CD10. Additional paraffin-embedded material may be used for immunophenotyping to determine lineage and clonality.

The typical immunophenotype includes CD5+, CD10-, CD19+, CD20 dim, surface immunoglobulin dim, CD23+, CD43+/-, and cyclin D1-. Distinguishing CLL/SLL from mantle cell lymphoma (MCL) is essential, as they are both CD5+ B-cell tumors. Though CD23 is often helpful, cyclin D1- is critical in this differentiation of tumor types. Stimulated cytogenetics or fluorescence in situ hybridization (FISH) for t(11;14) can help to distinguish MCL from CLL. FISH for detection of del(11q), del(13q), trisomy 12 and del(17p) and molecular genetic analysis to detect *IGHV* mutation status can provide useful prognostic information and may guide selection of therapy (see Discussion section below for 'Prognostic Factors'). Though FISH is optional for patients with Rai low risk disease where observation would be recommended, it should be evaluated at the time therapy is considered. Cytogenetic abnormalities can evolve over time; therefore, re-evaluation of FISH is necessary to direct treatment options in patients with indications for treatment. CD38 and/or zeta-associated protein 70 (ZAP-70) expression can be determined using immunohistochemistry or flow cytometry. However, evaluation of ZAP-70 expression (especially by flow cytometry) can be challenging and is not recommended outside the context of clinical trials.

Conventional metaphase cytogenetics is difficult in CLL as a result of the very low proliferative activity of the leukemic cells in vitro. Therefore, interphase cytogenetic analysis with FISH has been the standard method to detect chromosomal abnormalities that may have prognostic significance. However, FISH can only detect abnormalities specific to the probes utilized. Cytokine or CpG oligonucleotide stimulation has been utilized to promote efficient metaphase analysis.[95] Recent studies have demonstrated that stimulation with CpG oligonucleotide and interleukin-2 is more effective than that with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) for the detection of

chromosomal abnormalities in CLL.[96, 97] A prospective study conducted by CLL Research Consortium confirmed that abnormal clones in CLL are more readily detected with CpG oligonucleotide stimulation than with traditional B-cell mitogens; moreover, the clonal abnormalities revealed by CpG stimulated metaphase cytogenetics are consistent with that detected by interphase FISH and are reproducible among different cytogenetic laboratories.[98] However, the use of CpG stimulation for CLL cytogenetics is not yet universally available.

Prognostic Factors

During the past decade, numerous factors have been identified and evaluated in patients with CLL, which may provide useful prognostic information beyond clinical staging (see Discussion section below for 'Staging'). These factors include serum markers such as thymidine kinase and beta-2 microglobulin (β_2M), genetic markers including *IGHV* mutational status and cytogenetic abnormalities detected by FISH (e.g., del(13q), del(11q), del(17p)), CD38 expression, and ZAP-70 expression.[99-110]

IGHV mutational status is an important predictor of survival outcomes in CLL; unmutated *IGHV* (≥98% homology with germline gene sequence) is associated with poor prognosis and significantly decreased survival compared with cases with mutated *IGHV*, irrespective of the stage of the disease.[100, 105] In addition, *IGHV* rearrangements involving the *VH3-21* gene is associated with poor outcomes regardless of the mutation status (as defined by percent homology with germline sequence).[111] Unmutated *IGHV* or the use of *VH3-21* has been shown to be independent predictors of treatment-free intervals and/or survival outcomes, even when high-risk genomic abnormalities (see Discussion below on cytogenetic abnormalities detected by FISH) were included in the multivariable regression models.[112-115]

Expression of CD38 (≥7% of B lymphocytes)[100, 101, 107, 113, 114, 116] and/or ZAP-70 (≥20%of B lymphocytes)[99, 108-110, 117] are also associated with shorter progression-free survival and overall survival outcomes. Both CD38 and ZAP-70 positivity correlate with unmutated *IGHV*, and have been suggested as potential surrogate markers for *IGHV* mutational status.[99, 100, 110] However, discordant results between CD38 positivity and *IGHV* mutational status have been observed in up to 28% of patients in one study; moreover, CD38 expression levels may vary over the course of the disease.[106] Similarly, discordant results between ZAP-70 positivity and *IGHV* mutational status have been reported in 20-25% of cases.[109, 114] In addition, it has been suggested that ZAP-70 positivity may be a stronger predictor of outcomes (e.g., time to first treatment) than *IGHV* mutational status or CD38 levels.[109, 117, 118] It should be noted, however, that standardization and reproducibility of ZAP-70 flow cytometry methods across laboratories remains a challenge.

Elevated levels of serum beta-2 microglobulin (β_2M) have been shown to be a strong independent prognostic indicator for treatment-free intervals, response to treatment, and overall survival, including in patients treated with first-line chemoimmunotherapy regimens.[119-121] One of the advantages of β_2M is that it is readily measured by standard laboratory evaluations of blood samples. Wierda et al developed a prognostic nomogram using clinical and laboratory parameters that are available in the routine clinical practice setting (age, β_2M, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes); the nomogram was developed to estimate the median survival time, as well as the probability of 5-year and 10-year survival. In addition, based on the sum of points assigned to the six

parameters used for the nomogram, a more simplified prognostic index was developed to help stratify untreated patients with CLL into three different risk groups (low, intermediate and high).[122] The estimated median survival was not reached for the low-risk group. The median survival times for intermediate- and high-risk groups were 10 and 5 years, respectively. The 5-year survival rates were 97% for low-risk, 80% for intermediate-risk, and 55% for high-risk groups; the 10-year survival rates were 80%, 52%, and 26%, respectively.[122] It should be noted that sufficient data were not available for recently identified prognostic factors (e.g., *IGHV* mutational status, ZAP-70, cytogenetic abnormalities detected by FISH) to be incorporated into the prognostic model. Nevertheless, several studies have independently confirmed the utility of this prognostic index in estimating both survival probability and time to first treatment in previously untreated patients with CLL, including in patients with early-stage (Rai stage 0) disease.[123, 124]

Cytogenetic abnormalities that can be detected by FISH are present in about 80% of patients with previously untreated CLL. The most common abnormality is del(13q) (55%) followed by del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%).[102] Del(13q) is associated with a favorable prognosis and the longest median survival (133 months). Del(11q) is often associated with extensive lymphadenopathy, disease progression and shorter median survival (79 months).[102, 125] Among patients with del(11q), those with a complete loss of *ATM* function might have impaired response to irradiation or cytotoxic drugs, resulting in poor clinical outcome.[126] Recent studies showed that previously untreated patients with del(11q) respond well to combination therapy with fludarabine and cyclophosphamide (FC), suggesting that the addition of an alkylating agent to fludarabine may help to overcome the adverse prognostic significance of del(11q) in patients with CLL.[114, 127] Del(17p), which frequently results in abnormalities of a key tumor suppressor gene*TP53*, is associated with worst outcomes, with short treatment free intervals, short median survival (32 months), and poor response to chemotherapy.[102] The phase III randomized CLL8 study of the German CLL Study Group (first-line FC vs. rituximab combined with FC [FCR]) showed that both del(17p) and unmutated *IGHV* were significant independent predictors of poor survival outcomes, irrespective of the treatment arm.[128, 129] The prognostic importance of del(17p) may be dependent on the proportion of malignant cells with this abnormality. In the UK CLL4 trial (comparing first-line therapy with chlorambucil vs. fludarabine vs. FC), similar outcomes were observed between patient subgroups with 5-10% of cells with *TP53* deletion (i.e., del(17p13.1)) and the subgroup without *TP53* deletion (deletion in <5% of cells); patients with 10-20% *TP53* deletion had outcomes similar to patients with >20% *TP53* deletion.[114, 130] Patients with ≥10% cells with *TP53* deletion had a poor outcome with 29% response rate (6% complete or nodular partial response) and a median survival of <6 months.[114] The finding that del(17p) is more frequently observed in treated patients than in untreated patients suggests that treatment-driven clonal selection may occurs during therapy. Indeed, acquisition and/or expansion of CLL clones with del(17p) have been observed during the course of treatment.[131]

Abnormalities of *TP53* can be observed in the absence of del(17p).[132, 133] Studies with fludarabine-based regimens have identified *TP53* mutations as an independent predictor of decreased survival and resistance to chemotherapy.[132-135] The resistance to chemotherapy has been attributed to the presence of mutation in the remaining *TP53* allele.[136] Thus, the presence of *TP53* mutation predicts for poor survival outcomes regardless of 17p chromosome status.[132, 133]

The impact of these prognostic factors on the clinical outcome of patients has been examined in large prospective randomized studies. In the long-term follow up from the CALGB 9712 study (first-line therapy with concurrent vs. sequential fludarabine and rituximab), unmutated *IGHV* was a significant independent predictor for decreased PFS and overall survival, while poor-risk cytogenetic abnormalities (i.e., del(17p) or del(11q)) remained an independent predictor for decreased survival.[137] In the UK CLL4 trial, *TP53* loss was found to be the strongest predictor of poor outcomes.[114, 134] Among the subgroup of patients without *TP53* loss, unmutated *IGHV*/*VH3-21* usage and elevated β_2M (>4 mg/L) were significant independent predictors for both PFS and overall survival outcomes.[114] In addition, del(11q) and treatment allocation were independent predictors for PFS and age was an independent predictor for overall survival. In the German CLL8 trial (first-line FC vs. FCR), *TP53* mutations, del(17p), unmutated *IGHV*, and treatment arm were significant independent prognostic factors for both PFS and overall survival outcomes.[133]

Although these prognostic factors can be informative in the management of patients with CLL, treatment initiation should not be based on the presence of such factors. Moreover, in the general clinical practice setting, prognostic factors should not determine treatment choices, with the exception of cases with del(17p) or del(11q) (with indications for treatment initiation).

Workup

The workup for CLL/SLL is similar to the workup for other lymphoid neoplasms. Quantitative immunoglobulins may be informative in patients with recurrent infections. Measurement of β_2M may provide useful prognostic information.[120, 122] Though classically, the pattern of bone marrow involvement (diffuse versus nodular) had prognostic significance, this is no longer a factor when one uses more reliable prognostic markers such as *IGHV* mutational status and cytogenetic abnormalities determined by FISH, all of which can be obtained by analysis of circulating lymphocytes. Thus, bone marrow biopsy is no longer considered a required part of the evaluation of patients with CLL though it remains useful to evaluate the etiology of cytopenias.

Computed tomography (CT) scans may be useful to follow and monitor disease progression when peripheral adenopathy is present. For anemic patients, reticulocyte counts and a direct Coombs' test should be performed to evaluate for the possibility of hemolysis. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected.

Staging

The nearly universal involvement of the bone marrow and peripheral blood in CLL/SLL limits the utility of the Ann Arbor staging system. Two staging systems, the Rai and Binet systems, are currently used worldwide in the evaluation of patients with CLL both in the routine practice and clinical trial settings.[138, 139] Both staging systems rely solely on physical examination (presence of lymph node involvement, enlarged spleen and/or liver) and blood parameters (presence of anemia or thrombocytopenia) to assess the degree of tumor burden. The modified Rai classification stratifies patients into 3 risk groups. Survival of patients with low-risk disease (Rai stage 0; median survival 150 months) is essentially the same as the survival rate of age-matched controls. Patients with intermediate-risk disease (Rai stage I-II; median survival 71-101 months) have a shorter survival, particularly when other adverse factors coexist, such as a lymphocyte doubling time of less than one year. Patients with high-risk disease

(Rai stage III-IV; median survival 19 months) have a poor prognosis.[138] The Binet staging system is based on the number of involved areas and the level of hemoglobin and platelets and similar to the Rai staging system, provides meaningful correlation with clinical outcome.[139]

Response Criteria

The National Cancer Institute-sponsored Working Group (NCI-WG) on CLL published guidelines for the diagnosis and management of CLL in 1988 and 1996, primarily to facilitate consistency in the design and conduct of clinical trials. Most clinical trials of CLL reporting response outcomes have, until very recently, utilized the response criteria set forth in the 1996 NCI-WG guidelines.[140] In 2008, the NCI-WG guidelines were revised to reflect recent advances in our understanding of newer prognostic markers, diagnostic parameters, and treatments.[18] In particular, the 2008 guidelines provide further recommendations on the evaluations and response assessments appropriate for the general clinical practice setting versus for clinical trials.[18]

In the clinical practice setting, response assessment involves both physical examination and evaluation of blood parameters. For a complete response (CR), all of the following criteria must be met (at least 2 months after treatment completion): peripheral blood lymphocyte counts <4 $\times 10^9$/L; absence of lymphadenopathy (i.e., palpable nodes must be ≤1.5 cm in diameter); absence of splenomegaly or hepatomegaly; absence of constitutional symptoms (i.e., weight loss, significant fatigue, fevers, night sweats); and normalization of blood counts without growth factor support (i.e., neutrophils >1.5 $\times 10^9$/L, platelets >100 $\times 10^9$/L, hemoglobin >11 g/dL).[18] For a partial response (PR), at least 2 of the following criteria must be met for at least 2 months duration: ≥50% reductions from baseline in peripheral blood lymphocyte counts, lymphadenopathy (based on sum of the products of multiple affected nodes), hepatomegaly, and/or splenomegaly; in addition, at least 1 of the blood counts should be normalized or increase by ≥50% from baseline, for at least 2 months duration.

In the clinical trial setting, CT scans are desirable for evaluations of adenopathy and organ involvement. In addition, also in the clinical trial setting, a bone marrow evaluation should be conducted to confirm a CR (<30% lymphocytes, normocellular morphology, absence of lymphoid nodules) if all other criteria for clinical CR (see above) are met. For patients who fulfill the criteria for a CR (including evaluation of the bone marrow) but present with persistent cytopenias due to treatment-related toxicities, these patients should be considered as having achieved a CR with incomplete marrow recovery (CRi).[18]

Progressive disease comprises any of the following: ≥50% increase from baseline in lymphocyte counts, lymphadenopathy, hepatomegaly, or splenomegaly, appearance of any new lesions, or occurrence of cytopenias attributable to disease (i.e., ≥50% decrease from baseline in platelet count, >2 g/dL decrease from baseline in hemoglobin levels).[18] Patients who do not have progressive disease but do not meet the criteria for a CR or PR are considered to have stable disease. Relapse is defined as evidence of disease progression after a period of 6 months or more following an initial CR or PR. Refractory disease is defined as failure to achieve a response or having disease progression within 6 months of the last treatment.[18]

Treatment Options

During the last several decades, therapeutic options for CLL have evolved from the use of single-agent alkylating agents to purine analog-

containing regimens and chemoimmunotherapy combinations. The advent of immunotherapeutic agents such as monoclonal antibodies that target cell surface antigens (e.g., CD20, CD52) have led to the development of new and effective combination regimens that incorporate drugs with different mechanisms of action. A large number of clinical trials are currently ongoing to evaluate novel drug combination regimens, as well as investigational agents that target specific pathways of B-cell malignancies.

First-line Therapy

In an early clinical trial, the efficacy of chlorambucil plus prednisone was found to be comparable to that of CVP (cyclophosphamide, vincristine and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimens in previously untreated patients with advanced CLL.[141] The randomized CALGB 9011 study evaluated first-line treatment with fludarabine, chlorambucil or the combination (N=509).[142] The combination arm was stopped early due to excessive toxicity; response rates were similar to fludarabine alone. Fludarabine, compared with chlorambucil, resulted in significantly improved CR rate (20% vs. 4%), PR rate (43% vs. 33%), median response duration (25 months vs. 14 months) and median PFS (20 months vs. 14 months). The study found no significant difference in median overall survival between the 2 arms (66 months vs. 56 months for chlorambucil), although it should be noted that these results included data from patients who crossed over from one treatment arm to the other.[142] An European randomized study compared fludarabine with two alkylating agent-based combination regimens, CAP (cyclophosphamide, doxorubicin and prednisone) and CHOP as first-line treatment in patients with advanced CLL (N=938).[143] Fludarabine and CHOP produced similar overall remission rates (ORR; 71%) compared to CAP (58%); CR rates were significantly different between fludarabine (40%), CHOP (30%), and CAP (15%), although median survival times were similar (69, 67, and 70 months, respectively). Fludarabine was found to have a more preferable tolerability profile than CHOP.

Given that the median age of CLL diagnosis is 72 years (with approximately 70% of patients diagnosed at age ≥65 years),[144] the tolerability of a treatment regimen relative to a patient's physical fitness becomes an important consideration in the management of CLL. Older patients with CLL often present with comorbid conditions, which may decrease the patient's ability to tolerate certain regimens.[145] In a phase III randomized trial conducted by the German CLL Study Group, elderly patients (age >65 years; median age 70 years) were randomized to first-line treatment with fludarabine or chlorambucil (N=193).[146] Fludarabine, compared with chlorambucil, resulted in significantly improved ORR (72% vs. 51%), CR rates (7% vs. 0%), and median time to treatment failure (18 months vs. 11 months). However, no advantage with fludarabine was observed for PFS (median 19 months vs. 18 months) or overall survival (median 46 months vs. 64 months) outcomes.[146] Thus, in older patients (or in patients with comorbidities) with CLL for whom more intensive regimens are not appropriate, chlorambucil remains a valid treatment option.

The introduction of the anti-CD20 monoclonal antibody rituximab has led to important advances in the treatment of CLL, particularly in the context of combination regimens (see Discussion sections below). In the first-line treatment setting, rituximab as monotherapy resulted in modest activity with 51% ORR and 4% CR (based on the standard 4 weekly infusions; N=44); the median PFS was approximately 19 months.[147] Given the favorable tolerability profile, rituximab as single agent may be an appropriate treatment option for elderly patients with CLL who present with substantial comorbidities or decreased

performance status. Rituximab has also been evaluated in combination with high-dose methylprednisolone (HDMP) in a small number of patients with previously untreated CLL (N=28).[148] The median age of the patients was 65 years, and a large proportion of patients had poor-risk factors at baseline (e.g., high-risk Rai stage in 48%; unmutated *IGHV* in 57%; cytogenetic abnormalities in 39%). Treatment with rituximab combined with HDMP resulted in 96% ORR with CR in 32% of patients. At a median follow up of 36 months, the median PFS was 30.5 months and overall survival rate was 96%.[148] In the small subgroup of patients aged >70 years (n=8), all patients responded and 3 patients achieved a CR (38%).

Two recent phase II studies reported outcomes with the combination of rituximab and chlorambucil as first-line treatment in patients with CLL, including in elderly patients.[149, 150] In the multicenter Italian study (N=85 evaluable), elderly patients (age >60 years; median age 70 years) received induction therapy with chlorambucil combined with rituximab (up to 8 cycles); responders were subsequently randomized to receive rituximab maintenance (every 2 months for 2 years) or observation only.[149] Following induction therapy, the ORR was 81% with CR (confirmed by CT scan) in 16.5% of patients. The regimen was well tolerated, and treatment-related serious adverse events were reported in 7 patients (8%). The multicenter study from the UK (N=100) reported similar response outcomes and a favorable safety profile with chlorambucil combined with rituximab in previously untreated patients (median age 70 years; range, 43-86 years); the ORR and CR rate was 80% and 12%, respectively.[150] Median PFS in this study was approximately 24 months. An ongoing randomized phase III study is evaluating first-line therapy with chlorambucil combined with rituximab versus chlorambucil alone (CLL11 study).

For patients who are physically fit and do not present with substantial comorbidities, fludarabine constitutes the backbone for treatment regimens. In several large randomized phase III trials, the combination of fludarabine and cyclophosphamide (FC) was compared with fludarabine alone in relatively young patients (median age 58 to 64 years) with previously untreated CLL.[130, 151, 152] Combination chemotherapy with FC was associated with significantly improved ORR (74-94%), CR rates (23-38%) and PFS (median 32-48 months) compared with fludarabine alone.[130, 151, 152] No significant differences in overall survival outcomes were observed between treatment arms in these studies.

As previously mentioned, the advent of the anti-CD20 monoclonal antibody rituximab has led to the development of effective chemoimmunotherapy regimens in the treatment of CLL. The CALGB 9712 study evaluated the efficacy of fludarabine with concurrent or sequential administration of rituximab in untreated patients with CLL.[137, 153] The concurrent regimen was associated with a higher ORR (90% vs. 77% for the sequential regimen) and CR rate (47% vs. 28%) at the expense of higher incidence of grade 3 or 4 toxicity (primarily comprising neutropenia and infusion-related events). Comparison of the outcomes of patients treated with fludarabine alone in the CALGB 9011 trial with the pooled results from the CALGB 9712 study suggested that the addition of rituximab to fludarabine prolongs PFS and overall survival.[154] The long-term follow up from the CALGB 9712 study (median follow-up time 117 months) reported a median PFS of 42 months (5-year PFS rate 27%) and median overall survival of 85 months.[137]

The combination of fludarabine, cyclophosphamide and rituximab (FCR) evaluated at M.D. Anderson Cancer Center as initial therapy (N=300) produced high ORR and CR rate.[119, 155, 156] At a median follow

up of 6 years, the ORR was 95% (72% CR); the median time to progression was 80 months and the 6-year overall survival rate was 77%.[119] Recently, a large international randomized Phase III clinical trial (CLL8 study) showed that the addition of rituximab to fludarabine-based chemotherapy improved the outcome of patients with CLL with regard to response rates, PFS and OS compared to those receiving fludarabine-based chemotherapy alone.[128] In this trial, physically fit patients with previously untreated CLL (median age 61 years; N=817) were randomized to receive up to 6 courses of either FCR or FC regimen. The FCR regimen resulted in higher ORR (95% vs. 88%) and CR rate (44% vs. 22%) compared with FC. The median PFS was 52 months with FCR and 33 months with FC (*P*<0.001). At 3 years after randomization, the FCR regimen significantly improved both PFS rate (65% vs. 45%; hazard ratio [HR]=0.56, 95% CI 0.46-0.69; *P*<0.0001) and overall survival rate (87% vs. 83%; HR=0.67, 95% CI 0.48-0.92; *P*<0.0001) compared with FC alone. The FCR regimen was associated with significantly higher incidence of grade 3 or 4 neutropenia compared with FC (34% vs. 21%; *P*<0.0001); the incidence of severe infections and treatment-related deaths were similar between treatment arms. Based on the results of this trial, the FDA approved rituximab in combination with fludarabine and cyclophosphamide for patients with previously untreated CD20-positive CLL.

Pentostatin is another purine analog that has been evaluated as part of chemoimmunotherapy regimens in the first-line treatment of CLL. In a phase II trial initiated by two member institutes of the CLL Research Consortium, pentostatin, cyclophosphamide and rituximab (PCR) demonstrated significant clinical activity despite the large proportion of patients with poor-risk prognostic factors (e.g., high-risk Rai stage in 53%; unmutated *IGHV* in 71%; FISH abnormalities in 52%) in this trial (N=64).[157] Responses were observed in 91% of patients (41% CR); median response duration (among responders) was 34 months. The median PFS for all patients on the trial was approximately 33 months.[157]. The toxicities were manageable, and appeared less myelotoxic relative to FCR regimens. A community-based multicenter phase III randomized trial (N=184) was conducted by US Oncology Research to compare the safety of PCR with FCR regimens in previously untreated (80% of patients) or minimally pretreated patients.[158] The ORR with PCR and FCR were similar (45% vs. 57.5%), with a lower CR rate in the PCR group (7% vs. 17%; *P*=0.04). The incidence of grade 3 or 4 infectious events and neutropenia were similar between treatment arms, with increased incidence of leukopenia and thrombocytopenia in the FCR group. [158] Overall, the PCR regimen did not appear to provide an advantage over FCR in terms of toxicity profile or clinical activity. A subsequent study investigated the possibility of reducing the toxicity of the PCR regimen by omitting cyclophosphamide (and using a higher dose of pentostatin) in previously untreated patients (N=33). [159] The combination of higher dose pentostatin with rituximab (PR) resulted in 76% ORR, with CR in 27% of patients.[159] Relative to historical outcomes with the PCR regimen, however, the response rates with PR were lower and the median treatment-free survival was also decreased (16 months vs. 30 months for PCR), suggesting that cyclophosphamide is an important component in the activity of PCR regimens..

Bendamustine is an alkylating agent with a purine-like benzimidazole ring component, and was found to exhibit low or incomplete cross-resistance with other alkylating agents due to its unique cytotoxic properties.[160, 161] In a pivotal phase III randomized study (N=319), the activity and safety of bendamustine was compared to chlorambucil in

patients with previously untreated CLL.[162, 163] Treatment with bendamustine, compared with chlorambucil, resulted in significantly higher ORR (68% vs. 31%; *P*<0.0001) and CR rate (31% vs. 2%; *P*<0.0001). After a median observation time of 54 months, the median PFS was significantly longer with bendamustine (21 months vs. 9 months; *P*<0.0001).[163] The higher response rates and PFS benefit with bendamustine was retained in the subgroup of older patients (age >65 years) on this trial.[164] Bendamustine was associated with higher incidences of grade 3 or 4 hematologic toxicities, infections, and gastrointestinal events compared with chlorambucil.[162] No differences in overall survival outcomes were observed between the two groups and the efficacy of bendamustine compared to first-line therapies other than chlorambucil has not yet been established. Bendamustine is also being evaluated as part of a chemoimmunotherapy regimen in patients with CLL. In a multicenter phase II trial (CLL2M study) from the German CLL Study Group, bendamustine in combination with rituximab (BR) resulted in 91% ORR (33% CR) in patients with untreated CLL (N=117).[165] In the small subgroup of patients with del(17p) (n=7), the ORR (all partial remissions) was 43%. At a median observation time of 15 months, the median PFS has not yet been reached. The most common grade 3 or 4 adverse events were myelotoxicities (leukopenia, 15%; neutropenia, 6.5%; thrombocytopenia, 6%; anemia, 5% of courses) and infections (5% of courses).[165] A phase III randomized trial is currently ongoing to compare outcomes between FCR and BR (CLL10 study).

Alemtuzumab, a humanized monoclonal antibody targeting CD52, was initially approved in the setting of fludarabine-refractory CLL (see Discussion section for "Relapsed/Refractory Disease" below), and has since shown clinical activity as a first-line treatment for patients with CLL (and is approved for this indication).[166, 167 168-171]In an international, multicenter randomized phase III study (CAM307), previously untreated patients with CLL (N=297) were randomized to receive alemtuzumab or chlorambucil.[167] Alemtuzumab showed significantly higher ORR (83% vs. 55%; *P*<0.0001) and CR rate (24% vs. 2%; *P*<0.0001) compared with chlorambucil; in addition, a modest but statistically significant benefit in PFS was observed with alemtuzumab compared with chlorambucil (median 15 months vs. 12 months; HR=0.58, 95% CI 0.43-0.77; *P*=0.0001). In the small subgroup of patients (n=21) with del(17p), alemtuzumab showed numerically higher ORR (64% vs. 20%) and longer median PFS (11 months vs. 2 months). Treatment with alemtuzumab was associated with higher incidence of infusion-related events, cytomegalovirus (CMV) infections and grade 3 or 4 neutropenia (41% vs. 25%) compared with chlorambucil; symptomatic CMV infection was reported in 16% of patients in the alemtuzumab arm. After a median follow up of 25 months, median overall survival has not been reached for either treatment arm and no significant difference in survival was reported between treatment arms.[167]

Relapsed or Refractory Disease

The FCR regimen has also been shown to induce high response rates in the relapsed/refractory disease setting.[172, 173] In a phase II study evaluating FCR in patients with relapsed/refractory CLL (N=284; median 2 prior therapies, range 1-10), the ORR was 74% with a CR rate of 30%.[173] The median PFS was 21 months and the estimated median survival was 47 months. The subgroup of patients with fludarabine-refractory disease (n=54) had significantly lower ORR (56% vs. 79%; *P*<0.001) and CR rate (7% vs. 39%; *P*<0.001) compared with fludarabine-sensitive patients; the median PFS (8 months vs. 28 months; *P*<0.001) and OS (38 months vs. 52 months; *P*<0.05) was also significantly decreased among patients with fludarabine-refractory CLL.[173] In addition, the subgroup of patients

(n=20) with chromosome 17 abnormalities (based on standard karyotyping) had the worse outcomes with an ORR of 35% (no CR), median PFS of 5 months, and median survival of only 10.5 months. The investigators concluded that the patients most appropriate for therapy with FCR were those who were fludarabine sensitive, with no chromosome 17 abnormalities, and with fewer prior therapies (<4 prior regimens).[173] The most common adverse events with FCR were hematologic toxicities, including grade 3-4 neutropenia associated with 56% of treatment cycles and grade 3-4 thrombocytopenia in 19.5% of cycles. Pneumonia or sepsis was reported in 16% of patients.[173]. Recently, the phase III randomized REACH trial compared six cycles of FCR with six cycles of FC in patients with CLL at first relapse (N=552).[174] In this study, patients were excluded if they received prior FC (as a combination) or prior rituximab; moreover, patients were required to be fludarabine sensitive. After a median follow-up time of 25 months, patients in the FCR arm had significantly improved median PFS (based upon investigator assessment) compared with the FC arm (31 months vs. 21 months; *P*<0.001). The median PFS as assessed by an independent review committee also showed a significant benefit with FCR compared with FC (27 months vs 22 months; *P*=0.022). Based on independent review committee evaluation, both the ORR (61% vs. 49%; *P*<0.005) and CR rate (9% vs. 3%; *P*<0.005) were significantly higher with the FCR regimen. [174] At the time of follow up, overall survival was not significantly different between treatment regimens. Based on the results of this trial, the FDA approved rituximab in combination with fludarabine and cyclophosphamide for patients with previously treated CD20-positive CLL.

The combination of pentostatin and cyclophosphamide (PC) with or without rituximab (R) has shown significant activity in previously treated patients with relapsed or refractory CLL, including in patients with fludarabine-refractory disease.[175, 176] In a small study in patients with relapsed/refractory CLL (N=23; median 3 prior therapies, range 1-5), the PC combination resulted in an ORR of 74% and CR rate of 17%; the ORR among patients with fludarabine-refractory disease was 77%.[176] In a study that evaluated the PCR regimen, the ORR and CR rate in the subgroup of patients with previously treated CLL (n=32) was 75% and 25%, respectively; the ORR among patients with fludarabine-refractory disease was 75%.[175] Thus, the response rates with the PC and PCR regimens appeared similar. However, based on a historical retrospective comparison, the median duration of response (25 months vs. 7 months) and median survival (44 months vs. 16 months) were longer with the PCR regimen compared with the PC regimen..[175]

In a phase I-II trial, the combination of oxaliplatin, fludarabine, cytarabine and rituximab (OFAR) was shown to be highly active in fludarabine-refractory patients with CLL (n=30) and those with Richter's syndrome (n=20).[177, 178] The ORR was 50% in patients with Richter's syndrome and 33% in those with fludarabine-refractory CLL.[177] In addition, responses were achieved in seven (35%) of 20 patients with del(17p) and two (29%) of seven patients with del(11q). The median response duration was 10 months. The ORR in the subgroup of patients aged 70 years or older (n=14) was 50%.[177, 178]

The German CLL Study Group recently conducted a phase II trial combining bendamustine and rituximab for patients with relapsed CLL (N=78; median 2 prior therapies, range 1-5) which resulted in an ORR of 59% and CR rate of 9%.[179, 180] The ORR among the subgroup (n=22) with fludarabine-refractory disease was 45.5%. Among the patients with del(17p) (n=14), only 1 patient (7%) responded (with a CR). After a median follow up of 24 months, the median PFS and

overall survival for all patients was 15 months and 34 months, respectively. Patients with del(17p) had the worse outcomes with a median PFS of 7 months and median survival of 16 months.[180] The most common grade 3-4 adverse events included hematologic toxicities (50% of patients) and infections(13%; all grade 3 events).[180]

High-dose methylprednisolone (HDMP) combined with rituximab has been shown to be well tolerated and an active therapy for patients with refractory CLL, including in those with unfavorable prognostic features. In several small studies, treatment with HDMP combined with rituximab resulted in ORR of 78-93% with CR in 14-36% of patients; median PFS (or time to progression) was 7-15 months, and one study reported a median survival of 20 months.[181-183] In addition, this regimen was shown to be active in patients with fludarabine-refractory disease and/or del(17p).[181, 182] The regimen was associated with infectious complications (including opportunistic fungal infections) in about 30% of patients,[181, 183] which may necessitate adequate antiinfective prophylaxis and close monitoring for early signs of infections.

In an early phase II study, alemtuzumab was shown to induce significant responses in patients who were refractory to fludarabine based therapy (N=93).[184] The ORR with single agent alemtuzumab was 33% (CR 2%); median time to progression was 4.7 months for all patients (9.5 months for responders) and the median overall survival was 16 months (32 months for responders).[184] Several studies have also shown that alemtuzumab was effective in patients with fludarabine-refractory CLL with del(17p) or *TP53* abnormalities.[168-170, 185] In a recent retrospective analysis, favorable ORR, median PFS and median survival outcomes (49%, 7 months and 19 months, respectively) were observed with alemtuzumab in pretreated patients with del (17p).[186] It should be noted that bulky lymphadenopathy does not typically respond well to alemtuzumab monotherapy in patients with refractory CLL.[184, 187] Subcutaneous administration of alemtuzumab appeared as effective and safe as intravenous alemtuzumab in patients with advanced-stage relapsed or refractory CLL.[185, 188-190] The most common grade 3-4 toxicities with alemtuzumab in the setting of heavily pretreated, relapsed/refractory disease included myelosuppression and infections.[184, 187, 190] Appropriate antiinfective prophylaxis and routine monitoring for early signs of infectious events are warranted when administering alemtuzumab-containing regimens. CMV reactivation can occur in about 10%-25% of patients with relapsed/refractory CLL treated with alemtuzumab.[184, 187, 190-192] It is therefore important to monitor for CMV antigenemia during alemtuzumab therapy. Combination regimens with alemtuzumab and chemotherapy have been investigated with promising results in patients with relapsed/refractory CLL. In phase II and III studies, alemtuzumab combined with fludarabine (FluCam regimen) in relapsed CLL (primarily as second-line therapy) resulted in ORR of 82-85% and CR rates of 13-30%.[193-195] In the phase III randomized trial (N=335), the median PFS was significantly longer with FluCam compared with fludarabine alone (24 months vs. 16.5 months; *P*=0.003); infection rates were high, with 41% of patients in the FluCam arm experiencing infections (any grade, and including CMV reactivation) compared with 35% in the fludarabine arm.[194, 195] Alemtuzumab has also been evaluated in combination with FC (FCCam regimen) in patients with previously treated CLL (N=56), which yielded an ORR of 68% (CR 22%); with this regimen, infections considered serious adverse events were reported in about 20% of patients.[196] Immunotherapy combination with alemtuzumab and rituximab has also shown promising results. In a phase II study in patients with relapsed/refractory CLL (N=40), alemtuzumab (using continuous infusion followed by subcutaneous administration)

combined with rituximab resulted in ORR of 53% (CR 18%); infections (any grade, and including CMV reactivation) were reported in 28% of patients.[197] A more intensive chemoimmunotherapy regimen that combines cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR) has been evaluated in a phase II study in patients with heavily pretreated relapsed/refractory CLL with high-risk features (N=80; median 3 prior therapies, range 1-14; 39% fludarabine-refractory).[198] The ORR with the CFAR regimen was 65% (CR 29%); median PFS and overall survival was 11 months and 17 months, respectively.[198] Although this regimen may be an option for some patients with high-risk disease, it was associated with a high rate of grade 3-4 infections (46%) and was not as active in the subgroup of patients with del(17p) (CR 14%; median PFS 3 months) or fludarabine-refractory disease (CR 10%; median PFS 7 months).

The treatment of patients with fludarabine-refractory CLL remains a challenge, particularly for patients who do not respond with alemtuzumab therapy. Ofatumumab is a human CD20 monoclonal antibody with activity in patients with fludarabine-refractory CLL also refractory to alemtuzumab or considered unsuitable for alemtuzumab therapy due to bulky lymphadenopathy.[199] In the final analysis from the pivotal international clinical trial, which included data from 206 patients with fludarabine- and alemtuzumab-refractory (FA-ref; n=95) CLL or patients with fludarabine-refractory CLL with bulky lymphadenopathy (BF-ref; n=111), ofatumumab therapy resulted in an ORR of 51% in the FA-ref and 44% in the BF-ref patients.[199] The median PFS was 5.5 months for both groups, and the median OS was 14 months and 17 months for the FA-ref and the BF-ref groups, respectively. The most common ≥grade 3 adverse events were infections (24%) and neutropenia (12%).[200] Ofatumumab is currently approved in the US and EU for the treatment of CLL refractory to fludarabine and alemtuzumab.

Allogeneic hematopoietic stem cell transplant (HSCT) has been evaluated to improve the prognosis in patients with advanced disease and those with poor-risk features.[201-207] In a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT), allogeneic HSCT induced long-term remission in patients with del(17p).[206] At a median follow-up period of39 months, 3-year PFS and overall survival rates were 37% and 44%, respectively. The final results of the prospective multicenter trial (GCLLSG CLL3X study) also showed that nonmyeloablative allogeneic HSCT can induce sustained MRD-negative event-free survival (EFS) in a significant proportion of patients with poor-risk CLL (defined as refractoriness or early relapse to purine analog-containing therapy, relapse after autologous SCT, disease progression with presence of unfavorable genomic abnormalities).[207, 208] The 4-year EFS and OS rates for patients who underwent HSCT in this study (N=90) was 42% and 65%, respectively; 52% of patients had MRD negativity at 12 months post-HSCT.[208] The 4-year non-relapse mortality rate was 23%. The 4-year EFS and OS rates for the subgroup of patients with del(17p) (n=13) was 45% and 59%, respectively, and was not significantly different from the survival rates of patients without del(17p). Moreover, 6 of 13 patients (46%) with del(17p) achieved durable MRD-negative remissions.[208] It is understood that studies involving allogeneic HSCT are subject to strong selection biases. Nonetheless, available evidence from non-randomized clinical studies suggest that allogeneic HSCT may be an effective treatment option for patients refractory to chemoimmunotherapy or who develop recurrence within 12 months after purine analog treatment.[209]

NCCN Recommendations

Localized SLL (Ann Arbor stage I)

Locoregional radiation therapy (RT) is an appropriate induction therapy for this group of patients. In rare cases, RT may be contraindicated or may be a sub-optimal therapy due to the presence of comorbidities or the potential for long-term toxicity. Patients with localized SLL that has progressed after initial RT are treated as described below for patients with SLL (Ann Arbor stage II-IV).

SLL (Ann Arbor stage II-IV) or CLL (Rai stages 0-IV)

Early stage disease in some patients may have an indolent course and in others may progress rapidly to advanced disease requiring immediate treatment. Absolute lymphocyte count alone is not an indication for treatment unless it is above 200-300 x 10^9/L or symptoms related to leukostasis occur. Therefore, in patients with SLL (Ann Arbor stage II-IV) or CLL (Rai stages 0-II), treatment options depend on the presence or absence of the following indications: significant disease related symptoms including severe fatigue, weight loss, night sweats and fever without infection, threatened end-organ function, progressive bulky disease (enlarged spleen or lymph nodes), or progression to more advanced stage CLL with progressive anemia or thrombocytopenia. Patients with no indications for treatment should be observed until such indications (as mentioned above) become apparent, or be considered for clinical trials, as appropriate. Patients with advanced stage CLL (Rai stage III-IV) will be symptomatic and typically require immediate treatment.

Given the incurability of the disease, the NCCN Guidelines recommend enrollment in clinical trials, when locally available, as the preferred therapy for all patients. For patients presenting with indications for treatment and are not eligible or do not have access to clinical trials, the treatment recommendations included in the Guidelines are based on factors such as the presence or absence of high-risk genomic abnormalities (deletion 17p or 11q), age and performance status/comorbidities of the patient. Re-evaluation of cytogenetics by FISH is necessary to direct treatment options in patients with indications for treatment.

CLL without del(17p)or del(11q)

First-line Therapy

Patients are stratified according to their age and associated comorbid conditions. Comorbidities can be assessed using tools such as the cumulative illness rating scale (CIRS).[210]

For frail patients with significant comorbidities and not able to tolerate purine analogs, the options include treatment with chlorambucil (with or without rituximab), rituximab monotherapy or pulse corticosteroids.

For patients 70 years or older or younger patients with significant comorbidities, the NCCN Guidelines have included alkylating agent-based chemoimmunotherapy (eg, chlorambucil with or without rituximab, BR), monotherapy with alemtuzumab or rituximab, fludarabine with or without rituximab or cladribine as options. For patients 70 years or younger, or for older patients without significant comorbidities, the NCCN Guidelines have included rituximab in combination with purine analog-based chemotherapy (FCR, FR, PCR) or with bendamustine (BR) as options (see Guidelines section under "Suggested Treatment Regimens: CLL without del(17p)or del(11q)" for a list of specific regimens).

In patients younger than 70 without significant co-morbidities chemoimmunotherapy has emerged as the standard of care.[128, 137] A randomized comparison of FCR versus PCR demonstrated a higher CR rate for FCR but the ORR and survival were no different between the

regimens.[158] Both FCR and FR are highly active regimens, however, we do not have category 1 evidence to designate one as the preferred regimen over the other. In the absence of a del(11q), it is uncertain whether there are differences in long-term outcomes between these regimens.

Although the oral formulation of fludarabine has been investigated[211-213] and is approved by the FDA for the treatment of CLL (in patients who have not responded to or have progressed after treatment with at least one alkylating agent), its use in combination regimens for CLL has not yet been established. Moreover, no prospective randomized trials have evaluated the activity and safety of the oral formulation compared with IV fludarabine. Therefore, the NCCN Guidelines panel cannot recommend the appropriate use of oral fludarabine at this time.

Second-line Therapy

For patients relapsing after or refractory to first-line therapy, treatment options are dependent on the duration of response following the first-line treatment regimen. Among patients who failed FCR chemoimmunotherapy as initial therapy, those with a time to treatment failure of 3 years or more had better median survival (44 months) than those with a time to treatment failure of less than 3 years (12 months).[214] If the response to first-line treatment is of long duration, the NCCN Guidelines panel recommends retreatment with the same regimen that was used as first-line therapy for all patients.

If the response is of short duration, treatment options are dependent on the patient's age and presence of comorbid conditions. In the setting of a short response, regimens other than those administered as first-line therapy should be considered. For patients 70 years or older or for younger patients with comorbidities, options include reduced-dose FCR or PCR, bendamustine with or without rituximab, HDMP with rituximab, monotherapy with ofatumumab, alemtuzumab with or without rituximab, or dose-dense rituximab. For patients younger than 70 years or for older patients without significant comorbidities, the NCCN Guidelines have included chemoimmunotherapy (eg, FCR, PCR, BR, fludarabine with alemtuzumab, CHOP with rituximab, OFAR), monotherapy with ofatumumab, alemtuzumab with or without rituximab, or HDMP with rituximab as suggested options (see Guidelines section under "Suggested Treatment Regimens: CLL without del(17p)or del(11q)" in the for a list of specific regimens). It should be noted that long and short response durations cannot be rigorously defined based on currently available data. A major factor in evaluating the durability of a response is that the definition would be influenced by the prior treatment regimen. Therefore, physicians will need to exercise clinical judgement for individual cases. For instance, after a regimen such as FCR, response duration of 3 years may be a reasonable cutoff based upon data from the MD Anderson Cancer Center. However, after treatment with a less intensive regimen such as single-agent chlorambucil, response duration of 18-24 months may be a more reasonable cutoff.

Allogeneic HSCT can be considered for a select population of patients (without significant comorbidities) with short responses to chemoimmunotherapy regimen, but would generally be considered after re-induction of remission.

CLL with del(17p)

No standard treatment exists for patients with del(17p), as outcomes remain poor with currently available treatment regimens. Therefore, for patients with del(17p), enrollment in an appropriate clinical trial is recommended. In the absence of appropriate clinical trials in the patient's local area, suggested first-line therapy options include FCR

or FR, HDMP plus rituximab, or alemtuzumab with or without rituximab.

Patients who have achieved CR or PR to first-line therapy should be considered for allogeneic HSCT, if they are eligible. Patients with CR or PR following transplant can either be observed or enrolled in clinical trials. Alternatively, patients with PR could also be treated with chemoimmunotherapy.

Patients with no response to first-line therapy, patients who respond to first-line therapy but are not eligible for allogenic HSCT and for those with no response to transplant should be enrolled in clinical trials or be treated with second-line therapy for relapsed or refractory disease. The NCCN Guidelines have included chemoimmunotherapy regimens, monotherapy with ofatumumab, alemtuzumab with or without rituximab, or HDMP with rituximab as options (see Guidelines section "Suggested Treatment Regimens: CLL with del(17p)" for a list of specific regimens).

CLL with del(11q)

First-line therapy options are based on the patient's age and associated comorbid conditions. For patients with a del (11q) abnormality, an alkylating agent should be included in the treatment regimen. In patients older than 70 years of age or with significant co-morbidities, first-line treatment options include chlorambucil with or without rituximab, BR, cyclophosphamide and prednisone with or without rituximab, reduced-dose FCR, or single agent immunotherapy with alemtuzumab or rituximab; single agent alemtuzumab or rituximab should be used only if an alkylator is contraindicated or considered intolerable. For patients younger than 70 years of age or for older patients without significant comorbidities, first-line treatment options include FCR, BR or PCR.

Patients who have achieved CR to first-line therapy can either be observed until disease progression or enrolled in clinical trials. For those with disease progression following CR, treatment options are dependent on the duration of response to first-line therapy (similar to regimens discussed under "Second-line Therapy" above; also see Guidelines section "Suggested Treatment Regimens: CLL with del(11q)" for a list of specific regimens). Participation in a clinical trial is also a consideration in this setting. Patients with PR to first-line therapy should be considered for allogeneic HSCT, if they are eligible. Following transplant, treatment options are similar to those described for patients with del(17p).

Patients with no response to first-line therapy, patients with PR to first-line therapy but are not eligible for allogenic HSCT should be enrolled in clinical trials or can be treated with second-line therapy for relapsed or refractory disease (see Guidelines section "Suggested Treatment Regimens: CLL with del(11q)" for a list of specific regimens).

Histological Transformation to DLBCL or Hodgkin lymphoma

About 2-5% of patients with CLL will develop Richter syndrome (transformation into DLBCL or Hodgkin lymphoma) during the course of the disease and treatment.[215-217] The incidence of transformation increases with the number of prior regimens. Patients with Richter syndrome should be treated with a combination of chemoimmunotherapy regimens initially developed for DLBCL.[218] In addition to these regimens, the Guidelines have also included hyper-CVAD with rituximab as an option for patients with histological transformation as well as for those with relapsed or refractory CLL.[219, 220]

Allogeneic HSCT has also shown promising results in patients with RS responding to initial therapy. In a non-randomized comparative analysis, the estimated cumulative 3-year survival rate was significantly higher (75%) for patients who underwent allogeneic SCT after achieving CR or PR to initial therapy compared with those who responded to initial therapy but did not undergo allogeneic SCT, or who underwent allogeneic HSCT for relapsed or refractory RS (75% vs. 27% and 21%, respectively; *P*=0.019)).[218] Thus, allogenic HSCT can be a consideration following a response to initial therapy in patients with RS.

Supportive Care for Patients with CLL

Infections

Patients with CLL are susceptible to infectious events due to both the underlying disease and treatment with immunosuppressive agents. Infectious complications are influenced by the reduction in immunoglobulin levels and are more common in previously treated patients.[221] Hypoglobulinemia has been shown to be present in about 40% of patients up to 3 years prior to diagnosis of CLL.[222] Heavily pretreated patients who become refractory to fludarabine have high susceptibility to developing serious infections. In a retrospective analysis, 89% of patients with fludarabine-refractory CLL developed infectious complications requiring hospitalization.[223] Administration of IVIG (for recurrent infections and if IgG levels <500 mg/dL), antiinfective prophylaxis and vaccinations are the main options available to minimize the possibilities of developing infectious complications.

In randomized studies, IVIG has been associated with a significant decrease in the occurrence of infections but with no improvement in survival outcomes.[224-228] Antibacterial prophylaxis may be a useful alternative option. Protein and conjugate vaccines have been shown to induce better responses than plain polysaccharide vaccines.[229, 230] Some studies have reported that histamine type-2 (H2) receptor blockers can enhance vaccine response.[231, 232]

In selected patients (serum IVIG <500 mg/dL) with recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization, the Guidelines recommend monitoring IVIG levels and administering monthly IVIG (0.3-0.5 g/kg) to maintain nadir levels of approximately 500 mg/dL. The use of antiinfective prophylaxis is also appropriate for the management of patients who may be susceptible to certain infections due to a given treatment regimen. Antiviral and pneumocystis prophylaxis is recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter. Acyclovir or equivalent is recommended for herpes virus and sulfamethoxazole trimethoprim or equivalent is recommended for *Pneumocystis* pneumonia (PCP) prophylaxis. Annual influenza vaccine and pneumococcal vaccine (every 5 years) is recommended for all patients. All live vaccines should be avoided. Patients with CLL tend to have a poor response to influenza vaccine and should be counseled to exercise care during influenza season even with vaccination.

Cytomegalovirus (CMV) reactivation is a well documented infectious event in patients receiving treatment with alemtuzumab, occurring in up to 25% of patients.[166, 167, 184, 187, 190, 192] Although the standard approach to CMV monitoring and management remains under debate, current practices include the use of prophylactic ganciclovir (oral or IV) if CMV viremia is present prior to alemtuzumab therapy,[233] or preemptive use of these drugs when the viral load is found to be increasing during therapy.[234, 235]

Clinicians should be aware of the high risk of CMV reactivation in patients with CLL treated with alemtuzumab-containing regimens.

Monitoring for the presence of CMV antigens regularly using quantitative polymerase chain reaction (PCR) assays is an effective approach to the management of CMV reactivation.[236] The NCCN Guidelines recommend routine surveillance for CMV viremia (every 2-3 weeks) during the treatment course with alemtuzumab and for 2 months following completion of treatment. Consultation with an infectious disease expert may be necessary.

Autoimmune Cytopenias

Autoimmune hemolytic anemia (AIHA), immune-mediated thrombocytopenia, also known as immune thrombocytopenic purpura (ITP) and pure red blood cell aplasia (PRCA) are the most frequent autoimmune cytopenias in patients with CLL.[237, 238]

AIHA is the most common form of autoimmune cytopenia. Although direct antiglobulin test (DAT) has been used for the diagnosis of AIHA, most patients with AIHA have negative DAT; additional markers such as low haptoglobin and elevated reticulocyte and LDH are required to confirm the diagnosis of AIHA.[239] Patients with advanced disease, unmutated *IGHV*, increased serum beta-2 microglobulin level, and high expression of ZAP-70 are also at a higher risk of developing AIHA.[239-242] ITP in patients with CLL is associated with poorer survival independent of common clinical prognostic variables. [243] In a recent Italian study, high WBC count, unmutated *IGHV*, positive DAT and ZAP-70 positivity were associated with the development of ITP in patients with CLL.[243] PRCA is less common in patients with CLL.

Bone marrow evaluation is recommended to confirm the diagnosis of autoimmune cytopenias. Evaluation of parvovirus B19 is also recommended to exclude parvovirus-induced PRCA. AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporin[244] and splenectomy should be used in steroid-refractory cases. Rituximab has also been effective for the treatment of patients with autoimmune cytopenias [245-251] Corticosteroids tend to be less effective in PRCA than in ITP or AIHA. In the very refractory cases, allogeneic HSCT may be necessary. More recently, synthetic thrombopoietin-like agents such as romiplostim and eltrombopag have shown promising results in the treatment of thrombocytopenia associated with ITP.[252-255] Both romiplostim and eltrombopag are FDA-approval for the treatment of thrombocytopenia in patients with ITP that is refractory to steroids, IVIG and splenectomy.

Purine analog-based therapy has been associated with AIHA. Recent studies have reported higher incidence of AIHA in patients treated with fludarabine or chlorambucil compared to those who received fludarabine-based combination regimens (FC or FCR).[239, 256] AIHA should not preclude the use of combination therapy containing fludarabine, and patients should be observed carefully. In the case of severe AIHA, fludarabine therapy should be discontinued and subsequent use of the agent should be avoided.

Tumor Lysis Syndrome

Patients with CLL and high white blood cell counts may occasionally experience tumor lysis syndrome and should be managed as outlined under "Tumor Lysis Syndrome" in the "Supportive Care" section of the Guidelines.

Diffuse Large B-Cell Lymphoma

Diagnosis

Diffuse large B-cell lymphomas (DLBCL) are the most common lymphoid neoplasms in adults, accounting for approximately 30% of NHLs diagnosed annually.[11] DLBCL NOS, FL (grade 3 only), DLBCL coexistent with a low-grade lymphoma of any kind (e.g., FL of any

grade, gastric MALT or non-gastric MALT lymphoma), intravascular large B-cell lymphoma, DLBCL associated with chronic inflammation, ALK-positive DLBCL, EBV-positive DLBCL of the elderly and T-cell/histiocyte rich large B-cell lymphoma are also managed according to the DLBCL guidelines.

Studies with gene expression microarray analysis of DLBCL have revealed significant heterogeneity within this diagnosis.[27] However, incorporation of this information into treatment algorithms awaits further investigation. Immunohistochemical markers CD10, BCL6, and IRF4/MUM1 have been reported to recapitulate the gene expression profiling separating patients into tumors derived from germinal center (GC) origin (CD10+, or BCL6+, IRF4/MUM1-) and non-GC origin (CD10-, IRF4/MUM1+ or BCL6-, IRF4/MUM1-).[28] However, the validity of this classification scheme has been brought into question. An improved IHC algorithm has been proposed which includes GCET1, FOXP1, BCL6, IFR4/MUM1, and CD10.[29, 31] Although GC tumors are associated with an improved outcome compared to non-GC tumors, treatment remains the same and cell-of-origin should not be used to guide choice of therapy.

The typical immunophenotype is CD20+, CD45+, and CD3-. The recommended immunophenotyping panel includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, and IRF4/MUM1. When available, GCET1 and FOXP1 can provide information necessary for the Choi IHC cell of origin algorithm. Additional markers such as CD138, cyclin D1, ALK1, EBV and HHV-8 may be useful under certain circumstances to establish the subtype. Molecular genetic analysis for detection of gene rearrangements in *CCND1, BCL6*, or *MYC*, as well as conventional or FISH cytogenetic for detection of the translocations, t(14;18), t(3;v), or t(8;14), may also be useful in some cases. Rearrangement in *MYC* has been reported in 9%-17% of DLBCL cases, and often correlates with GC phenotype.[257-259] Concurrent abnormalities with *MYC* rearrangement and the t(14;18) ("double hit" DLBCL) has been observed in 2%-11% of newly diagnosed patients with DLBCL.[258, 259] Such cases are typically associated with an aggressive disease course with very poor clinical outcomes, even with treatments using rituximab-containing chemoimmunotherapy or intensive therapy with stem cell transplantation.[257, 260] Standard of care for "double hit" DLBCL with concurrent *MYC* rearrangement and t(14;18) has not been established.

Workup

The initial workup for newly diagnosed DLBCL should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms. Laboratory assessments should include standard blood work including CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH) and serum beta-2-microglobulin levels. Patients with high tumor burden and elevated LDH should be assessed for spontaneous tumor lysis syndrome, including measurements of uric acid level. HBV testing is recommended due to increased risks of viral reactivation when immunotherapy regimens are being considered for treatment. Adequate trephine biopsy (specimen ≥1.6 cm)[261, 262] should be obtained for initial staging evaluation, with or without bone marrow aspiration.

The staging workup is designed to identify all sites of known disease and determine prognosis with known clinical risk factors. Risk factors used to determine International Prognostic Index (IPI) scores include age, stage of disease, LDH level, performance status, and the number of extra-nodal sites of disease.[263] In patients who are 60 years or younger, the prognostic factors include tumor stage, performance status, and serum LDH level. The IPI and age-adjusted IPI can be used

to identify specific group of patients who are more or less likely to be cured with standard therapy.[263]

PET or PET-CT scans, have a more clear-cut role in selected cases of DLBCL than in other lymphoid neoplasms. PET scans are particularly informative in the initial staging where upstaging resulting in altered therapy occurs about 9% of the time, and for response evaluation after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor. As PET scans have now been incorporated into the response criteria, availability of a baseline study is necessary for optimal interpretation of the post-treatment study. In some centers, beta-2-microglobulin is considered a major determinant of risk (category 2B). Lumbar puncture is recommended in patients with one or more of the following sites of involvement: paranasal sinus, testicular, epidural, HIV-associated lymphoma, bone marrow (with large cells) or the presence of 2 or more extranodal sites and elevated LDH levels. Diagnostic yield is improved if flow cytometric analysis of CSF is undertaken. Patients with these risk factors should also be considered for prophylactic chemotherapy for the CNS.

Treatment Options by Clinical Stage

Treatment options for DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (Ann Arbor stage III-IV) disease. Prognosis is extremely favorable for patients with no adverse risk factors (i.e., none of the following: elevated LDH, stage II bulky disease, older than 60 years or ECOG performance status of 2 or more). Patients with advanced disease should be enrolled in clinical trials, whenever possible.

Stage I-II

In the SWOG 8736 study, 3 cycles of CHOP followed by involved field radiation therapy (IFRT) produced significantly better progression-free survival (PFS; 5-year estimated PFS: 77% vs. 64% for CHOP alone) and OS (82% vs. 72% for CHOP alone) than 8 cycles of CHOP alone in patients with localized aggressive NHL; [264] however, this difference disappeared with further follow-up. The benefit of CHOP (3 cycles) followed by IFRT (5-year OS of 95%) in patients with limited-stage DLBCL (60 years or younger with no adverse risk factors) was also confirmed in a series from the British Columbia Cancer Agency.[265] Another randomized trial (ECOG 1484 study) showed that the addition of RT to CHOP (8 cycles) prolonged disease-free survival (DFS) in patients with limited stage DLBCL who had achieved CR to CHOP alone (6-year DFS was 73% for IFRT and 56% for observation).[266] In the GELA study (LNH 93-4), the addition of RT to 4 cycles of CHOP did not provide any advantage over 4 cycles of CHOP alone for the treatment of elderly patients with low-risk localized aggressive lymphoma. The estimated 5-year event-free survival (EFS) was not different between the two groups (61% and 64%, respectively) and the 5-year estimated OS rate was 68% and 72%, respectively.[267] However, in this study, administration of RT was markedly delayed and 12% of patients on the RT arm did not receive RT.

The efficacy of the addition of rituximab to CHOP (R-CHOP) and IFRT has also been reported in patients with limited stage DLBCL. In the SWOG 0014 study that evaluated 3 cycles of R-CHOP followed by IFRT in patients with at least one stage-modified IPI risk factor (N=60), the 2- and 4-year PFS rates were 93% and 88%, respectively, after a median follow-up of 5 years; the corresponding OS rates were 95% and 92%, respectively.[268] In historical comparison, these results were favorable relative to the survival rates for patients treated without rituximab (4-year PFS and OS were 78% and 88%, respectively). The Mabthera International Trial (MInT) evaluated the role of rituximab in a phase III trial comparing 6 cycles of CHOP-like chemotherapy to 6

cycles of CHOP-like chemotherapy plus rituximab. All patients were under the age of 60 years and had 0-1 IPI risk factors. Three quarters of patients had limited stage disease, and radiation was included for all extranodal sites of disease or any site greater than 7.5 cm. The trial found a benefit to rituximab-containing therapy with a 3-year OS rate of 93% versus 84%.[269]

In two GELA studies, intensified chemotherapy [ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) followed by consolidation with methotrexate, etoposide, ifosfamide and cytarabine] with or without rituximab was found to be superior to CHOP with or without rituximab (3 cycles) plus RT in patients with low-risk early-stage disease.[270, 271] However, this regimen was also associated with significant toxicity and includes vindesine, which is not available in the United States.

Stage III-IV

R-CHOP-21 chemotherapy has been the standard treatment for patients with advanced stage DLBCL based on the results of the GELA study (LNH98-5) that demonstrated the addition of rituximab to CHOP-21 improved PFS and OS in elderly patients with advanced DLBCL. In this study, elderly patients (age 60-80 years; N=399) were randomized to receive 8 cycles of R-CHOP or CHOP.[272-274] Long-term follow-up of this study showed that PFS (36.5% vs. 20%), DFS (64% vs. 43%), and OS (43.5% vs. 28%) rates were significantly in favor of R-CHOP at a median follow-up of 10 years.[275] These findings have been confirmed in three additional randomized trials including the MabThera International Trial (MInT; 6 cycles of R-CHOP or CHOP) which extended the findings to young patients with 0 or 1 risk factors according to the IPI,[269, 276] the Dutch HOVON and Nordic Lymphoma group study (8 cycles of R-CHOP-14 or CHOP-14) and the ECOG/CALGB study confirming the findings in patients older than 60 years.[277, 278] The ECOG/CALGB 9703 study also showed that maintenance rituximab in first remission offered no clinical benefit to patients who received R-CHOP as their induction therapy.[278]

The German High Grade Study Group demonstrated that 6 cycles of dose dense CHOP (CHOP-14) as first-line therapy was superior to 6 cycles of CHOP-21, prior to the introduction of rituximab.[279-281] In the RICOVER 60-trial, the addition of rituximab to 6 or 8 cycles of CHOP-14 (R-CHOP-14) significantly improved clinical outcomes in elderly patients (age 61-80 years) compared to CHOP-14 alone.[282, 283] With a median observation time of 82 months, EFS was significantly improved after R-CHOP-14 (relative risk [RR]=0.50; P<0.001) compared with CHOP-14; OS rate was also significantly improved in R-CHOP-14 treated patients. No clinical benefit and increased toxicity was seen in patients treated with 8 cycles of therapy as compared to 6 cycles.[283]

Two randomized trials have now reported data comparing R-CHOP-21 with dose-dense R-CHOP-14.[284, 285] A large phase III randomized trial involving over 1000 adults with newly diagnosed DLBCL [284] found no significant difference in either PFS or OS at a median follow up of 37 months. The 2-year OS rate was 90% in the R-CHOP-14 arm and 81% in the R-CHOP-21 arm. Toxicity was similar, except for a lower rate of grade 3-4 neutropenia in the R-CHOP-14 arm (31% vs. 57%), reflecting that all patients in the R-CHOP-14 arm received primary growth factor prophylaxis with G-CSF whereas no primary prophylaxis was given with R-CHOP-21.[284] The ongoing phase III LNH03-6B GELA study is evaluating 8 cycles of R-CHOP-14 compared with R-CHOP-21 in elderly patients (age 60-80 years) with DLBCL. At the second planned interim analysis (N=202), no significant differences between R-CHOP-14 and R-CHOP-21 were observed in 2-year EFS (48% vs. 61%), PFS (49% vs. 63%) or OS rates (67% vs 70%).[285]

Grade 3-4 hematologic toxicities were observed more frequently in the R-CHOP-14 arm despite a higher proportion of patients having received G-CSF (90%) compared with patients in the R-CHOP-21 arm (66%). Collectively, these studies suggest that R-CHOP-21 remains the standard treatment regimen in patients with newly-diagnosed DLBCL with no improvement in outcome observed for dose-dense therapy in the rituximab era.

Dose-adjusted EPOCH plus rituximab (R-EPOCH) has shown significant activity in untreated patients with DLBCL.[286, 287] An ongoing phase III randomized study is evaluating dose-adjusted R-EPOCH vs. R-CHOP in untreated patients with DLBCL.

NCCN Recommendations

For patients with non-bulky (<10 cm) stage I or II disease, R-CHOP (3 cycles) with IFRT or R-CHOP (6 cycles) with or without IFRT is recommended. IFRT is recommended for patients who are not candidates for chemotherapy. Addition of RT to a full course of 6 cycles of R-CHOP for patients with no adverse factors is included with a category 2B recommendation. Patients with bulky disease (10 cm or greater) may be more effectively treated with 6 cycles of R-CHOP with or without locoregional RT (category 1).

For patients with advanced stage disease, treatment with 6 cycles of R-CHOP-21 (category 1) is recommended. In selected cases, RT to bulky sites may be beneficial (category 2B). Some patients are at increased risk for developing CNS relapse, including those with involvement of the paranasal sinus, testes, bone marrow with large cell lymphoma, or having two or more extranodal sites with elevated LDH.[288-291] Although the optimal management of these patients is still under investigation, the NCCN Guidelines panel currently recommends CNS prophylaxis with 4-8 doses of intrathecal methotrexate and/or cytarabine, or 3-3.5 g/m^2 of systemic methotrexate. For patients with concurrent presentation of parenchymal involvement of the CNS, systemic methotrexate (3-3.5 g/m^2) should be incorporated as part of the treatment plan; for patients with concurrent leptomeningeal disease, 4-8 doses of intrathecal methotrexate and/or cytarabine and/or 3-3.5 g/m^2 systemic methotrexate should be incorporated. When administering high-dose methotrexate, patients should receive leucovorin rescue and have full recovery of blood counts prior to initiating the next cycle of R-CHOP. Systemic methotrexate with leucovorin rescue has been safely incorporated into R-CHOP-21, with methotrexate administered on day 15 of the 21-day R-CHOP cycle.[292]

R-CHOP-21 is recommended as initial therapy; however, other comparable anthracycline-based regimens may also be acceptable in selected circumstances. Suggested alternate options include dose dense R-CHOP-14 or dose adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab. Both of which are listed as category 2B recommendations. The NCCN Guidelines have included the following regimens as first-line therapy for patients with poor left ventricular function (category 2B):

- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) + rituximab [293]
- CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) + rituximab [294-296]
- CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisone) + rituximab [297-300]
- Dose adjusted EPOCH + rituximab[286, 287]
- CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) + rituximab[301]

Participation in clinical trials of new regimens is recommended, if available. In patients with bulky disease or impaired renal function, initial therapy should include monitoring and prophylaxis for tumor lysis syndrome.

Response Assessment and Follow-up Therapy

Interim restaging is performed to identify patients whose disease has not responded to or has progressed despite induction therapy. Imaging studies using PET scans may be particularly useful in determining whether residual masses represent fibrosis or viable tumor. A negative PET scan after 2-4 cycles of induction chemotherapy has been associated with favorable outcomes in several studies.[302-305] In patients with aggressive lymphoma (N=90) treated with first-line anthracycline-containing induction chemotherapy (with rituximab in 41% of cases), patients with negative PET scans (n=54) after 2 cycles of induction therapy had significantly higher 2-year EFS rate (82% vs. 43%; *P*<0.001) and OS rate (90% vs. 61%; *P*=0.006) compared with those who were PET-positive (n=36).[303] In another study in patients with aggressive lymphoma (N=103) treated with first-line CHOP or CHOP-like regimens (with rituximab in 49% of cases), the 5-year EFS rates were significantly higher for PET-negative patients (n=77) compared to PET-positive patients (n=22) following 4 cycles of induction therapy (80% vs. 36%; *P*<0.0001).[302] However, interim PET scan can produce false positive results and some patients treated with chemoimmunotherapy have a favorable long-term outcome despite a positive interim PET scan. A recent prospective study in patients with DLBCL evaluated the significance of interim PET scans (after 4 cycles of accelerated R-CHOP) by obtaining biopsies from patients with an interim positive PET. Only 5 of 37 interim positive PET scans had a biopsy demonstrating persistent disease; PFS outcome in patients who were interim PET-positive, biopsy-negative was identical to that in patients with a negative interim PET scan.[306] Therefore, interim PET scan is not recommended outside the setting of a clinical trial, and is not recommended to be used to guide changes in therapy. If it is used, a repeat biopsy of residual masses is recommended to confirm true positivity. Patients who are receiving induction therapy should undergo evaluation prior to receiving RT, including all positive studies, after 3-4 cycles of chemotherapy. End of treatment restaging is performed upon completion of treatment. The optimal time to end of treatment restaging is not known. However, the panel recommends waiting for 6-8 weeks after completion of therapy before repeating PET scans.

Considerable debate remains in the routine use of follow-up imaging for surveillance in patients who achieve a CR after induction therapy. Although positive scans can help to identify patients with early asymptomatic disease relapse, false positive cases remain common and problematic, and may lead to unnecessary radiation exposure for patients as well as increased healthcare costs. In a study that evaluated the use of surveillance CT scans (at 3 and 12 months after completion of chemotherapy) in patients with DLBCL who achieved a CR with induction chemotherapy (N=117), 35 patients relapsed, and only 6% of these relapses were detected by follow-up CT scan in asymptomatic patients; 86% of cases of relapse were associated with development of new symptoms or signs of relapse.[307] The investigators therefore concluded that routine surveillance with CT scans had limited value in the detection of early relapse in patients with a CR following induction therapy. In a retrospective study evaluating the use of surveillance imaging in patients with relapsed aggressive lymphoma who had a CR to initial chemotherapy (N=108), 20% of relapses were detected by imaging in asymptomatic patients.[308] In the remaining 80% of cases, relapse was identified by clinical signs and/or symptoms. Moreover, the cases of relapse detected by imaging were more likely to

represent a population of patients with low-risk disease based on age-adjusted IPI at the time of relapse.[308] Thus, routine imaging during remission may help to identify patients with more limited disease at the time of relapse, but has not been shown to improve ultimate outcome. In a more recent prospective study evaluating the role of PET scans (at 6, 12, 18, and 24 months after completion of induction therapy) in patients with a CR after induction therapy for lymphomas, surveillance using PET scans was found to be useful in detecting early relapse.[309] Among the cohort of patients with aggressive lymphomas in this study (n=183), follow-up PET scans detected true relapses in 10% of patients at 6 months, 5% at 12 months, and 11% at 18 months; the rate of false-positive scans was low, at 1% (including cohorts of patients with indolent and aggressive NHL).[309] Inconclusive PET scans were obtained in 8 of 183 cases (4%), 6 of which were confirmed as relapses based on biopsy evaluation. In another recent study, the use of follow-up PET/CT scan was retrospectively evaluated in patients with DLBCL who achieved a CR after induction therapy (N=75).[310] In this study, a follow-up PET/CT scan detected 27 cases of relapse, of which 23 were confirmed as relapses based on biopsy evaluation; thus, the positive predictive value of PET/CT scan for detecting relapse was 0.85. Both patient age (>60 years) and the presence of clinical signs of relapse were significant predictors of disease relapse.[310] In the absence of a demonstrated improved outcome favoring early PET detection of relapse, PET scans are not recommended for routine surveillance once patients have achieved a CR. In light of the risks of ongoing surveillance imaging, the NCCN Guidelines panel recommends restaging CT scans for DLBCL patients in remission once every 6 months for up to 2 years, with no ongoing routine surveillance imaging after that time, unless prompted by clinical signs or symptoms.

Interim and End of Treatment Response Evaluation for Stage I-II

When the plan involves RT after short course therapy, restaging should be undertaken prior to RT including repeat PET scan as the dose of RT will be influenced by the result (see Guidelines section on "Principles of RT"). For full course therapy, if interim restaging demonstrates response, the planned course of treatment is completed.

If the interim restaging demonstrates a PR, treatment with a higher dose of RT (see Guidelines section on "Principles of RT") is appropriate. Alternatively, a repeat biopsy can be obtained and if positive, the patient can proceed to second-line therapy followed by HDT/ASCR. It is appropriate to enroll patients with an interim PR on a clinical trial. The choice between these two options is often made on clinical grounds. RT is appropriate for patients not eligible for HDT/ASCR. Higher dose RT is also a reasonable choice if there is a very good PR. Patients with refractory or primarily progressive disease are managed as refractory or relapsed disease.

End of treatment restaging is performed upon completion of treatment. Imaging scans for restaging should be obtained at least 6-8 weeks after the completion of treatment. After end of treatment restaging, follow-up at regular intervals (every 3-6 months for 5 years and then annually or as clinically indicated thereafter) is recommended for patients with CR. In these patients, follow-up imaging scans should be performed no more than every 6 months for 2 years after completion of therapy, and then only as clinically indicated thereafter. Patients with PR and those with no response to treatment or progressive disease are treated as described for relapsed or refractory disease.

Interim and End of Treatment Response Evaluation for Stage III-IV

After interim staging, the planned course of treatment (R-CHOP-21 to a total of 6 cycles) is completed for patients with CR and PR. End of

treatment restaging is performed upon completion of treatment. Imaging scans for restaging should be obtained approximately 6-8 weeks after the completion of treatment. Observation is preferred for patients with CR. RT to initially bulky disease (category 2B) or first-line consolidation with HDT/ASCR can be considered in selected high-risk patients (category 2B, see next section on Role of HDT/ASCR Consolidation in First Remission). Patients in CR are followed up at regular intervals (every 3-6 months for 5 years and then annually or as clinically indicated thereafter). In these patients, follow-up imaging scans should be performed no more than every 6 months for 2 years after completion of therapy, and then only as clinically indicated thereafter. Patients with PR and those with no response to treatment or progressive disease are treated as described below for relapsed or refractory disease.

Role of HDT/ASCR Consolidation in First Remission

In the randomized GELA LNH87-2 study, patients with DLBCL in first CR after induction therapy received consolidation therapy with either sequential chemotherapy or HDT/ASCR.[311] Although no difference in outcome was prospectively observed in this trial, a retrospective subset analysis of patients with aaIPI high/intermediate- or high-risk disease (n=236), found that HDT/ASCR resulted in significantly improved outcomes compared with sequential chemotherapy with regards to both 8-year disease-free survival rate (55% vs. 39%; *P*=0.02) and 8-year OS rate (64% vs. 49%; *P*=0.04) in the high-intermediate/high-risk subset.[311] This study was performed prior to rituximab-containing induction chemotherapy.

Recently, several randomized trials have prospectively evaluated the role of upfront HDT/ASCR after rituximab-containing first-line chemoimmunotherapy. In the French GOELAMS 075 study, patients aged ≤60 years with DLBCL (N=286 evaluable) were randomized to receive 8 cycles of R-CHOP-14 or HDT with rituximab (R-HDT) followed by ASCR.[312] The 3-year PFS rate and OS rate was 76% and 83%, respectively with no significant differences between treatment arms.[312] In a randomized trial of the German High-Grade NHL Study Group, patients aged ≤60 years with aggressive lymphomas (N=262 evaluable) were treated with 8 cycles of CHOEP-14 combined with 6 doses of rituximab (R-CHOEP-14) or 4 cycles of MegaCHOEP combined with 6 doses of rituximab and followed by ASCR (R-MegaCHOEP).[313] No significant differences were observed between the R-CHOEP-14 and R-MegaCHOEP arms for PFS (3-year rate: 74% vs. 70%, respectively) or OS outcomes (3-year rate: 85% vs. 77%, respectively); among patients with high/intermediate aaIPI (score of 2), OS rate was significantly higher with R-CHEOP-14 compared with HDT.[313]

In the randomized DLCL04 trial of the Italian Lymphoma Foundation, patients aged ≤65 years with DLBCL (N=375 evaluable) were randomized to receive rituximab-containing first-line regimens (8 cycles of R-CHOP-14 or 6 cycles of R-MegaCHOP-14) with or without HDT/ASCR.[314] The 2-year PFS rate was significantly higher in the HDT/ASCR groups compared with the non-HDT/ASCR groups (72% vs. 59%; *P*=0.008), but the OS rate was 83% with no significant differences between these groups. In addition, no significant differences were observed in PFS rates between the two rituximab-based first-line regimens.[314] In the SWOG 9704 trial, patients with high-intermediate/high IPI DLBCL were randomized (N=253) to receive 3 cycles of R-CHOP or HDT/ASCR, following initial remission with 5 cycles of CHOP or R-CHOP induction.[315] The 2-year PFS rate was significantly higher with HDT/ASCR compared with chemoimmunotherapy alone (69% vs. 56%; *P*=0.005); the 2-year OS rates were not significantly different (74% vs. 71%, respectively). On

retrospective subset analysis of high IPI patients, however, an OS benefit was observed; in this subgroup, the 2-year PFS rate with HDT/ASCR was 75% compared with 41% with chemoimmunotherapy; the 2-year OS rate was 82% and 63%, respectively.[315]

The above studies, overall, found no benefit to upfront HDT/ASCR as compared with first-line rituximab-based chemoimmunotherapy. The suggestion of benefit limited to high-IPI risk patients warrants further prospective evaluation. Presently, upfront HDT/ASCR is recommended only in selected high-risk circumstances (category 2B), or in the context of a clinical trial.

Relapsed or Refractory Disease

The role of HDT/ASCR in patients with relapsed or refractory disease was demonstrated in an international randomized phase III trial (PARMA study).[316] In this study, patients with DLBCL responding to induction DHAP (dexamethasone, cisplatin and cytarabine) chemotherapy after first or second relapse (N=109) were randomized to receive additional DHAP chemotherapy plus RT, or RT plus HDT/ASCR. The 5-year EFS rate was significantly higher among the transplant group compared with the non-transplant group (46% vs. 12%; *P*=0.001), as was the 5-year OS (53% vs. 32%; *P*=0.038).[316]This study was performed prior to the availability of rituximab.

The efficacy of second-line therapy is predicted by the second-line age-adjusted IPI.[317, 318] Furthermore, pre-transplantation PET scans have been identified as predictive factors following HDT/ ASCR.[319, 320] PET positivity before transplant, and chemoresistance, are associated with a poor outcome.[321, 322] The results of studies from the GEL-TAMO group and ABMTR suggested that HDT/ASCR should be considered for patients who do not achieve a CR but who are still chemotherapy-sensitive.[323-325]

Several chemotherapy regimens have been used as second-line therapy prior to HDT/ASCR.[326-330] However, none of these have emerged as a preferred regimen. Rituximab as a single agent was modestly active in patients with relapsed or refractory DLBCL and is reserved for the frail elderly patient.[331] In a phase II study, rituximab in combination with ifosfamide, carboplatin and etoposide (R-ICE) produced a CR rate of 53% in patients with relapsed or refractory DLBCL (N=34), which was significantly better than historical controls treated with ICE alone (27%).[332] In an outpatient setting, the R-ICE regimen produced an ORR of 71% (25% CR) and an estimated 1-year EFS rate and OS rate of 60% and 72%, respectively, in patients with refractory B-cell lymphoma (N=28).[333] Rituximab with other regimens has also been shown to be effective in patients with relapsed or refractory DLBCL.[334-340]

An international randomized intergroup study (CORAL study) evaluated second-line therapy of relapsed or refractory DLBCL with R-ICE versus R-DHAP, followed by ASCR in all chemosensitive patients.[341] No significant difference in outcome was found between R-ICE and R-DHAP; thus, both regimens remain acceptable options for relapsed/refractory DLBCL. Notably, patients relapsing less than 1 year after initial R-CHOP therapy had a particularly poor outcome with 3-year PFS of 23%. Novel approaches are needed for these patients

For patients with relapsed/refractory DLBCL not eligible for transplant, or relapsed after transplant, bendamustine in combination with rituximab (BR) has been evaluated in small studies with encouraging results. In a small dose-escalation study of BR in patients with relapsed/refractory aggressive NHL (N=9; DLBCL, n=5), the 90 mg/m^2 dose of bendamustine (n=3) in the BR regimen resulted in PR in 1 patient while the 120 mg/ m^2 dose of bendamustine (n=6) resulted in CRs in 5 patients and a PR in 1 patient.[342] In elderly patients with

relapsed/refractory DLBCL (N=43; median age 74 years; n=33 evaluable), the BR combination (with bendamustine dose 120 mg/m^2) resulted in an ORR of 52% (CR 15%); the most common grade 3-4 toxicities were myelosuppression.[343]

NCCN Recommendations

HDT/ASCR is the treatment of choice for patients with relapsed or refractory disease that is chemosensitive at relapse. Patients with relapsed or refractory DLBCL who are candidates for HDT/ASCR should be treated with second-line chemotherapy, with or without rituximab (depending on whether the patient is deemed to be refractory to prior rituximab regimens). Suggested regimens (with or without rituximab) include the following:

- DHAP (dexamethasone, cisplatin, cytarabine),
- ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOX (gemcitabine and oxaliplatin)
- ICE (ifosfamide, carboplatin and etoposide)
- MINE (mitoxantrone, ifosfamide, mesna, etoposide)

Patients with CR or PR to second-line chemotherapy regimen should be considered for further consolidation with HDT/ASCR (category 1) with or without RT. IFRT before HDT/ASCR has been shown to result in good local disease control and improved outcome.[344] Additional RT can be given before or after stem cell rescue to sites with prior positive disease. Pertinent clinical trials, including the option of allogeneic stem cell transplantation, may also be considered.

Patients who are not eligible for HDT/ASCR should be treated in the context of a clinical trial. Alternatively, in the absence of suitable clinical trials, patients can also be treated with single-agent rituximab, bendamustine with or without rituximab,[345] lenalidomide (in patients with non-germinal center DLBCL) with or without rituximab[346-349] or multiagent chemotherapy regimens (with or without rituximab) such as dose-adjusted EPOCH,[350, 351] CEPP (cyclophosphamide, etoposide, prednisone and procarbazine),[293] GDP (gemcitabine, dexamethasone and cisplatin/carboplatin)[328, 352] or GemOx (gemcitabine and oxaliplatin)[336-338].

Patients with disease relapse following HDT/ ASCR should be treated in the context of a clinical trial or individually. However, those with progressive disease after three successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for patients who have experienced a long disease-free interval.

Primary Mediastinal Large B-cell Lymphoma (PMBL)

PMBL is a distinct subtype of NHL that histologically can be indistinguishable from DLBCL. This subtype tends to occur in young adults with a median age of 35 years with a slight female predominance.[353, 354] PMBL arises from thymic B-cells with initial local regional spread to supraclavicular, cervical, hilar nodes and into the mediastinum and lung.[353] Widespread extranodal disease is uncommon at initial diagnosis, present in approximately one quarter of patients, but can be more common at recurrence.[354] Clinical symptoms related to rapid growth of mediastinal mass include superior vena cava (SVC) syndrome, pericardial and pleural effusions.

Gene expression profiling has indicated that PMBL is distinct from DLBCL; the pattern of gene expression in PMBL is more similar to classical Hodgkin lymphoma (cHL).[37, 355] PMBL expresses B-cell antigens and lacks surface immunoglobulins. PMBL is CD19+, CD20+, CD22+, CD21-, IRF4/MUM1+ and CD23+ with a variable expression of

BCL2 and BCL6. CD30 is weakly and heterogeneously expressed in more than 80% of cases and CD15 is occasionally present.[354] CD10 positivity is seen in 8-32% cases. PMBL is also characterized by a low expression of HLA I or II molecules. There have been rare cases of mediastinal gray zone lymphomas with combined features of PMBL and cHL. Cytogenetic abnormalities that are common in PMBL include gains in chromosome 9p24 (involving the *JAK2* in 50–75% of patients) and chromosome 2p15 (involving the *c-REL*, encoding a member of the NF-κB family of transcription factors) and loss in chromosomes 1p, 3p, 13q, 15q, and 17p. [354] Age-adjusted IPI is of limited value in determining the prognosis of PMBL at diagnosis.[353, 356, 357] In a retrospective analysis of 141 patients from MSKCC, two or more extranodal sites and the type of initial therapy received were predictors of outcome for EFS, whereas only the initial therapy received was a predictor for OS.[356]

In retrospective analyses, intensive chemotherapy regimens have appeared more effective than CHOP[357-359] and the addition of IFRT has been associated with improved PFS; however, these studies were conducted in the pre-rituximab era.[360, 361] The role of RT requires confirmation in prospective randomized trials. In a retrospective study, the addition of rituximab to MACOP-B or VACOP-B did not appear to result in significant differences in clinical outcomes, but it did appear to improve outcome when added to CHOP.[357, 362-364] A small prospective study of the dose-adjusted EPOCH-R regimen without RT[365] demonstrated an encouraging 91% EFS at a median follow-up of 4 years. These observations need to be confirmed in larger prospective studies.

In an analysis of the subgroup of patients with PMBL (N=87) from the randomized MInT study, which evaluated CHOP-like regimens with or without rituximab, the addition of rituximab significantly improved the CR rate (80% vs. 54% without rituximab; *P*=0.015) and 3-year EFS rate (78% vs. 52%; *P*=0.012), but not the OS rate (89% vs. 78%; *P*=NS).[363] This study, however, only included young low-risk patients with IPI scores 0-1. Sequential dose dense R-CHOP followed by ICE consolidation (without RT) was also highly effective in patients with PMBL, with similar outcomes to the above analysis with R-chemotherapy from the MInT study.[366] At a median follow up for surviving patients at 3 years, the OS and PFS rates were 88% and 78%, respectively.[366]

In the absence of randomized trials, there is no established optimal treatment for patients with PMBL. R-CHOP-21 is widely used in NCCN member institutions based on data in patients with DLBCL. Post-treatment PET-CT is considered essential; if PET-CT is negative at the end of treatment, patients may be observed. Residual mediastinal masses are common. If PET-CT is positive, biopsy is recommended if additional treatment is contemplated.

Burkitt Lymphoma

BL is a rare and aggressive B cell tumor typically involving extranodal disease sites. In the WHO Classification, three clinical variants of BL are described: endemic, sporadic, and immunodeficiency-associated BL.[367] The endemic variant is the most common form of childhood malignancy occurring in equatorial Africa and the majority of cases are associated with EBV infection. Sporadic BL accounts for 1-2% of all adult lymphomas in the US and Western Europe, and can be associated with EBV infection in about 30% of cases.[367-369] Immunodeficiency-associated BL occurs mainly in patients infected with HIV, in some posttransplant patients and in individuals with congenital immunodeficiency.

Diagnosis

The typical immunophenotype of BL is sIg+, CD10+, CD19+, CD20+, CD22+, TdT-, Ki67+ (>95%), BCL2 , BCL6+, and simple karyotype with MYC rearrangement. Translocations involving the MYC gene are detected in nearly all cases of BL. Most cases (80%) of classical BL are characterized by t(8;14) which results in the juxtaposition of MYC gene from chromosome 8 with the IgH region on chromosome14.[33] Other variants with MYC rearrangements [t(8;22) or t(2;8)] are less common. Some cases of DLBCL are also associated with an overexpression of MYC. Therefore, establishing the diagnosis of BL can be challenging using routine cytogenetic analysis. FISH using a break apart probe or long segment PCR are more reliable for the detection of t(8;14) and its variants.[370] Studies by Dave et al [34] and Hummel et al [35] have reported gene expression profiling as an accurate, quantitative method for distinguishing BL from DLBCL. However, this technique is not yet recommended for widespread clinical use.

The 2008 WHO lymphoma classification eliminates atypical BL. For cases without typical morphology or immunophenotype, a provisional category has been introduced, B cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL.[16, 371] This group also includes cases that harbor both MYC and BCL2 or bcl-6 translocations, the so called "double hit" lymphomas.[371] Such cases of "double hit" lymphomas have a highly aggressive disease course with poor prognosis; case series have reported a median overall survival (OS) time of 4-6 months among patients with "double hit" lymphomas.[372-374] The optimal management of patients with "double hit" or "triple hit" (involving BCL6 translocation in addition to MYC and BCL2 translocations)[374] lymphomas has not been identified.

Workup

The initial diagnostic workup for BL includes a detailed physical examination (with special attention to the node bearing areas, liver and spleen) and CT scans of the chest, abdomen and pelvis. Adult patients with BL commonly present with bulky abdominal masses, B symptoms, and laboratory evidence of tumor lysis; in addition, bone marrow involvement (up to 70% of cases) and leptomeningeal CNS involvement (up to 40% of cases) may also be common findings at the time of diagnosis.[375] PET or integrated PET CT scans are not recommended for routine use, since it is unlikely that findings of PET or PET CT would alter therapy for patients with newly diagnosed BL. If the treatment includes an anthracycline-containing regimen, cardiac evaluation with MUGA scan or echocardiogram is recommended, particularly for older patients. Evaluations of bone marrow aspirates, biopsy, lumbar puncture and flow cytometry of cerebrospinal fluid are essential. In these highly aggressive lymphomas, as in DLBCLs, the serum LDH level has prognostic significance. These tumors exhibit a high degree of cellular proliferation, as determined by Ki 67 expression levels. Because BL is frequently associated with HIV infection, HIV serology should be part of the diagnostic workup for these diseases. In addition, testing for HBV should be performed, as chemoimmunotherapy regimens (often used in the treatment of BL) are associated with increased risks for HBV reactivation.

Treatment Options

BL is curable in a significant subset of patients when treated with dose-intensive, multiagent chemotherapy regimens that also incorporates CNS prophylaxis. 60 90% of pediatric and young adult patients with BL achieve durable remission if treated appropriately.[376] However, the overall survival of older adults with BL appears to be less favorable, compared with younger patients.[377] Although the SEER database

suggests that older adults (patients aged >40 years) represent about 60% of BL cases (with about 30% aged >60 years), this patient population is underrepresented in published clinical trials.[376, 377] It is preferred that patients with BL receive treatment at centers with expertise in the management of this highly aggressive disease.

Most contemporary regimens used in adult patients have been developed from the pediatric protocols, and include intensive multiagent chemotherapy along with CNS prophylaxis with systemic and/or intrathecal chemotherapy. Tumor lysis syndrome is more common in patients with BL and should be managed as outlined under "Tumor Lysis Syndrome" in the Supportive Care section of the Guidelines and Discussion.

CODOX M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate), alternating with IVAC (ifosfamide, etoposide and high dose cytarabine) is a highly effective regimen developed by Magrath et al.[378] Both cycles included intrathecal chemotherapy (cytarabine or methotrexate) for CNS prophylaxis in addition to high-dose systemic cytarabine and methotrexate. In the updated results obtained with 4 cycles of CODOX M/IVAC protocol given to previously untreated patients (n=55, BL or Burkitt-like lymphoma; n=11, DLBCL), the 1-year event-free survival (EFS) rate was 85%.[379]

In an international phase II study, Mead et al established the value of a modified CODOX M/IVAC regimen in adults with BL (N=52 evaluable).[380] Low-risk patients (n=12) received modified CODOX M (3 cycles) and high-risk patients (n=40) received modified CODOX M and IVAC (alternating cycles for 4 cycles). In low-risk patients, 2 year EFS and OS rates were 83% and 81%, respectively, compared with 60% and 70%, respectively, for high- risk patients.[380] The efficacy of the modified CODOX-M/IVAC regimen in high-risk BL (n=42) was confirmed in a subsequent trial, which reported 2-year progression-free survival (PFS) and OS rates of 62% and 64%, respectively.[381] Modified CODOX M regimen with or without alternating IVAC was also effective and well tolerated in older patients with BL or Burkitt-like lymphoma (N=14)[382] and in patients with HIV-associated BL (n=8).[383] More recently, the addition of the anti-CD20 monoclonal antibody rituximab has been investigated in combination with this intensive chemotherapy regimen, given that most cases of BL are CD20-positive. In a small study that evaluated CODOX-M/IVAC with or without rituximab in patients with BL or B-cell lymphoma unclassifiable (N=15), the 5-year PFS and OS rates were 87% for both outcome measures.[384] In a larger retrospective study in patients with BL (N=80) treated with CODOX-M/IVAC with or without rituximab, the 3-year EFS and OS rates with rituximab were 74% and 77%, respectively; the 3-year EFS and OS rates without the addition of rituximab was 61% and 66%, respectively.[385] Although a trend for improvement in outcomes with the addition of rituximab was observed, the differences were not statistically significant.

The hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine, including intrathecal methotrexate) , developed by the MD Anderson Cancer Center, was evaluated in patients with Burkitt-lymphoma/leukemia (N=26).[386] With this regimen, complete remission (CR) was achieved in 81% of patients and the 3-year OS rate was 49%; OS rate was higher among patients aged <60 years (77% vs. 17% for patients aged >60 years).[386] The addition of rituximab to the hyper-CVAD regimen (R-hyper-CVAD) has also been evaluated in recent studies. In a phase II trial in patients with newly diagnosed BL or B ALL (N=31), 86% achieved a CR, and the 3 year EFS and disease-free survival rates were 80% and 88%, respectively.

[387] The 3 year OS rates were similar among the elderly and younger patients (89% vs. 88%).[387] In the updated report (with a median follow up of 46 months; n=39 with non-HIV-associated BL, Burkitt-like or B-ALL), the 4-year OS rate with R-hyper-CVAD was 75%; the OS rates in patients younger than 60 years and those older than 60 years were 70% and 72%, respectively. [388] In a historical comparison with patients treated with hyper-CVAD alone (corresponding OS rates 50%, 70%, and 19%, respectively), outcomes were superior with the R-hyper-CVAD regimen. The results of this study showed that the addition of rituximab to hyper-CVAD improved long-term outcomes in patients with BL or B-ALL, particularly in the older patient subgroup.

The CALGB 9251 study evaluated the efficacy of intensive multiagent chemotherapy with and without cranial radiation for central nervous system (CNS) prophylaxis in adult patients with Burkitt leukemia or lymphoma.[389] Given the severe neurotoxicity, the protocol was amended after the first 52 of 92 patients were enrolled. The 3 year EFS rate was 52% in the cohort of patients who received intensive CNS prophylaxis (cranial RT and 12 doses of triple intrathecal chemotherapy) compared to 45% in those who received only 6 doses of intrathecal chemotherapy and cranial irradiation (the latter for high-risk patients only).[389] The subsequent CALGB 10002 study investigated the addition of rituximab and growth factor support to the above CALGB 9251 regimen, and without the use of prophylactic CNS irradiation.[390] Among patients with previously untreated BL or Burkitt-like lymphoma/leukemia (N=103 evaluable), 82% achieved a CR and 7% had a partial remission (PR). The 2-year EFS and OS rates were 77% and 79%, respectively; as would be expected, these survival outcomes were more favorable among the subgroup of patients with low-risk IPI scores (2-year EFS and OS rates 90% and 90%, respectively) compared with high-risk scores (55% and 55%, respectively).[390]

In a recent prospective study, dose-adjusted EPOCH with rituximab (DA-EPOCH-R) was evaluated in previously untreated patients with BL (N=29).[391] At a median follow up of 57 months, the EFS and OS rates with this regimen were 97% and 100%, respectively. The highly favorable outcomes seen in this study may reflect the inclusion of more low-risk patients compared to other studies, with approximately half of patients presenting with normal LDH levels.

The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) demonstrated the feasibility of intensive high-dose induction chemotherapy (prednisone, cyclophosphamide, doxorubicin, etoposide and mitoxantrone, without high-dose methotrexate or high-dose cytarabine) followed by consolidation with BEAM and autologous stem cell transplant in untreated adults with BL, Burkitt-like lymphoma, or B-ALL.[392] Among the patients with BL/Burkitt-like lymphoma (n=27), CR was achieved in 81% of patients with a PR in 11%; the 5-year EFS and OS rates were 73% and 81%, respectively.[392]

The management of patients with B cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL, as well as those patients with "double hit" B-cell lymphoma has not been well studied. Patients with "double-hit" lymphomas have very poor prognosis, with a median OS of 4-6 months with chemotherapy combinations (e.g., CHOP, CODOX-M/IVAC, hyper-CVAD, EPOCH), with or without the incorporation of rituximab.[260, 373, 374, 381] Therefore, these patients are best managed in the context of clinical trials evaluating novel targeted agents.

For patients with BL who relapse after first-line regimens, the treatment options remain undefined. Patients who have had reasonable remission duration with initial therapy may be considered for regimens such as DA-EPOCH-R, IVAC combined with rituximab (R-IVAC). R-GDP

(gemcitabine, dexamethasone, cisplatin, combined with rituximab), R-ICE (ifosfamide, carboplatin, etoposide, combined with rituximab), and high-dose cytarabine. However, it should be noted that these suggestions are based on very limited, retrospective studies with only a few patients. For instance, the R-ICE regimen was evaluated in a small group of pediatric patients with relapsed BL and B-ALL (n=14), which resulted in CR in 29% and PR in 36% of patients.[393] The best options for patients requiring second-line therapy for relapsed/refractory disease are investigational treatments in the context of clinical trials.

NCCN Recommendations

Participation in clinical trials is recommended for all patients. The NCCN Guidelines panel recommends the following regimens as initial therapy, which should also include adequate CNS prophylaxis with systemic and/or intrathecal chemotherapy with methotrexate and/or cytarabine:

- CALGB 10002 regimen
- CODOX M/IVAC (original or modified) with or without rituximab
- Dose-adjusted EPOCH with rituximab (DA-EPOCH-R)
- Hyper-CVAD with rituximab (R-hyper-CVAD)

Patients with CR to initial therapy should be followed up every 2-3 months for 1 year then every 3 months for 1 year and every 6 months thereafter. Consolidation therapy in the context of a clinical trial may be considered for high-risk patients with CR to induction therapy. Disease relapse after 2 years is rare following CR to induction therapy, and follow up should be individualized according to patient's characteristics. Patients with less than CR to initial therapy and those with relapsed or refractory disease should be treated in the context of a clinical trial. Second-line chemotherapy with rituximab-containing regimens followed by high-dose therapy and autologous stem cell rescue can be considered in selected patients. In the absence of suitable clinical trials or for patients unlikely to benefit from additional intensive multiagent chemotherapy regimens, best supportive care or palliative RT may be considered appropriate.

Lymphoblastic Lymphoma

Lymphoblastic lymphoma (LBL) is a rare disease that represents only <2% of non-Hodgkin lymphoma (NHL) diagnosed in adults.[11] The vast majority (approximately 90%) of LBL is a T-cell malignancy that occurs most often in young men. T-LBL is a clinically aggressive disease with frequent involvement of extranodal sites, particularly the bone marrow and central nervous system (CNS).

Diagnosis

Immunophenotyping studies are essential to distinguish between the precursor T- and B-cell LBL. Typical immunophenotypes of lymphoblastic lymphoma include dim expression of slg, CD10+/-, CD19+, CD20-/+, TdT+ for precursor B cell lymphomas; Precursor T cell lymphomas are characterized by dim expression of slg, CD10- , CD1a+/- , CD2+, CD3-/+, CD4/8+/+, CD7+, CD19/20-, TdT+. In addition to immunophenotyping, conventional or FISH cytogenetics may be performed for detection of abnormalities involving *MYC* rearrangements, t(8;14) or variants involving *MYC*, and t(9;22) resulting in *BCR-ABL1* fusion gene (Philadelphia chromosome).

Workup

The initial diagnostic workup for LBL includes a detailed physical exam (with special attention to the node bearing areas, liver and spleen) and CT scans of the chest, abdomen and pelvis. Bone marrow aspiration, biopsy, flow cytometry of cerebrospinal fluid and

lumbar puncture are essential. If the treatment plan includes an anthracycline-containing regimen, pre-treatment cardiac evaluation with MUGA scan or echocardiogram is recommended. If significant cardiac dysfunction is identified, cardiac consultation is necessary prior to the use of anthracyclines or anthracenediones.

Treatment Options

The prognosis of adult patients with LBL treated with regimens used for other subtypes of aggressive NHLs has generally been poor.[394] LBL has typically been treated with regimens appropriate for acute lymphoblastic leukemia (ALL). Tumor lysis syndrome (TLS) is more common in patients with LBL and should be managed as outlined under "Tumor Lysis Syndrome" in the Supportive Care section of the Guidelines and Discussion. The therapeutic regimens for adult patients with LBL are based on the treatment protocols developed for ALL, and often include several phases of treatment including induction, consolidation/intensification, and maintenance. The maintenance regimen generally includes weekly oral methotrexate, daily oral mercaptopurine, and monthly pulses of vincristine and prednisone, and is given for a total duration of 2 years. CNS prophylaxis is given with all types of ALL regimens, and generally comprises intrathecal methotrexate (with or without intrathecal cytarabine and prednisone) as well as CNS irradiation (for patients with CNS involvement at diagnosis or as otherwise indicated).

The 5-drug intensive induction chemotherapy regimen (the 'Larson regimen' with cyclophosphamide, daunorubicin, vincristine, asparaginase, and prednisone for induction; followed by early intensification, CNS prophylaxis with intrathecal methotrexate and cranial irradiation 24 Gy, late intensification and maintenance) used in the CALGB 8811 study for adult patients with ALL (N=197; median age 32 years; range 16-80 years) produced a CR rate of 85%.[395] The CR rate was 94% in patients aged <30 years compared with 39% in patients aged ≥60 years. The median overall survival (OS) was 36 months for the entire patient cohort. The estimated 3-year OS rate was 69% for patients <30 years old, 39% for those between 30 to 59 years and 17% for patients aged ≥ 60 years.[395]

A study from the German Multicenter Study Group for Adult ALL (GMALL) reported favorable outcome in adult patients with T-LBL (N=45; median age 25 years; range 15-61 years) treated with the T-ALL regimen from prior GMALL protocols similar to the pediatric BFM-90 protocol (8-drug induction chemotherapy with prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytarabine, 6-mercaptopurine and intrathecal methotrexate; followed by consolidation, re-induction, and maintenance; CNS prophylaxis with intrathecal methotrexate, CNS irradiation 24 Gy, and triple intrathecal therapy with methotrexate, cytarabine, and dexamethasone).[396] The CR rate was 93%, and the estimated 7-year OS, continuous CR, and disease-free survival rates were 51%, 65%, and 62% respectively. Mediastinal recurrence was common (47% of relapses) despite mediastinal irradiation (24 Gy) administered in this study.[396]

In a study conducted by the M.D. Anderson Cancer Center, the hyper-CVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with high-dose methotrexate and cytarabine; followed by maintenance; CNS prophylaxis with intrathecal methotrexate and cytarabine) produced a CR rate of 91% in adult patients with lymphoblastic lymphoma (N=33; median age 28 years; range, 17-59 years). The 3-year PFS rate (66%) and OS rate (70%) compared favorably with the previously published results for ALL regimens.[397, 398] In this trial, involved field

radiation therapy (30-39 Gy) was recommended for all patients with mediastinal involvement to reduce the risk of mediastinal recurrence. A retrospective analysis showed that consolidative radiation therapy to the mediastinum improved local disease control.[399]

The LMB regimen (cytoreduction with COP [cyclophosphamide, vincristine and prednisone] followed by induction with COPADM [cyclophosphamide, vincristine, prednisone, doxorubicin, and high-dose methotrexate]; followed by consolidation and maintenance; CNS prophylaxis with systemic high-dose methotrexate, intrathecal methotrexate, cytarabine and steroids) for pediatric patients with Burkitt lymphoma/leukemia has been evaluated in adult patients with Burkitt lymphoma, but not in patients with LBL. In a retrospective analysis of the LMB regimens in adult patients (N=65; median age 26 years; range, 17-65 years), 89% achieved a CR and the 3-year OS rate was 74%.[400]

High-dose therapy (HDT) followed by autologous stem cell transplant (ASCT) has also been investigated as consolidation.[401, 402] In a prospective randomized multicenter study, adult patients with LBL (N=119 enrolled for induction therapy; median age 26 years; range, 15 to 65 years) in first remission were randomized (n=65 in remission after induction) to receive consolidation with HDT/ASCT or consolidation with conventional chemotherapy and maintenance.[402] The use of HDT/ASCT was associated with a trend toward improved relapse-free survival (3-year rate: 55% vs. 24%; *P*=0.065) although no improvement in OS was observed compared with conventional dose therapy.[402] In a retrospective report from the IBMTR of patients (both pediatric and adults) treated for LBL, allogeneic stem cell transplant (SCT) recipients (n=76) were shown to have significantly lower relapse rates at 1 year (32% vs. 46%) and 5 years (34% vs. 56%) compared to patients undergoing ASCT (n=128).[401] However, no significant difference was observed in the 5-year lymphoma-free survival rates or OS rates between treatment groups. Allogeneic SCT was also associated with higher toxicity and early treatment- related mortality (TRM) compared with ASCT (TRM at 6 months: 18% vs. 3%, respectively).[401]

NCCN Recommendations

Patients with systemic LBL should be considered for participation in appropriate clinical trials, or in the absence of such trials, can be treated with any one of the multiagent chemotherapy regimens (BFM regimen, CALGB 8811 regimen, GMALL T-ALL, LMB-86 regimen or hyper-CVAD).[395-398, 400, 403] Patients with CR to induction therapy should continue with the remainder of the treatment protocol (i.e., consolidation/re-induction, maintenance) and then can be observed or be treated in the context of clinical trials. Poor-risk patients can be considered for allogeneic SCT. Patients with biopsy-proven PR are considered treatment failures and should be treated in clinical trials. Maintenance chemotherapy (up to 2 years) based on the treatment protocol is recommended. It is important that patients be treated with a given treatment protocol in its entirety (from induction, consolidation/re-induction, to maintenance), and not be treated with different components taken from different treatment protocols. In addition, CNS prophylaxis and maintenance should be included with all treatment regimens.

For patients with relapsed disease, the NCCN Guidelines recommend reinduction with combination chemotherapy or allogeneic SCT. Enrollment in clinical trials is especially encouraged to refine these approaches; the most appropriate therapy should be chosen in consultation with an expert in lymphoma management.

The following sections of the discussion are being updated to correspond with the newly updated algorithm.
Last updated on 05/18/2011.

Follicular Lymphoma

Diagnosis

FL is the most common indolent subtype of NHL accounting for about 22% of all newly diagnosed cases. About 90% of the cases have a t(14;18) translocation, which juxtaposes *BCL2* with the *IgH* locus that results in the deregulated expression of BCL2.

Follicular lymphoma has a characteristic immunophenotype, which includes CD20+, CD10+, BCL2+, CD23+/-, CD43-, CD5-, CCDN1- and BCL6+. Rare cases of FL may be CD10- or BCL2-. In BCL2-negative young patients with localized disease, the diagnosis of pediatric follicular lymphoma may be considered. The diagnosis is easily established on histological grounds, but immunophenotyping is encouraged to distinguish from a nodular MCL or SLL. Low grade FL with a high proliferation index as determined by Ki-67 immunostaining has been shown to be associated with aggressive clinical behavior. But there is no evidence that it should guide selection of therapy.[404, 405] Molecular genetic analysis to detect *BCL2* rearrangement, cytogenetics or FISH to identify t(14;18) and paraffin section immunohistochemistry for Ki-67 will be useful under certain circumstances.

Follicular Lymphoma International Prognostic Index (FLIPI) is based on age, Ann Arbor stage, number nodal sites involved, hemoglobin levels and serum LDH levels.[406] In the National LymphoCare study, which analyzed the treatment options and outcomes of 2,728 patients with newly diagnosed FL, FLIPI was used to define patients into three distinct groups with outcomes ranging from 52% to 90% survival at 5 years.[407] In a recent study conducted by the International Follicular Lymphoma Prognostic Factor Project, a prognostic model was developed from prospective accumulated data which includes: age, hemoglobin, dimension longest lymph node, beta-2 microglobulin, bone marrow involvement. FLIPI 2 was highly predictive of treatment outcome in newly diagnosed patients with FL treated with chemoimmunotherapy.[408] With follow up to date the FLIPI-2 does not predict for overall survival; furthermore, it is only applicable to patients requiring therapy. Both the FLIPI-1 and -2 predict for prognosis, but they have not yet been established as a means of selecting treatment options.

Workup

The diagnostic workup for FL is similar to the workup for other indolent lymphomas. The majority of patients present with disseminated disease. The approach to therapy differs dramatically between patients with localized and those with disseminated disease. Bone marrow biopsy with aspirate is essential to document clinical stage I-II disease. This can be deferred if observation is the initial treatment option. The majority of NCCN investigators routinely employ chest, abdominal and pelvic CT as part of the diagnostic evaluation. CT scan of the neck may also assist in defining the extent of local disease. In patients presenting with what appears to be localized disease, a PET scan may be helpful in identifying occult sites of disease or if there is concern about histologic transformation.[409] PET does not replace histologic confirmation of the diagnosis; however, if there are sites with discordant high FDG-avidity these represent the most likely sites of transformation.

Treatment Options based on Clinical Stage

NCCN guidelines for FL apply to FL 1-2. FL3A and FL3B are commonly treated according to DLBCL. It should be noted that in most centers the

proportion of patients diagnosed with FL3 is greater than that previously diagnosed as follicular large cell lymphoma in the International Working Formulation.

Stage I-II

IFRT (24-30 Gy, with an additional 6 Gy in selected patients with bulky disease) is the preferred treatment option for patients with stage I or contiguous stage II disease. In a retrospective analysis of 43 patients with stage I-II disease, carefully selected patients (requirement of large abdominal radiation field, advanced age, concern for xerostomia or patient refusal) who did not receive immediate treatment had comparable outcomes to those who were treated with RT.[410] In selected cases where toxicity of IFRT outweighs the potential clinical benefit, observation may be appropriate. Alternate treatment options include immunotherapy with or without chemotherapy with or without RT. The addition of cyclophosphamide, vincristine, prednisone, and bleomycin (COP-bleomycin) or CHOP-bleomycin improved failure free survival but did into impact overall survival in patients with early stage disease.[411] The addition of adjuvant CHOP to RT did not improve relapse free survival (RFS) in patients with early stage low-grade lymphoma.[412] Therefore, chemotherapy plus RT is included with a category 2B recommendation.

For patients with a clinical PR or CR, clinical follow-up with examination and laboratory assessment is initially done every three months with repeat imaging every 6 months or as clinically indicated. Patients no response to initial therapy should be managed in the same manner as patients with advanced disease, as described below.

Stage II (bulky disease) and Stage III-IV

Rituximab has demonstrated single agent activity in previously untreated patients as well in those with relapsed or refractory disease.[413-415] The addition of rituximab to combination chemotherapy regimens has consistently increased the ORR, response duration and PFS. In addition, some studies have demonstrated OS benefit; a recent meta-analysis has confirmed the benefit in OS despite what is still limited follow up for FL.[416]

The safety and efficacy of R-CHOP was demonstrated in a small study that demonstrated excellent long-term results.[417, 418] The superiority of R-CHOP to CHOP in treatment naïve patients was established in a prospective randomized phase III study conducted by the German Low-Grade Lymphoma Study Group (GLSG) involving 428 patients. R-CHOP was associated with a 60% reduction in the relative risk for treatment failure, significantly prolonged time to treatment failure, higher ORR and prolonged duration of remission.[419] OS analysis is complicated by a second randomization which included high dose therapy followed by autologous stem cell rescue (HDT/ASCR). There OS was the same with and without rituximab, if there was consolidation with HDT/ASCR. However, OS was significantly improved for patients receiving R-CHOP followed by interferon compared to CHOP followed by interferon. R-CHOP also improved outcome of elderly patients with previously untreated FL.[420]

Addition of rituximab to CVP chemotherapy (R-CVP) significantly improved outcome in patients with previously untreated FL, with no significant increase in toxicity.[421] At a median follow-up of 53 months, R-CVP was associated with improved ORR (81% vs. 57%), median time to progression (34 months vs. 15 months) and 4-year OS (83% vs. 77%).[422]

The addition of rituximab to fludarabine or fludarabine-based combination has improved outcomes in various clinical studies.[423-426] In a prospective randomized trial, FCM-R regimen (fludarabine,

cyclophosphamide, mitoxantrone and rituximab) was associated with superior outcomes in patients with relapsed or refractory FL and MCL.[424] In another randomized trial, concurrent administration of rituximab with FND regimen (fludarabine, mitoxantrone and dexamethasone) resulted in a significantly higher 3-year FFS rate (84% vs. 59% for sequential arm) in a subset of patients with FL. [425]

Bendamustine, as a single agent or in combination with rituximab (BR), has shown promising results with acceptable toxicity in patients with newly diagnosed as well as heavily pretreated patients with relapsed or refractory indolent or mantle cell histologies as well as transformed NHL.[427-431] A randomized phase III study conducted by the StiL (Study Group Indolent Lymphomas) compared BR and R-CHOP as first-line treatment in patients with advanced follicular, indolent, and mantle cell lymphomas. The ORR was similar in both arms though the CR rate was significantly higher in the BR arm (40% vs. 31%).[427] However, the BR patients had a significantly longer median PFS (55 months vs. 35 months) and EFS (54 months vs. 31 months). Bendamustine plus rituximab also showed a better toxicity profile. Overall survival is similar. In a phase II multicenter study, BR resulted in an ORR of 92% (41% CR and 38% PR) in patients with relapsed or refractory indolent and mantle cell lymphomas. Median duration of response and progression-free survival was 21 months and 23 months respectively. Outcomes were similar for patients with indolent or mantle cell histologies.[430]

Radioimmunotherapy (RIT) with ^{131}I-tositumumab[432-435] and ^{90}Y-ibritumomab tiuxetan[436-438] has also been evaluated in patients with newly diagnosed as well as those with relapsed, refractory or histologically transformed FL. Initial treatment with single one-week course of ^{131}I-tositumomab induced prolonged clinical and molecular remissions in patients with advanced FL.[432] After a median follow-up of 10 years, the median duration of response was 6 years. For the 57 complete responders, median PFS was 11 years.[439] Ten-year PFS and OS rates were approximately 40% and 82% respectively. In an international phase II trial, ^{90}Y ibritumomab when used as a first-line therapy resulted in an ORR of 72% (52% CR and 20% PR) at 12 months after therapy. At a median follow-up of 23 months the PFS is 18 months.[440]

A single course of ^{131}I-tositumumab was significantly more efficacious than last qualifying chemotherapy in extensively pretreated patients with refractory, low-grade, or transformed NHL.[434] The final results of the study demonstrated that ^{131}I-tositumumab resulted in long-term durable CRs a subset of patients who had received no prior rituximab.[441] In a randomized phase III study, ^{90}Y ibritumomab tiuxetan also produced statistically and clinically significant higher ORR and CR compared with rituximab alone in patients with relapsed or refractory low-grade, follicular or transformed lymphoma.[437] At a median follow-up of 44 months, median TTP (15 vs.10.2 months), duration of response (16.7 vs. 11.2 months) were longer for patients treated with ^{90}Y-ibritumomab compared with the rituximab.[438]

NCCN Recommendations Stage II (bulky disease) and Stage III-IV disease

Despite therapeutic advances that have improved the survival of patients with FL, it remains an incurable disease with conventional therapy. Four prospective randomized trials have failed to demonstrate a survival advantage for immediate treatment.[442-445]

Modified Groupe d'Etude des Lymphomes Folliculaire (GELF) criteria are used to decide when to initiate therapy in patients with advanced-stage disease including: symptoms attributable to FL (not limited to B-symptoms); threatened end-organ function; cytopenia secondary to lymphoma; bulky disease (singe mass >7cm or 3 or

more masses >3cm), splenomegaly; steady progression over at least 6 months. Patient preference should be considered; however, patients wanting treatment without a clinical indication should be referred for an appropriate clinical trial. The selection of treatment should be highly individualized according to age, extent of disease, comorbid conditions, and the goals of therapy. When choosing an initial therapy, care should be given to avoid excessively myelotoxic regimens in patients who may subsequently be candidates for HDT/ASCR. In patients with hepatitis-B, treatment with an antiviral should be given if rituximab is used. See "Hepatitis B Reactivation" in the Supportive Care section of this manuscript.

First-line therapy

In the absence of an appropriate clinical trial, patients with indications for treatment should be treated with systemic therapy. In selected cases such as the elderly frail patient who would not tolerate chemotherapy, IFRT (4 Gy) may be used for local palliation. Asymptomatic patients especially those older than 70 years can be observed.[444] The results of an interim analysis of the intergroup randomized trial of rituximab vs. a watch and wait strategy showed that at 36 months after randomization, the estimated PFS was significantly better for asymptomatic patients with stage II-IV non-bulky disease receiving rituximab alone or rituximab followed by rituximab maintenance compared to observation, but there was no difference in OS between the treatment arms.[445] Further follow-up is needed to determine if immediate treatment has an impact on time to second therapy. The panel felt that these data were not sufficiently compelling that they should change practice. The ECOG RESORT trial is examining rituximab maintenance versus rituximab delayed until progression in a similar patient population and will provide some additional insight.

Based on the reported data, rituximab in combination with bendamustine, CHOP or CVP chemotherapy for first-line therapy in patients with advanced FL are all category 1 recommendations. BR has been shown to have less toxicity and a superior PFS compared to R-CHOP; however, the OS is not different. Furthermore, we have limited data on the risk of secondary MDS/AML after bendamustine. Data from a limited subset of patients suggests that peripheral blood stem cells can be collected after both BR and R-CHOP; more data is needed to confirm this finding. We do not have a comparative trial of R-CHOP and R-CVP. Therefore, choice of first-line therapy in advanced stage FL remains a challenge for the clinician. Other suggested regimens include rituximab either as a single agent or in combination with fludarabine-based chemotherapy. RIT is included as category 2B option for first-line treatment. IFRT (4-30 Gy) with or without systemic therapy can be considered for palliation in patients with locally bulky or symptomatic disease if they are unable to tolerate systemic therapy.

Single agent rituximab is the preferred first-line therapy for elderly or infirm patients. Single agent cyclophosphamide had equivalent OS and CR rates compared to cyclophosphamide-based combination chemotherapy.[446] The guidelines have also included RIT, alkylating agent-based chemotherapy (cyclophosphamide or chlorambucil) with or without rituximab as alternative options for elderly or infirm patients.

First-line Consolidation or Extended Dosing

Chemotherapy followed by RIT

First-line chemotherapy followed by RIT with ^{131}I-tositumumab[447-450] or ^{90}Y-ibritumomab [451-454] has been evaluated in several phase II studies. In the Southwest oncology Group (S9911) trial, CHOP followed by ^{131}I-tositumomab resulted in an ORR of 91%, including a 69% complete

remission (CR) rate in patients with previously untreated FL.[449] After a median follow-up of 5 years, the estimated 5-year OS rate was 87%, and PFS rate was 67%.[448] In historical comparison, these statistics were better than those reported for CHOP alone. In a multicenter phase II study, CVP chemotherapy followed by ^{131}I-tositumomab resulted in an ORR of 100% with 93% CR in untreated patients with FL. The 5-year PFS and OS rates were 56% and 83%, respectively.[450]

In the international phase III trial (First-line Indolent Trail), 414 patients with advanced stage FL responding to first-line induction therapy were randomized to receive ^{90}Y-ibritumomab or no further treatment.[453] After a median follow-up of 5.5 years, the 5-year PFS was 47% and 29%, respectively, for the ^{90}Y-ibritumomab tiuxetan consolidation group and the control group. Median was 49 months and 14 months respectively.[455]There is no significant difference in OS between treatment arms. The rate of secondary malignancies (MDS/AML) were higher among patients in the consolidation group (3%) compared to those in the control group 1%). This trial included only a limited number of patients (14%) who received rituximab in combination with chemotherapy as induction therapy. Among these patients, the 5-year PFS rates were 64% and 48% respectively, for the ^{90}Y-ibritumomab group and the control group.

Maintenance therapy with Rituximab

Prolonged administration of rituximab significantly improved EFS in chemotherapy-naïve patients responding to rituximab induction, but did not extend OS.[456-458] In another study, maintenance rituximab improved PFS (31 vs. 7 months). However, retreatment with rituximab at progression provided the same duration of benefit as did maintenance rituximab (31 vs. 27 months).[459] The randomized phase III study (ECOG1496) demonstrated PFS benefit for rituximab maintenance in patients with advanced indolent lymphoma responding to first-line chemotherapy.[460] The 3-year PFS rate was 68% for maintenance rituximab compared to 33% for observation for all patients with advanced indolent lymphoma with response or stable disease after CVP chemotherapy. The corresponding PFS rates were 64% vs.33% respectively for patients with FL.[460]

The PRIMA trial prospectively evaluated the role of rituximab maintenance in patients responding to first-line chemotherapy in combination with rituximab. In this study, 1,018 eligible patients responding to first-line chemoimmunotherapy (R-CVP, R-CHOP or R-FCM) were randomized to observation or rituximab maintenance for 2 years.[461] The interm analysis with a median follow-up of 24 months showed that rituximab maintenance significantly improved PFS (primary endpoint) compared to observation. After a median follow-up of 36 months, 3-year PFS rate was 75% in the rituximab maintenance arm and 58% in the observation arm.[462] At 2 years after randomization,72% of patients in the rituximab maintenance group were in CR or Cru compared to in the observation group.[462] However, the OS was not significantly different between the two groups. Follow-up is ongoing to evaluate the effect of rituximab maintenance on OS.

Patients with CR or PR to first-line therapy can be observed or they can be treated with consolidation therapy. Based on the results of the PRIMA study,[461] maintenance rituximab up to 2 years is recommended (category 1) for patients responding to first-line chemoimmunotherapy. RIT is recommended (category 1) only for patients who received first-line chemotherapy based on the results of the FIT trial.[453] The recommendation to limit RIT to patients receiving induction chemotherapy rather than chemoimmunotherapy is based on the small proportion of patients who received induction chemoimmunotherapy in the FIT trial. For patients receiving

consolidation therapy, clinical follow-up is initially recommended every 3 months with repeat imaging every 6 months and/or as clinically indicated.

Second-line Therapy for Relapsed or Progressive Disease

Frequently, patients will benefit from a second period of observation after progressing from first line therapy. Thus, treatment for relapsed or progressive disease is based on the modified GELF criteria as in first-line therapy. Progressive disease should be histologically documented to exclude transformations, especially if there are raising LDH levels, disproportional growth in one area, development of extranodal disease or new "B" symptoms. Non-uniform uptake on a FDG-PET scan can be an indication of transformation; areas of high SUV, especially in excess of 13.1 are suspicious for transformation. However, a PET scan does not replace a biopsy; it should used to direct a biopsy to enhance the diagnostic yield from the biopsy. The options include chemoimmunotherapy regimens used for first-line treatment, FCMR regimen (category 1) or RIT (category 1) or any of the second-line regimens used for patients with DLBCL.

Second-line Consolidation or Extended Dosing

Rituximab maintenance following second-line therapy for relapsed/refractory disease has been established in two large randomized trials to provide a PFS advantage over observation for patients treated with chemoimmunotherapy.[463, 464, 465]

In a prospective randomized study by the GLSG, rituximab maintenance after second line treatment with R-FCM (rituximab with fludarabine, cyclophosphamide and mitoxantrone) significantly prolonged duration of response in patients with recurring or refractory FL and to a lesser degree in patients with MCL.[463] In a phase III Intergroup trial (EORTC 20981), maintenance rituximab significantly improved median PFS and OS in patients with relapsed or resistant FL responding to CHOP or R-CHOP.[464] With a median follow-up of 6 years, the 5-OS rate was 74% and 64% in the rituximab maintenance arm, and the observation arm respectively.[465]

HDT/ASCR has been shown to prolong OS and PFS in patients with relapsed or refractory disease.[466-468] The GELA recently conducted a retrospective analysis of patients treated with chemotherapy alone in the first line and found that EFS and survival after relapse (SAR) were superior if patient with treated with rituximab containing regimens compared to chemotherapy only-based HDT/ASCR in patients with relapsed or refractory FL.[469] The combination of rituximab-based second-line therapy followed by HDT/ASCR had the best results with SAR 90% at 5 years. Allogeneic HSCT is associated with high treatment related mortality rates (30-38% for myeloablative and 25% for nonmyeloablative).[470, 471] In a recent report from IBMTR, both myeloablative and nonmyeloablative transplant had similar TRM rates but nonmyeloablative allogeneic HSCT was associated with an increased risk of disease progression.[472]

Rituximab maintenance is recommended (category 1) for patients in second-line remission. However, the panel recognized that the efficacy of maintenance rituximab in second-line remission would likely be impacted by first-line maintenance. If a patient progressed during or within 6 months of first-line maintenance rituximab, the value of maintenance in the second-line is likely very minimal. HDT/ASCR is an appropriate consolidative therapy for patients with second or third remission. Allogeneic HSCT may be considered for highly selected patients. For patients receiving consolidation therapy, clinical follow-up is initially recommended every 3 months with repeat imaging every 6 month and/or as clinically indicated.

Histological Transformation to DLBCL

Transformation to DLBCL in patients with FL occurs at a rate of approximately 2-3% per year for at least 15 years and the risk of transformation falls after that time, for reasons that remain unclear.[473] Transformation to DLBCL is generally associated with a poor clinical outcome. However, patients with limited disease with no previous exposure to chemotherapy can have the favorable outcomes similar to de novo DLBCL.[474] In cases where the patient has had multiple prior therapies, the prognosis is much poorer and enrollment in clinical trial is the preferred option. In the absence of a clinical trial, treatment options include RIT, chemotherapy with or without rituximab, IFRT or best supportive care. HDT/ASCR or allogeneic HSCT can be considered for patients with responsive disease after initial treatment.

If the patient has had minimal (IFRT alone or one course of single agent therapy including rituximab) or no prior chemotherapy, anthracycline-based chemotherapy with rituximab, with or without RT is included as a treatment option. Enrollment in clinical trial is recommended for all patients following initial therapy. Patients responding to initial treatment could be considered for HDT/ASCR or allogeneic HSCT. Alternatively, patients with CR to initial therapy can be observed and RIT may be considered for those with PR. Patients with no response or progressive disease following initial therapy should be treated with RIT or best supportive care.

AIDS-related B-Cell Lymphoma

Overview

AIDS-related lymphoma (ARL) is usually an AIDS-defining diagnosis in patients infected by the human immunodeficiency virus (HIV). Prior to the development of highly active antiretroviral therapy (HAART), ARL often presented with widespread, extra nodal disease, B symptoms, CNS involvement, and poor prognosis.[475] However, in the HAART era the incidence of HIV-associated lymphoma has fallen.[476] With the use of combination antiretroviral therapy, the survival of patients diagnosed with HIV-related systemic NHL has improved, with two thirds of patients surviving for longer than 1 year after diagnosis.[477] BL and DLBCL are the most common forms of ARLs. The patients who develop BL generally have higher CD4 counts though a small fraction may present with CD4 counts less than 100. Primary CNS lymphoma (PCNSL) develops in patients with very low CD4 counts and is most often seen in uncontrolled AIDS, the incidence of this presentation has fallen dramatically in the HAART era. DLBCL occurs in the patients between these extremes.

Plasmablastic lymphoma (PBL) and primary effusion lymphoma (PEL) are two forms of lymphoma seen more commonly associated with HIV compared to lymphoma in patients without HIV. PEL accounts for less than 5% of the ARL cases most often occurring in the pleural, pericardial, and abdominal cavities.[478, 479] PELs are associated with human herpes virus 8 (HHV8) infection and many are also coinfected with Epstein Barr virus (EBV). PBL is another unique large B cell lymphoma that mainly involves the jaw and oral cavity of the HIV infected patients.[480] Multicentric Castleman's disease (MCD) is prevalent in HIV infected individuals and it has also been associated with HHV8 infection and increased incidence of lymphoma in HIV infected patients.[481]

Diagnosis

The diagnostic evaluation of HIV-associated lymphoma is not different from the non HIV-associated disease. The major factor is to distinguish between BL and DLBCL. Hodgkin lymphoma and indolent lymphoma are seen in patients with HIV at an incidence higher than in

the general population but they are much less common than BL or DLBCL.

Workup

The diagnostic evaluation is as outlined above for BL. However, all patients (without regard to histology) should have a lumbar puncture to rule out CNS involvement. In addition, baseline values for CD4 counts and viral load should be obtained.

Treatment

Optimal management of HIV-associated lymphoma is not established. However, several key factors have emerged as being important to improve outcome. In general, studies have demonstrated that early introduction of HAART therapy is associated with superior outcomes. This has allowed for the administration of more dose-intense regimens and a reduction in treatment-associated toxicity.[482, 483]

In the NHL HIV 93 trial of risk adapted intensive chemotherapy in ARL patients, Mounier et al reported that HIV score, IPI (international prognostic index) score, and HAART affect survival in patients with ARL but not the intensity of the chemotherapy.[484] Combination chemotherapy regimens such as CHOP or CDE (cyclophosphamide, doxorubicin and etoposide) given with concomitant HAART,[485-487] or EPOCH regimen without HAART,[488] have proven to be effective and tolerable in patients with ARL.

In the HAART era, the median survival of patients with HIV-associated DLBCL is similar to that of patients with non-HIV-associated DLBCL. There has been conflicting data regarding the outcomes of patients with HIV-associated BL. One study demonstrated that there was a median survival of only 6 months.[489] However, a retrospective analysis by Wang et al. reported that HIV-positive patients with BL treated with CODOX M/IVAC had outcomes similar to that observed in HIV-negative patients treated with the same regimen.[383]

The safety and efficacy of rituximab in combination with chemotherapy has also been evaluated in clinical trials. In the randomized phase III trial conducted by the AIDS Malignancies Consortium (AMC010), the addition of rituximab to CHOP was associated with improved tumor responses; but this combination also increased the risk of neutropenia and infection, particularly in patients with CD4 counts of less than 50.[490] In subsequent phase II trials, however, rituximab in combination with CHOP or infusional CDE regimens was feasible and highly effective with an acceptable toxicity level in patients with ARL.[491-493] Long term follow up of patients with ARL treated with the combination of rituximab and CDE concomitantly with HAART produced CR rate of 70% and TTF at 5 years was 52%, which are comparable to those observed in non-HIV positive patients.[494]

In a recent report, Dunleavy et al demonstrated that the addition of rituximab to EPOCH regimen is highly effective and tolerable in patients with ARL and enables the administration of fewer treatment cycles.[495] In this study, the addition of rituximab did not appear to cause serious infection related complications or deaths. The AMC034 randomized trial evaluated the use of sequential vs. concurrent infusional EPOCH regimen in combination with rituximab. CR was observed in 73% and 55% of evaluable patients in the concurrent and sequential arms, respectively.[496] Toxicity was comparable in the two arms, although patients with a baseline CD4 count of less than 50 had a high infectious death rate in the concurrent arm. The 2-year PFS rates in the concurrent and sequential arms were 64% and 60%, respectively. The authors concluded that concurrent rituximab plus

infusional EPOCH is an effective regimen for HIV-associated lymphoma which merits further evaluation.

NCCN Recommendations

The NCCN guidelines recommend the use of HAART and growth factor support along with full dose chemotherapy. Any change in antiviral therapy should be done in consultation with an infectious disease specialist. Patients on antiretrovirals with persistently low CD4 count of less than 100 tend to have a poor prognosis and higher risk of infection associated with the addition of rituximab. The omission of rituximab is strongly suggested for these patients due to the higher risk of infectious toxicities. Prophylaxis with intrathecal chemotherapy is used at some NCCN institutions for all patients, whereas at other NCCN institutions patients with AIDS related DLBCL with selected high-risk features (involvement of 2 or more extranodal sites, bone marrow involvement, or other high-risk site involvement such as epidural, testicular or paranasal sinuses).

Patients with AIDS related BL should be treated with chemotherapy (with or without rituximab) such as CODOX-M alternating with IVAC, dose adjusted EPOCH, CDE (cyclophosphamide, doxorubicin and etoposide) or CHOP chemotherapy with or without high dose methotrexate (not exceeding 3 g/m2). Patients with AIDS related DLBCL should be treated with dose adjusted EPOCH, CDE, CHOP or CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone). Patients with lymphoma associated with MCD and PEL can also be treated with the same regimens as described for patients with DLBCL. Since most cases of PEL are CD20 negative, the addition of rituximab is not indicated.

PBL was associated with a poor prognosis in the pre HAART era. In the HAART era, the prognosis is better with the use of intensive chemotherapy regimens along with HAART. The outcome of the HIV positive patients with PBL treated at the Memorial Sloan Kettering Cancer Center was superior to the majority of reports in the literature.[497] Among six patients treated with anthracycline based multiagent chemotherapy with HAART, five were alive and diseases free, with a median follow-up of 22 months. The NCCN guidelines recommend CODOX M/IVAC, EPOCH or hyperCVAD regimens for patients with PBL.

PCNSL is associated with severe immunosuppression and poor prognosis. In a retrospective study, patients with PCNSL treated with HAART and RT had a more favorable outcome.[498] High dose methotrexate, RT or antiretroviral therapy can be considered for patients with PCNSL. Selected patients with good performance status receiving HAART can be treated as per CNS lymphoma guidelines.

Cutaneous B-cell lymphomas

Cutaneous B-cell lymphomas (CBCLs) are a group of B-cell lymphomas originating in and usually confined to the skin. CBCLs are estimated to represent approximately 20-25% of all primary cutaneous lymphomas.[58, 499] In the United States, the SEER (Surveillance, Epidemiology, and End Results) data from the National Cancer Institute (NCI) indicated that the incidence of cutaneous T-cell lymphomas accounted for 71%, whereas CBCLs accounted for 29% from 2001-2005.[500] The new WHO-EORTC classification for cutaneous lymphomas distinguishes 3 main types of CBCL.[499]

- Primary cutaneous marginal zone B-cell lymphoma (PCMZL)
- Primary cutaneous follicle center lymphoma (PCFCL)
- Primary cutaneous diffuse large B-cell, leg type (PCDLBCL, leg type).

PCFCL is the most common type of CBCL whereas PCDLBCL leg type is rare. PCMZL and PCFCL are indolent or slow growing, whereas PCDLBCL, leg type is an aggressive lymphoma with a generally poorer prognosis.[501,502] In an Italian series of 467 patients with CBCL, PCFCL and PCMZL accounted for 57% and 31% respectively. PCDLBCL leg type was reported only in 11% of patients.[502] While the various types of CBCL can occur anywhere on the skin, PCFCL is more prevalent in the scalp and the forehead, whereas the trunk and extremities are the most common sites for PCMZL. Leg remains the most common, but not the only, site for PCDLBCL. Extracutaneous involvement is more frequent with PCDLBCL, leg type. In the same large Italian series extracutaneous involvement eventually developed in 6% of patients with PCMZL, 11% with PCFCL, and 17% percent with PCDLBCL, leg type. In patients with PCMZL and PCFCL, the DFS and OS rates were higher for patients with single lesions than those with regional or disseminated lesions (5-year DFS, 62% vs. 44%; 5-year OS, 97% vs. 85%), whereas the difference between single and regional or disseminated cutaneous involvement in patients with PCDLBCL, leg type was only of borderline significance (5-year DFS rate was 55% vs. 44% and 5-year OS rate was 79% vs. 67% for single and regional or disseminated lesions respectively).[502] In another series of 145 patients with CBCL, Grange et al also identified location on the leg and multiple skin lesions as independent poor prognostic factors for patients with CBCLs.[25]

Diagnosis

Adequate biopsy of the lesions and the slides should be reviewed by a pathologist with expertise in the diagnosis of primary cutaneous B-cell lymphomas. Incisional, excisional or punch biopsy is preferred to shave biopsy as CBCL have primarily dermal infiltrates, often deep, which are less well sampled and can even be missed by a shave biopsy.

Adequate immunophenotyping with a panel that evaluates B- and T-cell markers is recommended to establish the diagnosis of the exact subtype of CBCL. The panel should include CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, Ki-67, kappa/lambda and IRF4/MUM1. PCFCL is consistently BCL6-positive, whereas CD10 and BCL2 are expressed in only a few cases with a follicular growth pattern. PCMZLs are always negative for BCL6 and CD10, but are often BCL2-positive.[503]

While the diagnosis of PCMZL is generally straightforward and reproducible among pathologists, it is more difficult to distinguish between PCFCL and PCDLBCL, leg type. Part of the difficulty is that cell size, large vs. small, is not a defining feature as it is in nodal B-cell lymphomas. Most of the patients with PCFCL have lesions with a germinal center phenotype, whereas most with PCDLBCL, leg type have an activated B cell phenotype.[24] In nodal DLBCL, the germinal center phenotype is associated with a better prognosis than the activated B-cell phenotype. Both PCFCL and PCDLBCL are CD20 and BCL6 positive. BCL2 is usually negative in PCFCL but highly expressed in PCDLBCL, leg type. In addition, PCFCL is usually for MUM/IRF4-negative while PCDLBCL, leg type is usually IRF4/MUM1-positive and shows strong expression of FOXP1.[504] IRF4/MUM1 and FOXP1 may serve as additional diagnostic markers in the differential diagnosis of PCFCL and PCDLBCL. Assessment of surface IgM and IgD expression may be helpful in distinguishing PCDLBCL, leg type from PCFCL.[505]

The t(14;18) translocation only rarely occurs in PCBCLs. Therefore, the detection of a t(14;18) translocation in CBCL suggests the presence of systemic disease.[506] Molecular genetic analysis to detect TCR gene rearrangements, PCR to detect IgH gene rearrangements and cytogenetics or FISH to detect t(14;18) may be useful in selected circumstances. In selected cases, the use of cyclin D1 may be useful to

differentiate PCMZL (negative for CD5 and cyclin D1) from mantle cell lymphomas (positive for CD5 and cyclin D1). Mantle cell lymphoma is not a primary cutaneous lymphoma and finding it in the skin requires a careful search for extracutaneous disease.

Workup

The initial workup is geared toward evaluating extent of disease on the skin and seeking extracutaneous disease. The absence of extracutaneous disease at diagnosis is part of the definition of PCBCL. The initial workup includes a complete physical examination, a comprehensive skin examination and CT scans of the chest, abdomen and pelvis. PET-CT may have higher sensitivity in finding otherwise occult systemic disease but this is not validated and the higher rates of false positive findings can create confusion. Bone marrow biopsy is essential for PCDLBCL, leg type whereas its role is unclear for PCFCL and PCMZL. Senff et al evaluated 275 patients with histological features consistent with MZL (n = 82) or FCL (n = 193) first presenting in the skin.[65] Bone marrow involvement was seen in about 11% of patients in the FCL group compared to less than 1% in the MZL group. FCL patients with skin lesions and a positive bone marrow had a significantly worse prognosis than those with PCFCL. The 5-year OS rate was 44% and 84% respectively.

The International Society of cutaneous lymphomas (ISCL) and the EORTC task force recommend that bone marrow biopsy is required for cutaneous lymphomas with intermediate to aggressive behaviors and it should be considered for cutaneous lymphomas with indolent behavior and when there is any evidence of extracutaneous disease, as indicated by other staging assessments (e.g., radiographic evidence or serologic clues such as elevated monoclonal or polyclonal immunoglobulins).[64] The guidelines recommend considering bone marrow biopsy for patients with PCFCL. It is optional for patients with PCMZL. Peripheral blood flow cytometry will be useful in selected cases, if CBC demonstrates lymphocytosis.

Treatment

Primary CBCLs have a different clinical course and prognosis that distinguish them from their nodal counterparts. Treatment options for CBCLs depend on the histology and stage of the disease. Most commonly used therapies include excision, radiation therapy (RT), rituximab or systemic chemotherapy.[58, 499]

In a large retrospective analysis by the Italian Study Group for Cutaneous Lymphomas involving 467 patients with PCBCL, the CR rate, 5-and 10-year OS rates for all patients with PCFCL and PCMZL who received treatment were 90%, 96% and 90%, respectively.[502] The relapse rate was 44% and extracutaneous spread was observed in 6-11% of patients. Relapse rate did not vary by type of initial therapy.

In patients with PCDLBCL, leg type, the CR rate, 5-and 10-year OS rates were 82%, 73% and 47% respectively. PCDLBCL, leg type is also associated with higher relapse rates (55%) and higher incidences of extracutaneous spread (17%). Higher relapse rate was confirmed both for patients with single or regional lesions treated with RT and for patients with disseminated cutaneous involvement treated with chemotherapy as first-line treatment.

RT is very effective when used as initial local therapy as well as for cutaneous relapses in most patients with indolent CBCLs.[507-509] In patients with indolent histologies, RT and excision were associated with higher response rates compared to chemotherapy (96%, 97% and 79% respectively) but are generally used for those with more limited disease.[502] However, the majority of patients with regional or

disseminated disease will relapse after any type of treatment. Relapses are generally confined to the skin.

In a retrospective of 34 patients with CBCL treated with RT, 5-year RFS rate ranged from 62-73% for PCFCL and PCMZL but was only 33% PCDLBCL, leg type.[509] Five-year OS was 100% for PCFCL and PCMZL but was 67% for PCDLBCL, leg type. Senff et al evaluated the outcome of 153 patients with CBCL (25 with PCMZL; 101 with PCFCL and 27 with PCDLBCL) that were initially treated with RT with a curative intent.[508] Overall, 45% of patients had single lesions and localized or disseminated lesions were seen in 43% and 12% of patients respectively. Complete remission was reached in 151 of 153 patients (99%). Relapse rates for PCMZL, PCFCL, and PCLBCL, leg type were 60%, 29%, and 64%, and the 5-year disease-specific survival was 95%, 97%, and 59%, respectively. The PCFCLs presenting on the legs had a higher relapse rate (63%) and a lower 5-year disease-specific survival (44%) than PCFCLs at other sites (25% and 99%).[508]

Thus, local therapy is suitable for patients with indolent histologies, whereas patients with PCDLBCL, leg type which has a more unfavorable clinical course are generally treated with more aggressive treatment modalities, often combined modality therapy.[510]

NCCN Recommendations

Since there are no data from randomized clinical trials, the treatment recommendations included in the guidelines are derived from the management of patients with CBCL in NCCN member institutions based on the limited data from retrospective analyses and studies involving small cohort of patients.

PCFCL and PCMZL

Initial Treatment

The guidelines recommend local RT or excision as the initial treatment options for patients with solitary lesions or regional disease (T1-2). Selected patients with local disease that is not amenable to local therapy (e.g., lesions on the scalp or forehead) can be observed.

For patients presenting with generalized skin lesions (T3), several treatment options are available. Chlorambucil has been shown to be effective in the treatment of PCMZL with multifocal skin lesions.[59] In patients presenting PCFCL, multiagent chemotherapy or RT were equally effective for multifocal skin lesions.[511-513] Rituximab has been effective as a first-line treatment option for patients with indolent CBCLs with multiple lesions for which local therapy is not effective.[514-518] In a series of 16 patients with PCBCL, 14 patients (87.5%) achieved complete remission; 35% patients with complete remission relapsed between 6 and 37 months.[518] In another retrospective analysis of 15 patients with indolent CBCLs, the overall objective response rate (ORR) was 87% (60% CR, 27% PR) with a median follow-up was 36 months.[517] The ORR was 100% for patients with PCFCL and 60% for PCMZL. Median time to response, duration of response, and time to progression was 30 days, 24 months, and 24 months, respectively. There are case reports showing the efficacy of topical therapy with using steroids, imiquimod, and nitrogen mustard or bexarotene gel.[511, 519-522]

For patients presenting with generalized disease, the guidelines have included observation, rituximab, topical therapy, local RT, intralesional steroids or systemic therapy (chlorambucil or CVP) with or without rituximab as options. In patients with very extensive or symptomatic

disease, other chemotherapy regimens recommended for the treatment of follicular lymphoma may be used.

Patients presenting with extracutaneous disease should be managed according to the follicular lymphoma guidelines.

Treatment for relapsed or refractory disease

While most of the patients respond to initial therapy, relapses do commonly occur. Patients with regional or localized relapse should receive additional therapy (excision, intralesional steroids, local RT or topical therapy using steroids, imiquimod, nitrogen mustard or bexarotene gel) and those with generalized disease relapse confined to the skin should receive additional therapy with treatment options recommended for generalized disease at presentation.

Patients with a PR or persistent progressive disease following additional treatment should be treated with the other options included in the initial treatment to improve response before starting treatment for refractory disease. Patients with extracutaneous relapse or those with cutaneous relapse that are not responding to any of the initial treatment options should be managed according to the follicular lymphoma guidelines.

PCDLBCL, leg type

Initial Treatment

PCDLBCL, leg type has a poorer prognosis than other CBCL, particularly in patients with multiple tumors on the legs. RT alone is less often effective in patients with PCDLBCL. While these lesions do respond to radiation, remissions are often short lived and higher rates of dissemination to extracutaneous sites occur. In a retrospective multicenter study from the French Study Group on 60 patients with PCDLBCL, leg type, although no particular therapy (RT or multiagent chemotherapy with or without rituximab) was significantly associated with improved survival, patients treated with anthracycline-containing chemotherapy and rituximab had a more favorable short-term outcome.[501] Among 12 patients treated with anthracycline-based chemotherapy with rituximab, the CR rate was 92% compared to 62% for patients who received other therapies. The 2-year survival rate between these two groups was 81% and 59% respectively.

For patients with localized disease, the guidelines recommend local RT alone or in combination with R-CHOP. RT alone can be used in elderly patients or patients who are not able to tolerate systemic therapy. In patients with generalized disease, R-CHOP with or without RT is recommended. Extracutaneous disease should be managed according to the DLBCL guidelines. The guidelines recommend enrollment in clinical trials for all patients with PCDLBCL, leg type.

Treatment for Relapsed or refractory disease

In patients with regional relapses, R-CHOP is recommended if they have not received prior chemotherapy. Patients who have received prior chemotherapy should be treated with local RT or second-line chemotherapy regimens recommended for relapsed or refractory DLBCL. Local RT or second-line chemotherapy regimens recommended for relapsed or refractory DLBCL are the options for patients with generalized relapse. In a pilot study of 10 patients, RIT with yttrium-90-ibritumomab tiuxetan was effective in patients with relapsed CBCLs.[523] The guidelines have included RIT as one of the treatment options for patients with relapsed disease.

Peripheral T-Cell Lymphomas

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of lymphoproliferative disorder arising from mature T-cells of post-thymic origin.[524] The most common subtypes of are PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and anaplastic large cell lymphoma (ALCL).

PTCL-NOS is the most common subtype of PTCL. It most often involves nodal sites, however, many patients present with extranodal involvement including the liver, bone marrow, GI tract and skin. PTCL-NOS is associated with poor OS and EFS rates compared to B-cell lymphomas.[525-527]

AITL usually presents with generalized lymphadenopathy, often with associated hepatomegaly or splenomegaly, hypergammaglobulinemia, eosinophilia, skin rash and fever. It occurs mainly in older patients. Prognosis is poor. In a single institution study which reviewed the data of 199 patients with PTCLs, the 5-year OS and PFS rate were 36% and 13% respectively for the subgroup of patients with AITL.[527] In the most recent report from the GELA study, which included the largest series of patients with AILT (n=157), five and seven-year OS rates were 33% and 29% respectively, reaching an apparent plateau around 6 years.[528] The corresponding EFS rates were 29% and 23% respectively.

ALCL is a CD30 expressing subtype of PTCL which accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: systemic ALK1 expressing ALCL, systemic ALK1 negative ALCL, and primary cutaneous ALCL. ALK1 positive ALCL is most common in children and young adults. It is characterized by the overexpression of anaplastic lymphoma kinase (ALK1) protein, which is the result of a chromosomal translocation [t(2;5)] in 40-60% of patients.[39] Systemic ALK1 positive ALCL predominantly occurs at younger age and has a good prognosis compared to ALK1 negative ALCL, which occurs in older patients. The majority of patients with ALCL present with advanced stage III or IV disease (65% for ALK1 positive and 58% for ALK1 negative) frequently associated with systemic symptoms and extra nodal involvement.[15] ALK-positive ALCL is associated with better clinical outcomes than ALK-negative ALCL, PTCL-NOS or AITL. Five-year OS rate following anthracycline-based therapy was 79% for ALK-positive ALCL compared to 46% for ALK-negative ALCL.[40] Recent survival analysis from the International T-cell lymphoma project also reported similar outcomes.[15, 41] The differences in prognosis are most pronounced for younger patients with favorable prognostic factors. In this report, ALK-negative ALCL patients had a better outcome than those with PTCL-NOS. The 5-year FFS for ALK-negative ALCL and PTCL-NOS were was 36% vs. 20% respectively and OS was 49% vs. 32%.[41]

Primary cutaneous variant of ALCL is noted for the absence of ALK1 protein and indolent course characterized by frequent relapses, generally confined to the skin, and very good long-term survival despite cutaneous relapses. As a result combination chemotherapy is rarely indicated for these patients.

Enteropathy-associated T-cell lymphoma (EATL) is a rare T-cell lymphoma of the small intestine, accounting for less than 1% of all the NHLs and has a poor prognosis. The median age of diagnosis is 60 years. The typical immunophenotype of EATL is CD3+, CD5–, CD7+, CD8–/+, CD4– and CD103+. Anthracycline-based chemotherapy with CHOP or CHOP-like regimens are most commonly used for patients with EATL.[529-532] Recent studies have shown that HDT/ASCR improves outcomes in patients with EATL.[533, 534]

Staging and Prognosis

Staging is similar to that of the other aggressive lymphomas. Historically the IPI derived for DLBCLs has been used and shown to be prognostic for patients with PTCL. Recently, the Italian Intergroup for lymphoma proposed a new prognostic index for PTCL-NOS.[525] Risk factors include age older than 60 years, elevated LDH levels, performance status of 2 or more, stage III or higher with bone marrow involvement. Five-year OS rate was only 32.9% for patients with two risk factors and 18.3 % for those with three or four risk factors. This schema also identifies a relatively good prognosis subset of patients who have no adverse risk factors. This, so called, group 1 represented 20% of patients and had a 5-year OS of 62%. In the NCCN guidelines, patients with stage I-II disease are stratified into two groups (low intermediate risk and high intermediate risk) based on the age-adjusted prognostic index (aaPI).

In a retrospective GELA study, the prognoses of PTCL (including all subgroups) patients were compared with B-cell lymphoma patients with similar characteristics receiving similar aggressive combination chemotherapy and in some patients high dose therapy and stem cell transplantation.[526] The CR rates were 63% and 54% for patients with B-cell lymphoma and PTCL respectively. Five-year OS rate was also slightly better for patients with B-cell lymphomas (53%) compared to 41% for patients with PTCL. The 5-year EFS rates were 45% and 32% for B-cell and PTCL patients respectively. The difference in 5-year OS rates were most pronounced in patients with 2 or 3 adverse risk factors as determined by IPI (36% and 23% respectively for PTCL; 53% and 35% respectively for B-cell lymphomas). Initial characteristics and prognostic features were analyzed in another retrospective study in 174 patients with PTCL. Most patients were treated with anthracycline-based regimens.[535] The complete response rates (69% vs. 45%) and median survival (65 months vs. 20 months) were better for ALCL subgroup compared to other PTCL subtypes.

Diagnosis

Diagnosis of PTCL is similar to that described for other lymphomas, requiring adequate immunophenotyping to distinguish PTCL from B-cell neoplasms. The initial paraffin panel for immunohistochemical studies may only include Pan T-cell markers and can be expanded to include antibodies of T-cell lymphoma if suspected. Additionally, PTCL is often associated with clonal rearrangements of the receptor genes that are less frequently seen in non-cancer T-cell diseases. Molecular and cytogenetic analysis can further clarify the T-cell origin of the lymphoma.

PTCL-NOS has variable T-cell associated antigens and usually lacks B-cell associated antigens (although aberrant CD20 expression in T-cell lymphomas is infrequently encountered). With the exception of CD30 expression in ALCL, antigen expression is variable across the aggressive T-cell lymphomas. The majority of the nodal cases express CD4+ and lack CD8-, however CD4-/CD8+, CD4-/CD8-, and CD4+/CD8+ cases are seen.[536] Systemic ALCL has a strong expression of CD30. Evaluation of ALK1 status, either based on immunophenotyping or genetic analysis of the t(2;5) or variant chromosomal rearrangements, is extremely important to identify the ALK1 positive tumors that have a better prognosis. AILT cells express T-cell associated antigens and are usually CD4+. Recently, expression of CXCL13 has been identified as a useful marker in distinguishing AILT from PTCL-NOS.[537, 538] It is also characterized by the presence of Epstein-Barr virus (EBV)-positive B-cells and cases of co-existent EBV+DLBCL are reported. EBER (EBV-encoded RNA) is positive in

about 40% of PTCL and some case series have reported that EBER positive tumors have a worse prognosis.

Workup

The workup for PTCL is similar to the workup for other lymphoid neoplasms. The workup focuses on determining the stage of the disease, based on routine laboratory studies, physical exam, and imaging studies, as indicated. MUGA scan or echocardiogram is also recommended, since chemotherapy is usually anthracycline based. In selected cases, HIV and HTLV-1 (human T-cell lymphoma virus) may be useful.

Treatment

Induction Therapy

PTCLs are less responsive to and have less frequent durable remissions with standard chemotherapy regimens such as CHOP and thus carry a poorer prognosis compared to diffuse large B-cell lymphomas. In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas.[539, 540] However, it has not been possible to assess the impact of chemotherapy in this subgroup of patients with PTCLs due to small sample size. There have been no randomized studies comparing the chemotherapy regimens exclusively in patients with PTCL.

CHOP chemotherapy is the most commonly used first-line regimen for patients with PTCL. However, with the exception of ALK+ ALCL, outcomes are disappointing. Chemotherapy regimens that are more intensive than CHOP did not show any significant improvement in OS in patients with PTCL, with the exception of ALCL.[541, 542]

CHOP chemotherapy is frequently curative in only the small number of patients with favorable prognostic features.[15, 41] In the International PTCL clinical and pathologic review project, anthracycline-based chemotherapy was associated with poor outcome in all patients, except for those with one or no risk factors and the inclusion of an anthracycline did not appear to favorably impact survival in this retrospective study.[15] In a retrospective study conducted by the British Columbia cancer agency, 5-year OS rates were higher (64%) in low risk IPI group compared to only 22% in high-risk IPI group, in patients with PTCL treated with CHOP or CHOP-like chemotherapy.[41]ALK-positive ALCL patients had superior outcome compared to ALK-negative ALCL patients (5-year OS: 58% vs. 34% respectively). In an analysis of a large cohort of patients with PTCL treated in the German high-grade NHL study group, patients with ALK-positive ALCL had excellent outcomes with CHOP or CHOP with etoposide (CHOEP). Three-year EFS and OS rates were 76% and 90% respectively for ALK-positive ALCL, 50% and 67.5% respectively for AITL, 46% and 62% respectively for ALK-negative ALCL and 41% and 54% respectively for PTCL-NOS. Among patients with ALK-negative ALCL, AITL and PTCL-NOS, those with low IPI had a favorable prognosis.[542]

CHOEP induced better response rates (CR: 88% vs. 79 %) and 5-year EFS rates (69 % vs. 58%) than CHOP in younger patients.[543] Aggressive chemotherapy [CHOP followed by ICE or CHOP followed by IVE (ifosfamide, etoposide and epirubicin alternating with intermediate dose methotrexate)] and HDT/ASCR has also been evaluated as primary therapy.[544, 545] The poor results with conventional chemotherapy have led many to explore the role of HDT/ASCR as a first-line consolidation therapy.[546, 547] Several retrospective [548-554] and prospective studies [555-559] have demonstrated that HDT/ASCR as first-line consolidation improves treatment outcome in patients responding to induction therapy.

Nordic lymphoma group evaluated induction therapy with CHOEP followed by ASCR in patients responding to induction therapy.[555] Of the 77 evaluable patients, 58 (75%) patients underwent ASCR. At one-year post-transplant follow-up, in the 39 patients for whom follow-up data were available, 30 were in complete remission. In the prospective study conducted by the GELTAMO Study group, 19 out of 26 patients showing CR or PR to induction therapy with MegaCHOP received ASCR.[556] At 2-year post-transplant follow-up, OS, PFS and DFS rates were 84%, 56% and 63% respectively in patients who received ASCT consolidation (n = 19). In a phase II study conducted by Mercadal et al. newly diagnosed patients with PTCL responding to high-dose CHOP regimen alternating with etoposide, cisplatin, cytarabine and prednisone, were treated with ASCT.[558] With a median follow-up of 3.2 years, the 4-year PFS and OS were 30% and 39% respectively.

Reimer et al recently reported the final analysis of the first prospective first prospective PTCL-restricted multicenter study on upfront HDT/ASCR in 83 patients.[559] The treatment regimen consisted of four to six cycles of CHOP followed by mobilizing therapy with either the dexamethasone, carmustine, melphalan, etoposide, and cytarabine protocol or the etoposide, methylprednisolone, cytarabine, and cisplatin protocol and stem-cell collection. The ORR following CHOP chemotherapy was 79% (39% CR and 40% PR). Fifty-five (66%) of the 83 patients received transplantation. After HDT/SCT, 48 of the 55 patients achieved a CR, and 7 patients achieved a PR. In an intent-to-treat analysis, the ORR after myeloablative therapy was 66% (56% CR and 8% PR). The estimated 3-year OS, DFS and PFS rates for patients in CR were 48%, 53%, and 36%, respectively. The transplant related mortality rate was 3.66%. However, ALK-positive ALCL patients were excluded in all of these studies.

The outcome of ALK-positive ALCL patients undergoing ASCT compared to those with other histological subtype of PTCL was reported in only one prospective study by Corradini et al.[557] The pooled results from two prospective studies (n = 62) showed that at a median follow-up of 76 months, the estimated 12-year OS, DFS and EFS rates were 34, 55 and 30%, respectively for the whole study cohort. Overall treatment-related mortality rate was 4.8%. The 10-year OS and EFS rates were significantly better in patients with ALK-positive ALCL (63% and 54% respectively), as compared with the remaining PTCL (21% and 19% respectively). In the subgroup of patients with PTCL-NOS the corresponding survival rates were 37% and 25% respectively. In a multivariate analysis the achievement of CR before transplant was a strong predictor of survival benefit. The projected 10-year OS and EFS rates for patients in complete remission before transplant were 48% and 47% respectively, compared to 22% and 11% respectively for whose who were not in complete remission.

Longer follow-up and preferably a randomized trial, is necessary to evaluate the impact of first-line consolidation therapy on time-to-treatment failure and OS. In the absence of randomized trials comparing conventional chemotherapy to first-line consolidation with HDT/ASCR, this is a reasonable treatment option only in patients showing good response to induction therapy.

NCCN Recommendations

CHOP plus RT is the standard induction therapy for patients with ALK-positive ALCL. For patients with other subtypes, since there is no standardized treatment, clinical trials, whenever available, are the preferred treatment options. Clinical trials are essential to advancing our treatments form these diseases. Multiagent chemotherapy (4-6 cycles) with adjuvant locoregional radiation therapy to involved region is recommended for patients with stage I-II disease (low/low-intermediate

risk), whereas patients with stage I-II (high/high-intermediate risk) or stage III-IV disease are treated with multiagent chemotherapy (6-8 cycles) with or without radiation therapy. Suggested regimens include CHOEP, HyperCVAD or CHOP followed by ICE or IVE.

AILT is a very heterogeneous disease and can at times be treated solely with corticosteroids or other immunosuppressive agents. Cyclosporine has been effective in patients with relapsed disease following treatment with steroid or multiagent chemotherapy.[560] Patients with AILT are managed similarly to above; however the guidelines suggest a trial of singe agent corticosteroid for symptom management in elderly patients or in patients with comorbid conditions in whom the risks of combination chemotherapy are excessive.

Follow-up Therapy

All patients (except for those with ALK-positive ALCL) undergo interim restaging following initial therapy by repeating all prior positive studies. If a PET-CT scan is positive, rebiopsy is recommended before changing course of treatment. Patients are then divided into three groups according to treatment response (CR, PR or no response or progressive disease). Subsequent treatment options depend on whether the patient initially presented with Stage I-II or Stage III-IV disease.

Stage I or II disease (low-intermediate)

In patients showing CR after interim restaging, planned RT is completed. RT or HDT/ASCR with or without RT is considered for patients showing PR at interim staging. Clinical trials including allogeneic transplant or radiation therapy is another option for this group of patients. End of treatment restaging is performed after completion of treatment. No further treatment is necessary for those showing CR. Patients with PR at end of treatment restaging and those with no response or progressive disease following initial or follow-up therapy are treated as described for relapsed or refractory disease.

Stage I or II disease (high-intermediate) or stage III-IV

Patients with a CR can be observed or they can be consolidated with HDT/ASCR. Local RT can be given prior to HDT/ASCR. Patients with PR or no response or progressive disease after initial therapy are treated similarly to patients with relapsed or refractory disease.

Treatment for Relapsed or Refractory Disease

Several studies have shown that second-line consolidation with HDT/ASCR produces similar outcomes patients with relapsed or refractory PTCL compared to those with B-cell lymphomas.[561-565] In a retrospective review of patients with PTCL who underwent HDT/ASCR at the Stanford University, the 5-year PFS for patients in first complete or partial remission, complete or partial remission after second-line therapy and those with refractory disease was 51%, 12%, and 0%, respectively, and the OS rates were 76%, 40%, and 30%, respectively.[565] The disease status and the number of prior regimens received prior to transplant were significant prognostic factors. Thus, HDT/ASCR as first-line consolidation therapy may be associated with a durable survival benefit. However, HDT/ASCR only infrequently results in durable benefit in patients with relapsed or refractory disease.

Recent reports have shown that allogeneic transplantation may be an effective second-line therapy for patients with relapsed or refractory PTCL.[566-568] In a phase II study, Corradini et al investigated the role reduced intensity conditioning (RIC) followed by allogeneic transplantation in patients (n = 17) with relapsed or refractory PTCL.[566] The estimated 3-year OS and PFS rates were 81% and 64% respectively. Donor lymphocyte infusion induced responses in some patients progressing after allografting. The estimated probability of

non-relapse mortality at 2 years was 6%. Long-term data on 53 patients with relapsed or refractory PTCL who received a RIC followed by allogeneic SCT with a median follow-up of 4 -years showed that patients with chemosensitive disease had advantage from allogeneic SCT and there was no significant difference in outcome between the different histopathological subtypes of PTCL.[569] The 4-year OS and PFS were 50% and 47% for all patients. OS (62% vs.15% respectively) and PFS (58% and 13% respectively) were significantly higher for chemosensitive patients compared to those who were chemorefractory. The OS and PFS were 42% and 40% for PTCL-NOS, 50% and 44% for ALCL, 67% and 80% for AILT. The crude cumulative incidences (CCI) of non-relapse mortality were 4% and 10% at 6 months and 4-year, respectively. Similar results were reported in a retrospective study from French national survey of 77 patients where the majority of the patients (57/77) were treated with myeloablative regimen.[568] Treatment related mortality was higher (34%) in this study compared to only 6% observed with RIC regimen. A retrospective study from the lymphoma working party of the European group for blood and marrow transplantation demonstrated that allogeneic HSCT is able to induce long-term remissions in patients (n = 45; 27 had chemosensitive disease, and 18 had chemotherapy refractory disease) with AITL.[567] PFS and OS rates were 62% and 53% and 66% and 64% at 1 and 3 years, respectively. Patients with chemotherapy sensitive disease had a significantly superior PFS compared with to those with chemotherapy refractory disease (66% v 33%, respectively) and were significantly better in chemotherapy sensitive patients.

Until recently, data to guide the treatment of patients with relapsed and refractory PTCL came from small series of patients treated with various single agents. Gemcitabine,[39, 570, 571] denileukin diftitox [572, 573] and alemtuzumab [574, 575] have shown activity in such experiences. Zinzani et al recently reported the outcome of 39 pretreated T-cell lymphoma patients treated with gemcitabine (on days 1, 8, and 15 on a 28-day schedule; 1200 mg/m/day for a total of three to six cycles). Among 20 patients with PTCL-NOS, CR and PR were observed in 30% and 25% of patients respectively.[39] In a phase II study, Dang et al evaluated the safety and efficacy of denileukin diftitox in 27 patients with relapsed/refractory T-cell- lymphomas excluding CTCL.[572] The predominant histology was PTCL-NOS (19 of 27 patients). The ORR was 48%, with a median PFS of 6 months.

In a pilot study, alemtuzumab at standard dosing produced an ORR of 36% among 14 patients with relapsed or chemotherapy-refractory PTCLs.[574] But, it was associated with significant hematologic toxicity and infectious complications including 5 deaths from opportunistic infections. The preliminary results of another phase II study showed that in 10 patients with pretreated T-cell lymphoma including 6 with PTCL and 4 with CTCL, alemtuzumab at lower dose was less toxic and equally effective as the standard dose used in the pilot study.[575] The ORR was 60%. In the subset of patients with PTCL-NOS, ORR was 50% (33% CR and 17 % PR). CMV reactivation was observed only in 10% of patients, as compared with 42% of the patients reported by Enblad et al. The median duration of response was 7 months.

Pralatrexate is a new antifolate with a high affinity for reduced folate carrier type 1 (RFC-1) and a significant activity in patients with relapsed/refractory T-cell lymphoma.[576, 577] The median number of prior therapies was 3 including combination chemotherapy regimens and HSCT.[578, 579] The results of the pivotal, international, phase II study (PROPEL) showed that pralatrexate resulted in an ORR of 27% (10% CR and 17% PR) in 109 pretreated patients with relapsed or refractory PTCL. [580] Compared to smaller studies above, this study is distinguished not only by its size, but also by central pathology review

and independent central response review. The most common side effect was stomatitis (70% any grade, 21% with grade 3-4) and the most common hematologic adverse effect was thrombocytopenia (41% any grade, 33% with grade 3-4). Eight patients achieved a response with pralatrexate adequate to proceed to subsequent SCT.[581] In September 2009, after FDA review, pralatrexate became the first approved single agent for the treatment of patients with relapsed or refractory PTCL.

Romidepsin, a potent HDAC inhibitor approved by the FDA for patients with CTCL who have received at least one prior systemic therapy, has demonstrated significant single agent activity in patients with relapsed or refractory PTCL. In the pivotal multicenter phase II study, romidepsin induced responses in patients with all major subtypes of PTCL refractory to multiple prior therapies including SCT.[582] The ORR was 26% (evaluated by the independent review committee) and 29% (investigator assessment). The corresponding CR/Cru was 13% and 16% respectively. Median duration of overall response was 12 months.

Brentuximab vedotin is an antibody-drug conjugate that targets CD30-expressing malignant cells by binding to CD30 on the cell surface. After internalization, a potent antimicrotubule agent (monomethyl auristatin E) is released within the cell.[583, 584] A multicenter phase II study evaluated brentuximab vedotin (IV 1.8 mg/kg every 3 weeks, up to 16 cycles) in patients with relapsed or refractory systemic ALCL (N=58). Patients had received a median of 2 prior systemic therapies (range, 1-6) and 62% were considered to have primary refractory disease; in addition, 50% of patients were refractory to their most recent prior therapy and 22% had never responded to any therapy.[583] The ORR was 86% (evaluated by an independent review committee) with CR in 53% of patients. The median duration of response had not yet been reached at the time of the report. Among the subgroup of patients who had malignant cutaneous lesions at baseline (n=15), 93% experienced resolution of all lesions. The most common grade 3-4 adverse events reported in this study included neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (10%).[583] No treatment-related deaths were reported. Based upon the results from this study, brentuximab vedotin was recently approved by the FDA (August 2011) for treating patients with systemic ALCL after failure of at least one prior multiagent chemotherapy regimen. This agent has not been evaluated in patients with relapsed/refractory cutaneous ALCL and therefore cannot be recommended for those patients at this time.

NCCN Recommendations

Patients who are candidates for transplant can be treated with second-line chemotherapy prior to transplant. Consolidation therapy with HDT/ASCR or allogeneic HSCT is recommended for those with a CR or PR. Localized areas can be treated with RT before or after high-dose therapy. Patients who are non-candidates for transplant are treated with RT or second line regimens for palliative intent only. Suggested treatments include alemtuzumab, bortezomib, brentuximab vedotin (for patients with nodal ALCL only), cyclosporine (for patients with refractory AITL only), denileukin diftitox, gemcitabine or pralatrexate. Participation in a clinical trial is strongly preferred for these patients. The panel has also included romidepsin as an option for second-line therapy for patients with relapsed or refractory disease. In patients receiving romidepsin, serum potassium and magnesium levels need to be monitored since low levels can be associated with ECG abnormalities.

Mycosis Fungoides and Sezary Syndrome

Cutaneous T-cell lymphomas (CTCLs) are a group of NHLs primarily developing in the skin and ultimately involve lymph nodes, blood and

visceral organs. In a recent population-based study of 3884 cases of cutaneous lymphomas diagnosed during 2001-2005, CTCLs accounted for 71% compared to 29% for cutaneous B-cell lymphomas.[500] Mycosis fungoides (MF) and Sezary syndrome (SS) are the most common types of CTCLs. MF accounts for 60% of new cases of CTCL and SS occurs only to an extent of 5%. MF is an extranodal NHL of mature T-cells with primary cutaneous involvement. SS is an erythrodermic, leukemic variant of CTCL and it is characterized by significant blood involvement and lymphadenopathy. In updated EORTC and WHO classification of CTCL, MF is characterized as an indolent neoplasm and SS is characterized as an aggressive neoplasm.[23]

Large cell transformation (LCT) has been documented in a subgroup of patients and is diagnosed when there are more than 25% of large cells in a biopsy of an MF lesion.[585],[586] The incidence of LCT is strongly dependent on the stage of the disease at diagnosis (1.4% in patients with early-stage disease, compared with 27% for those with stage IIB disease 56%-67% for those with disease) and the median OS from the diagnosis of LCT was 2 years.[587] LCT is often but not always aggressive. Limited preliminary data indicate in some patients with advanced-stage disease in whom the large cells express CD30 may have a more indolent course.[588]

Staging

The TNM staging system developed by the mycosis fungoides cooperative group (MFCG) has been the standard for staging and classification of patients with MF and SS.[589] Recently, ISCL and EORTC recommended revisions to the MFCG staging system are based on the new data available in the area of immunohistochemistry, biology and prognosis of MF and SS since the publication of MFCG.[590] In the revised staging system, all staged patients should have a definitive diagnosis of MF and SS. T1 disease is defined as less than 10% of the skin surface involvement with patches or plaques and T4 disease is erythroderma with at least 80% of the skin surface diffusely involved. The extent of skin involvement is based on the percentage of body surface area (BSA) where the patient's palm (without digits) is equivalent to 0.5% BSA. Lymph node biopsy for staging is recommended only for clinically abnormal node (1.5 cm or larger in diameter). Visceral disease with the involvement of an organ other than the skin, nodes or blood should be documented using imaging studies. Blood involvement is classified into three groups: B0 is associated with the absence of significant blood involvement (5% or less of Sezary cells); B1 is defined as having a low tumor burden (more than 5% of Sezary cells but does not meet the criteria for B2); B2 is associated with high tumor burden with more than 1000 Sezary cells/mcL. According to the updated staging system, patients with stage III are further divided into two subgroups IIIA and IIIB to differentiate the extent of blood involvement (B0 and B1 respectively).

Prognosis

The most significant prognostic factors of survival include patient's age at presentation, extent and type of skin involvement, overall stage (T-classification), presence or absence of extracutaneous disease and peripheral blood involvement.[591-594] Patients diagnosed with limited patch or plaque disease have an excellent prognosis, whereas those who have tumor stage disease or erythrodermic skin involvement have a less favorable prognosis and patients with who present with extracutaneous disease have a very poor prognosis. Long-term follow-up data involving 525 patients with MF and SS, showed that the 5-year OS was significantly better (80% vs. 56%) for patients less than 57 years of age compared to that of patients 57 years or older.[594] The risk of disease progression, development of extracutaneous disease or

death due to MF was correlated with initial stage. In a retrospective cohort study of 106 patients with erythrodermic MF and SS, older age and extracutaneous disease including peripheral blood involvement were identified as adverse prognostic factors. Three distinct prognostic groups (favorable, intermediate and unfavorable) were identified, according to the number of unfavorable prognostic factors: 65 years or older at presentation, lymph node or visceral (stage IV) disease and peripheral blood involvement. The median survival in each group was 10.2, 3.7, and 1.5 years, respectively.[592] In a recent retrospective analysis involving patients with erythrodermic cutaneous T-cell lymphoma (124 out of 1197 patients with CTCL), the median OS in all 124 erythrodermic -CTCL patients was 5.1 years (range, 0.4-18.6 years).[595] In multivariate analysis, advanced age and elevated lactate dehydrogenase were the strongest predictors of poor prognosis.

Diagnosis

In the algorithms developed by the International Society for Cutaneous Lymphoma (ISCL), the diagnosis of MF is based on integration of clinical, histopathologic, immunopathologic, and molecular biological characteristics.[596] According to the revised criteria, SS is defined as a clonal T-cell receptor (TCR) gene rearrangement in the blood (clones should be relevant to clone in the skin) and either an absolute Sézary cell count of 1000 cells/mm3 or more, or an increased CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or higher or an increased CD4+ cells with an abnormal phenotype (CD4+/CD7:40% or more, or CD4+/CD26:30% or more). Complete skin exam, biopsy of suspicious skin sites and immunohistochemical studies of skin biopsy are essential to confirm the diagnosis. Biopsy of suspicious lymph nodes and assessment of peripheral blood for Sezary cells are recommended in the absence of a definitive skin diagnosis. MF and SS cells are characterized by CD2+, CD3+, CD4+, CD5+, CCR4+, CD45RO+ and they lack certain T-cell markers CD7 and CD26.[597] There are subtypes of MF that are also CD8+. If there is a histological evidence of LCT phenotyping with CD30 is recommended. The T-cells also express cutaneous lymphocyte antigen (CLA) and TH2 cytokines. They are also associated with a loss of TH1 and IL-12 cytokines. TCR gene rearrangement should be interpreted with caution since TCR clonal rearrangements can also be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood and/or lymph node may be helpful in selected cases. TCR gene rearrangement analysis by PCR is a useful technique to support the diagnosis of MF and SS, especially in distinguishing MF from inflammatory dermatoses.[598]

Work Up

The workup of patients diagnosed with MF or SS involves complete skin examination to assess the extent of the disease, examination of lymph nodes or other masses for the evaluation of lymphadenopathy or organomegaly. Laboratory studies should include CBC with Sezary screen and Sezary flow cytometry to assess for expanded CD4+ cells with increased CD4:CD8 ratio or with abnormal immunophenotype. Patients with unfavorable features (T2 or higher, folliculotropic or large-cell transformation, palpable adenopathy or abnormal laboratory studies) should undergo either CT or PET-CT scan of the neck/chest/abdomen and pelvis. Integrated PET-CT was found to be more sensitive for the detection of lymph node involvement than CT alone and can help direct biopsies.[599] Bone marrow biopsy is not needed for staging of patients, but may be helpful in those with suspected marrow involvement or in those with an unexplained hematologic abnormality. TCR gene arrangement analysis of peripheral blood lymphocytes is recommended if SS is suspected. Biopsy of

suspicious lymph nodes is recommended with evaluation for TCR gene rearrangements, especially due to the poor prognosis of patients with clonal rearrangement in lymph nodes.[600]

Treatment alternatives for MF and SS

Initial treatment in patients with patch/plaque disease consists of skin-directed therapies (localized or generalized), with the addition of systemic biologic therapy for refractory, or progressive disease. Those patients who have unfavorable prognostic features (e.g., folliculotropic or large-cell transformed MF) may have systemic biologic therapies introduced earlier in the treatment algorithm. Patients who do not respond to biologic therapy or those with very aggressive or extracutaneous disease may be treated with chemotherapy.[601-603] Due to the rarity of the condition and the need for an individualized approach, referral to a multidisciplinary academic specialty center is preferred.

Skin-directed therapies

Localized skin-directed treatments include topical therapy with corticosteroids, mechlorethamine hydrochloride, carmustine, or topical bexarotene. Generalized skin directed therapies such as phototherapy [UVB or PUVA (psoralen and UVA)] and total skin electronic beam therapy (TSEBT) are indicated in patients with widespread skin involvement.

Topical corticosteroids are effective especially for the treatment of patch-stage MF, producing a CR rate of over 90%.[604, 605] However, long-term use of topical steroid may lead to skin atrophy or striae formation and the risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption. Topical chemotherapy with nitrogen mustard or carmustine has been used for the management of MF for many decades.[606, 607] Long term follow-up results in 203 patients have confirmed the safety of topical therapy with nitrogen mustard.[608] The efficacy were similar for aqueous and ointment preparations, however, the ointment was associated with reduced toxicity. Patients with T1 disease had better response rates (93% vs. 72%) and survival outcomes (65% vs. 34%) than those with T2 disease. Freedom from progression (FFP) in T1 disease at 5 and 10 years were 92% and 85% respectively and in T2 disease FFP was 83% at 5 and 10 years. An ongoing multicenter trial is evaluating the efficacy of topical nitrogen mustard in patients with stage I or IIA MF.

Synthetic retinoids (bexarotene and tazarotene) and imiquimod have been used as topical therapy for the treatment of patients with MF and SS. FDA-approved bexarotene gel was evaluated in two open-label, historically-controlled clinical studies involving 117 patients with CTCL.[609, 610] In the phase I-II trial involving 67 patients with early stage MF, CR was attained in 21% and PR was observed in 42%. Patients with no prior therapy responded at a higher rate than those who had received prior topical therapies. In the phase III multicenter study of 50 patients with early stage refractory MF, ORR was observed in 44% of patients with 8% of patients achieving CR. In a small open-label pilot study, tazarotene 0.1% gel was a well-tolerated and effective adjuvant topical therapy for the treatment of 20 adult patients with early patch or plaque MF lesions (stable or refractory to therapy) by clinical and histologic assessments.[611] In a small number of case studies imiquimod was effective for patients with early stage MF that is refractory to other therapies.[519, 612, 613] Bexarotene gel is the only FDA approved synthetic retinoid for topical therapy in patients with MF and SS.

MF is extremely radiosensitive and patients with minimal stage IA MF may be managed effectively with local superficial RT without adjuvant therapy.[614] Wilson et al reported that the actuarial DFS at 5 and 10

years was 75% and 64% for patients with early stage disease treated with RT alone.[615] The 10-year DFS was 85% for patients with unilesional disease. The optimal RT dose was 20 Gy which resulted in a DFS rate of 91% with no distant failures. TSEBT is effective especially in patients with thick generalized plaque (T2) or tumorous disease (T3). In a retrospective analysis involving 148 patients with T2 and T3 disease, TSEBT alone or in combination with adjuvant topical mechlorethamine hydrochloride yielded significantly higher CR rates for T2 and T3 disease compared to mechlorethamine hydrochloride alone (76% vs. 44% for T2; 44% vs. 8% for T3).[616]

Phototherapy with UVB (including narrow-band) and photochemotherapy with psoralen and UVA (PUVA) are effective alternative treatment options for patients with early stage MF.[617, 618] In long-term follow-up studies, PUVA was associated with prolonged disease-free remissions. In a retrospective analysis, phototherapy with narrow-band UVB and PUVA produced comparable complete remission rate (81% vs. 71%), partial remission rate (19% vs. 29%) and RFS (24.5 months vs. 22.8 months) in patients with early stage MF.[619] However, cumulative doses of UV are associated with increased risk of UV-associated skin neoplasms. Thus, phototherapy may not be appropriate for patients with the history of squamous or basal cell carcinoma or melanoma. Since narrowband UVB has less skin toxicity than broadband and PUVA, it is preferred to start with narrowband UVB than PUVA in early stage patients with patch or thin plaque disease.

Systemic therapies

Systemic therapies with extracorporeal photopheresis (ECP), interferons, systemic retinoids, denileukin diftitox or vorinostat are preferred over traditional chemotherapy for patients who do not respond to initial skin-directed therapies. Multiagent chemotherapy is reserved only for patients who do not respond to single agent chemotherapy or those with bulky lymph node or solid organ disease. In the absence of other unfavorable prognostic features, it is recommended that systemic therapy be deferred until the patient has failed multiple treatments with local and skin directed therapy.

ECP is an immnunomodulatory therapy using psoralen and UVA radiation extracorporeally. It involves the removal of leukocytes by leukopheresis. The leukocytes are treated with 8-methoxypsoralen, exposed to UVA and returned to the patient. ECP is a long standing treatment of MF, and is particularly indicated in patients with or at risk of blood involvement (erythrodermic stage III disease or IVA with Sezary Syndrome).[620-622] In a long-term follow-up of 20 patients with CTCL treated with ECP for at least 6 months, CR (disappearance of all lesions) was obtained in five patients (25%) and a PR (disappearance of at least 50% of lesions) in five patients (25%).[622] Median survival time for the entire cohort was 96 months (range, 16 to 152 months). In a meta-analysis of 19 studies (5 studies using ECP as a monotherapy and 14 studies as combination therapy) involving more than 400 patients with CTCL, the combined ORR for all stages of CTCL was 55.7% with 17.6% achieving a CR.[621] ECP as a monotherapy resulted in 55.5% ORR with 14.8% CR.[621] The corresponding response rates were 58% (15% CR) for erythrodermic disease (T4) and 43% (9.5% CR) for SS.

Retinoids [all-trans retinoic acid (ATRA),13-cis retinoic acid and their synthetic analogs acitretin and isotretinoin] and interferons have been used for many years for the treatment of CTCL.[623, 624] Interferon alpha as a single agent, has produced PR rates of greater than 50% and CR rates of greater than 20%.[623] Interferon gamma has been shown to be effective in the treatment of patients with various stages of CTCL that is refractory to interferon alpha and other topical or systemic therapies.[625]

Oral bexarotene has been evaluated for the treatment of refractory or persistent early and advanced stage CTCL in two multicenter clinical trials.[626, 627] In early stage CTCL, bexarotene was well tolerated and effective in 54% of patients at doses of 300 mg/m2 per day. In advanced CTCL, clinical CR and PR were observed in 45% of patients receiving 300 mg/m2/d. At more than 300 mg/m2/d, response rate was 55%, including 13% clinical CR. Side effects were reversible and manageable with appropriate medications prior to initiation of treatment. Bexarotene capsules received FDA approval in December, 1999 for the treatment of refractory CTCL. In retrospective comparison, ATRA and bexarotene had similar efficacy in the treatment of patients with relapsed MF and SS.[628]

Denileukin diftitox is a recombinant fusion protein with interleukin-2 (IL-2) and diphtheria toxin, and targets the high-affinity interleukin-2 receptor (CD25) expressed on malignant T-cells and B-cells. In a pivotal phase III study the safety and efficacy of denileukin diftitox was evaluated in two different dose levels in pretreated patients with CTCL.[629] The ORR was 30% with a median duration of 6.9 months in patients who have received other treatments. Median duration of response was 6.9 months (with a range of 2.7- 46.1 months). The response rates and the duration of response were not statistically different between the two doses. Clinically significant improvement in self-rated overall QOL, skin appearance, and pruritus severity was observed in 68% of the patients who had significant pruritus at baseline. However, denileukin diftitox is associated with significant side effects including hypersensitivity reactions and vascular leak syndrome. Myelosuppression is an uncommon side effect. Denileukin diftitox was approved in February, 1999 for the treatment of persistent or recurrent CTCL in patients whose malignant cells express CD25 component of IL-2 receptor. The results of the phase III, placebo-controlled, randomized trial confirmed that denileukin diftitox results in significant and durable clinical benefit in patients with early- and late-stage CTCL.[630] In this trial, 144 patients with biopsy-confirmed, CD25 assay-positive CTCL were randomly assigned to denileukin diftitox (9 or 18 micrograms/kg/day) or placebo. The ORR was 44% (10% CR and 34% PR) compared with 15.9% for placebo-treated patients (2% CR and 13.6% PR). ORR was higher in the 18 micrograms group vs. the 9 micrograms group (49.1% v 37.8%, respectively) and both doses were significantly superior to placebo. The median PFS was significantly longer (more than 2 years) for both doses compared with placebo (124 days; $P < .001$). An ongoing phase III trial is evaluating the efficacy of denileukin diftitox according the CD25 status.[631]

Histone deacetylase inhibitors (HDACIs) are a new class of drugs that are potent inducers of histone acetylation, cell cycle arrest and apoptosis. Activity and safety of vorinostat and romidepsin in patients with refractory CTCL was confirmed in a phase II trials.[632-635] In a phase IIB study involving 74 patients with persistent, progressive or refractory CTCL, vorinostat resulted in an ORR and median time to progression were 29.7% and 4.9 months respectively.[633] Median time to progression was greater than 9.8 months in responders with advanced disease (stage IIB or higher). The response rates and median response durations were comparable to those obtained with bexarotene capsules and denileukin diftitox. Vorinostat was the first HDACI to receive FDA approval in October 2006 for the treatment of patients with progressive, persistent, or recurrent CTCL, on or following two systemic therapies. A post hoc subset analysis of patients who experienced clinical benefit with vorinostat in the previous phase IIb study provided evidence for the long-term safety and clinical benefit of vorinostat in heavily pretreated patients with CTCL, regardless of previous treatment failures.[636]

Romidepsin demonstrated single agent activity in 2 open-label clinical studies [pivotal phase 2B study (GPI-04–0001) and NCI 1312 (supportive study)] of 167 patients with CTCL that was refractory to prior therapies.[635, 637] In a pooled analyses of these two international multicenter clinical studies, objective response rate was seen 41% of patients (7% CR and 33% PR) in the evaluable population (who had at least 2 cycles).[634] Responses were noted in 42% of patients with stage ≥IIB MF and 58% of patients with SS. Median duration of response and median time to disease progression were 15 months and 8 months respectively. The pivotal phase IIb study (GPI-04-0001) enrolled 96 patients and 68 (71%) of these had advanced stage disease (≥IIB). The objective response rate was 34% including 6 CRs. Among patients with advanced stages of disease, 38% achieved an objective response, including 5 CRs. The median time to response was 2 months and the median duration of response was 15 months. Improvement in pruritus was observed in 28/65 patients (43%) with moderate to severe symptoms at baseline, including 11 who did not achieve an objective response.[638] These results are consistent with the findings of the phase NCI 1312 (supportive study) in a similar population (n = 71) using the same dose and schedule of romidepsin, where the ORR was 34% including 4 CRs and the median duration of response was 14 months.[634] In the pivotal study (GPI-04–0001), romidepsin also induced clinically significant responses in 37 patients with blood involvement.[639] In 27 evaluable patients, the objective response rate was 32% by composite assessment including 2 complete clinical responses. In November of 2009, romidepsin was approved by the FDA for the treatment of patients with CTCL in patients who have received at least one prior systemic therapy.

Systemic chemotherapy is used as a primary treatment only for patients with advanced disease or LCT and second-line therapy for early stage disease that is refractory to skin-directed therapies and systemic biologic therapies. Low dose methotrexate has been used to treat early stage MF and SS for many years, although there is not extensive literature documenting outcomes.[640, 641] Gemcitabine as a single agent has also been effective in patients with advanced, heavily pretreated CTCL and as front-line therapy in untreated CTCL patients.[642-645] Zinzani et al evaluated the long-term outcome of patients with T-cell lymphoma patients treated with gemcitabine. The ORR was 51%. Patients with MF had a CR rate of 16% and a PR rate of 32% compared with a CR rate of 30% and a PR rate of 25% of PTCLU patients.[645] Pentostatin has shown activity either as a single agent or in combination with interferon alfa in patients with advanced MF or SS.[646, 647,648] Anecdotal reports suggest activity for temozolomide and bortezomib.[649, 650] Pegylated liposomal doxorubicin have also shown significant activity in patients with pretreated, advanced or refractory CTCL.[651,652, 653] In a retrospective multicenter study (n = 34), 15 patients achieved a CR and PR was seen in 15 patients. The OS, EFS and DFS rates were 18-28 months, 12-22 months and 13-24 months respectively.[651] In a prospective phase II trial (n =19), Pulini et al reported an overall and CR rates of 84.2% and 42.1% (with no significant differences between stage I-IIA and IIB-IV patients) of patients with relapsed CTCL.[652] OS, EFS and PFS rates at 46 months were 44%, 30% and 37% respectively. In a multicenter dose-finding study, low-dose pralatrexate (15 mg/m^2) was active with acceptable toxicity inducing ORR in 43% of patients with relapsed or refractory CTCL.[654]

In clinical studies and case report, liposomal doxorubicin, denileukin diftitox and gemcitabine have demonstrated activity in patients with transformed MF/SS. [653,655, 656] Pralatrexate (30 mg/m^2) has demonstrated significant activity in the 12 patients with refractory

transformed MF enrolled in the PROPEL trial with an investigator assessed response rate of 58%. The median duration of response and PFS were 4 months and 5 months respectively.[657]

Combination therapies

Combinations of biologic or non-cytotoxic therapies as distinct from combination chemotherapies are used when single agent therapies fail or in advanced, progressive, refractory, or symptomatic disease. Several combination therapies have been studied in clinical trials for CTCL.[658-660] In a retrospective non-randomized series, ECP given concurrently with, or immediately after, TSEBT significantly improved both PFS and cause specific survival for patients with erythrodermic MF compared with TSEBT alone.[661] Most commonly used combinations are phototherapy plus either interferon or systemic retinoid and ECP plus either IFN or systemic retinoid or both.[660, 662-667] PUVA when used in combination with interferon alfa produced an ORR of 93% in patients with stage IB to stage IVB disease, with a median duration of response exceeding 23 months.[662] In another prospective phase III trial, combination of low-dose interferon alfa and PUVA resulted in a CR rate of 84% and an ORR of 98% in patients with early stage MF.[663] Low-dose bexarotene in combination with PUVA also resulted in an ORR of 93% (47% CR) in patients with all stages of CTCL resistant or intolerant to previous therapies.[668] The addition of PUVA to the combination of ECP, interferon and bexarotene resulted in rapid sustained remission in patients with SS.[664] In a long-term follow-up study involving patients with advanced CTCL and poor prognostic factors, combined modality therapy (ECP with interferons and/or systemic retinoids) resulted in better response rates and median survival (84% and 74 months respectively) compared to ECP alone (75% and 66 months respectively).[660] Combination therapy was well tolerated. Combination of bexarotene with PUVA, ECP and/or interferon also resulted in higher response rates in patients with advanced disease.[665]

Systemic retinoids have been studied in combination with other biological response modifiers in patients with advanced disease.[669, 670] The combination of bexarotene and denileukin diftitox is particularly interesting since bexarotene has been shown to increase CD25 expression in CTCL cells and thereby increasing the susceptibility of T-cells to denileukin diftitox.

NCCN Recommendations based on Clinical Stage

Primary Treatment

Patients with Stage IA have an excellent prognosis using skin-directed therapies alone. Stage IA is managed primarily with skin-directed therapies, alone or in combination with other skin-directed therapies including local RT. Local RT (24-36 Gy) is recommended particularly for unilesional presentation. Treatment options include topical corticosteroids, nitrogen mustard or carmustine, topical retinoids (bexarotene or tazarotene), topical imiquimod, phototherapy with UVB for patch or thin plaques or PUVA for thicker plaques.

Patients with Stage IB-IIA disease require generalized skin treatment. Topical retinoids are not recommended for generalized skin involvement since they can cause a lot of irritation. In addition to the other skin-directed therapies used for Stage IA disease, TSEBT is another treatment option for those with severe skin symptoms or generalized thick plaque or tumor. Although TSEBT is highly effective in T1 disease (stage IA), it is reserved for generalized or recalcitrant skin disease due to its toxicities and lack of superior long-term outcome. It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response. For patients with sites

that are not responsive to generalized treatment, additional treatment may be needed.

Patients with early stage disease (stage IA, stage IB-IIA) with B1 blood involvement are best managed with more intensive treatments as described for stage III with B1 blood involvement and those with histological evidence of folliculotropic or large cell transformation (LCT) are managed as described for stage IIB disease.

Patients with Stage IIB disease and/or histological evidence of folliculotropic or LCT can be separated into two categories: limited extent tumor disease with or without patch/plaque disease or generalized tumor disease. In patients with tumor disease, rebiopsy is necessary to confirm histological evidence of LCT.

Patients with limited extent tumor disease can be managed with local radiation. Adjuvant systemic therapy (SYST-CAT A) may be considered to improve response duration in patients who are free of disease after local RT. Skin directed therapies, as described above for stage I-IIA disease can be used for the residual patch or plaque disease. Alternatively, they can also be treated with systemic therapy (SYST-CAT A: ECP, bexarotene, ATRA, 13-cis-retinoic acid or their synthetic analogs acitretin and isotretinoin, interferons, HDACIs (vorinostat or romidepsin), interferons, denileukin diftitox or low-dose methotrexate) with or without RT or skin-directed therapy.

Patients with generalized tumor disease are treated with TSEBT or systemic therapy, with or without skin directed therapy. Suggested systemic therapy options include ECP, systemic retinoids (bexarotene, ATRA, 13-cis-retinoic acid or their synthetic analogs acitretin and isotretinoin), interferons, HDACIs (vorinostat or romidepsin) or denileukin diftitox, chemotherapy single agents such as methotrexate, liposomal doxorubicin, gemcitabine for first-line therapy and chlorambucil, pentostatin, etoposide, cyclophosphamide, temozolomide for second-line therapy.

Systemic therapy is the initial treatment for patients with LCT. If there is no evidence of aggressive growth, systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. For LCT with aggressive clinical course, the guidelines recommend systemic therapy (SYST-CAT C) with liposomal doxorubicin, gemcitabine, denileukin diftitox, romidepsin, low or standard dose pralatrexate or any of the regimens recommended for PTCL. Combination regimens are generally reserved for patients with relapsed or refractory or extracutaneous disease.

Management of patients with stage III disease depends on the extent of blood involvement: no significant blood involvement (B0) or some blood involvement (B1), which is less than that observed for SS. Patients with no significant blood involvement are treated with generalized skin-directed therapies (similar to those recommended for stage IB-IIA). Generalized skin-directed therapies other than topical steroids may not be well tolerated for patients with stage III disease. ECP may be a more appropriate systemic therapy for patients with stage III disease with blood involvement. Alternative options include low dose methotrexate or systemic biologic therapies as recommended for stage IIB disease. Mid-potency steroids should be used in combination with systemic therapy to reduce skin symptoms. Antibiotic therapy should be considered for this group of patients since they are at increased risk of developing secondary infections.

Stage IV disease includes SS and non-Sezary or visceral (solid organ) disease. SS patients are treated with singe agent systemic therapy (ECP, systemic retinoids, interferons, vorinostat or romidepsin, denileukin diftitox or low dose methotrexate) or combination therapies.

Safety data on the use of systemic retinoids in combination with TSEBT and vorinostat in combination with phototherapy or TSEBT is currently lacking. Non-Sezary or solid organ disease is frequently managed with systemic therapy (SYST-CAT B or SYST-CATC) with or without RT for local control. Adjuvant biologic therapy may be considered following chemotherapy to improve response duration.

All patients (stage IA through stage IV) showing response should be considered for maintenance or tapering therapy to optimize response duration. Patients with a PR or disease relapse following primary treatment should be treated with the other options included in the primary treatment to improve response before starting treatment for refractory disease. In addition, patients with disease relapse or persistent disease may be considered for clinical trials. Patients with stage IV disease should be considered for clinical trials.

Refractory or Progressive Disease

Autologous stem cell transplantation (SCT) has been used infrequently for patients with CTCL. In general, the durations of response have been short thus limiting its usefulness. Allogeneic SCT has been reported only in case reports and small series in patients with advanced MF and SS.[671] A recent meta-analysis compared the outcome of allogeneic versus autologous SCT in patients with MF and SS. OS and durable response rates were more favorable in patients who received allogeneic SCT.[672] In the allogeneic group, the majority (70%) of patients experienced persistent GVHD, mostly with mild to moderate severity, whereas the majority of the deaths (8 of 10) in the autologous group were because of progressive disease. Data on allogeneic SCT, particularly using non-myeloablative conditioning, suggest the existence of graft versus T- cell lymphoma effect and success with long-term durable remissions has been reported in highly selected patients. Duvic et al have evaluated the safety and efficacy of total skin electron beam with allogeneic HSCT in 19 patients with CTCL.[673] The overall intent-to-treat response was 68%, and the CR rate was 58%. Eleven (58%) of the initial 19 patients are currently in complete clinical and molecular remissions with median follow-up of 19 months. Median OS has not been reached. Additional study in high-risk patients with advanced disease is warranted.

Systemic therapy (SYST-CAT A), single agent or combination therapy is recommended for patients with stage IA, IB-IIA disease that is progressive or refractory to primary skin-directed therapies. Skin-directed therapy can be used as adjuvant treatment to reduce skin symptoms. Patients who do not respond to treatment with SYST-CAT A agents are treated with single agent systemic chemotherapy (SYST-CAT B). Allogeneic SCT may be considered for patients with stage IIB -IV disease that is progressive or refractory to multiple primary treatment options. Appropriate patients (stage IIB or greater MF who have failed multiple systemic therapies and adequate trial of skin-directed therapy or whose disease is not amenable to skin-directed therapy) may be referred for a transplant consultation. Ideal time for allogeneic SCT is when their disease is well controlled with induction therapy and before their disease has progressed to a state where the chance of response or survival with allogeneic SCT is low. Patients should have failed biologic options and single agent chemotherapy prior to allogeneic SCT. When appropriate, TSEBT may be considered as cytoreductive therapy before transplant.

Alemtuzumab, anti-CD52 antibody has shown promising activity in patients with advanced MF and SS.[575, 674-678] In a study of 14 patients, subcutaneous alemtuzumab at very low doses (10 mg maximum per administration), given for a short period based on Sezary cell count, was associated with a good toxicity profile, high response rate and durable remissions in SS patients with high tumor burden in the

peripheral blood.[676] Alemtuzumab (IV or subcutaneous) may be considered for patients with stage III-IV (specifically, SS) disease that is refractory to previous treatments.

Currently there is no definitive treatment for advanced disease that can produce reliable durable remissions or curative results, other than possibly, allogeneic SCT. The guidelines recommend participation in a clinical trial as a treatment option for all patients with relapsed or progressive disease.

Adult T-Cell Leukemia/Lymphoma (ATLL)

ATLL is a distinct T-cell lymphoma associated with a retrovirus, human T-cell lymphotropic virus type I (HTLV-1). The annual rate of ATLL among HTLV-1 carriers older than 40 years is estimated at 1.5 per 1,000 in males and 0.5 per 1,000 in females.[679] HTLV-1 infection appears to be rare in the United States and is highly prevalent in southwestern Japan, Caribbean islands, tropical Africa and south America.[680]

Advanced performance status (PS), high lactate dehydrogenase (LDH) level, increased number of total involved lesions, hypercalcemia and age 40 years or more have been identified as major adverse prognostic factors by multivariate analysis.[681] For the chronic subtype, high LDH, high blood urea nitrogen, and low albumin levels have been identified as poor prognostic factors. These factors were used to stratify patients into three different risk groups: low risk, standard high risk and extremely high-risk group. Median survival time and projected 2- and 4-year survival rates were 37 months, 66.3% and 41.2% for low risk, 8 months 20.6%, and 4.5% for standard high risk, and 2.4 months, 5.6% and 0% for extremely high-risk groups, respectively.[681] Recently, the International Peripheral T-Cell Lymphoma Project reported that IPI is a useful model for predicting outcome in ATLL of the lymphoma type.[682]

Phillips et al recently identified 3 prognostic categories based on ECOG performance status, stage, age, and calcium level at diagnosis for patients with HTLV-1-associated ATLL. In this series (n = 89), despite initial responses to therapy with alkylator-based chemotherapy regimen, the median OS for all subtypes was 24 weeks.[683]

The Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) have classified ATLL into four subtypes (smoldering, chronic, acute, or lymphoma) based on the characteristic features of ATLL which include generalized lymphadenopathy, hepatosplenomegaly, skin involvement, hypercalcemia, and organ infiltration.[684] The smoldering and chronic subtypes are considered indolent. Both have 5% or more of abnormal T-lymphocytes in the peripheral blood and may have skin or pulmonary lesions. In addition the chronic subtype is characterized by absolute lymphocytosis (4 x 10^9/L or more) with T-lymphocytosis more than 3.5 x 10^9/L, lymphadenopathy and involvement of liver and spleen. The lymphoma type has 1% or less abnormal T-lymphocytes, no lymphocytosis, and histologically-proven lymphadenopathy with or without extranodal lesions. The acute type usually has leukemic manifestation and tumour lesions, with a rapidly progressive course, but involves cases that are not classified as any of the three other types.

The smoldering and chronic subtypes have a better prognosis than the acute or the lymphoma subtypes. In an analysis of 818 patients with a mean age of 57 years, 4-year survival rates for acute, lymphoma, chronic, and smoldering subtypes were 5.0%, 5.7%, 26.9%, and 62.8%, respectively. The median survival time was 6.2 months, 10.2 months, 24.3 months, and not yet reached, respectively. The maximum duration of follow-up was 7 years.[684] In a recent report from a long-term follow-up of 90 patients with newly diagnosed indolent ATLL, the 5-, 10-, and 15-year survival rates were 47.2%, 25.4%, and 14.1%,

respectively.[685] In the subgroup analysis, the 15-year OS rate and median survival time tended to be higher for chronic subtype (14.7% and 5.3 years respectively) than the smoldering subtype (12.7% and 2.9 years respectively).

In the NCCN guidelines patients are classified into 4 subtypes (chronic, smoldering, acute and lymphoma) according to the Shimoyama criteria.[684]

Diagnosis

The diagnosis of ATLL requires the histopathology and immunophenotyping of tumor lesion, peripheral blood smear analysis for atypical cells, flow cytometry on peripheral blood and/or HTLV-1 serology.[686, 687] The presence of 5% or more of T-lymphocytes with an abnormal immunophenotype in the peripheral blood is required for the diagnosis of ATLL in patients without histologically proven tumor lesions.[684] HTLV-1 integration patterns have been reported to have clinical implications for ATLL.[688] Bone marrow involvement is considered an independent poor prognostic factor.[689] However, a bone marrow biopsy is generally not required for the diagnosis of ATLL. If the diagnosis of ATLL is not established on peripheral blood examination, bone marrow biopsy and biopsy of lymph nodes, skin and GI tract should be performed. Biopsy of the suspicious lesion may also help to rule out certain underlying infections. Excisional biopsy is recommended instead of core needle biopsy for the lymph nodes.

If a biopsy is performed the immunophenotyping panel should include CD3, CD4, CD7, CD8, and CD25. The typical immunophenotype in most patients with ATLL involves CD4-positive T cells with the expression CD2, CD5, CD25, CD45RO, CD29, T-cell receptor $\alpha\beta$ and HLA-DR. Most ATLL cells lack CD7 and CD26 and have a dim CD3 expression.

Workup

The initial workup involves a complete physical examination, including complete skin examination, and CT scans of the chest, abdomen and pelvis. Most patients with ATLL have elevated LDH levels and lymphocytosis is found in patients with the acute or chronic type at presentation. The guidelines recommend performing a complete blood count (CBC), checking serum LDH and serum electrolyte levels including serum calcium, creatinine and blood urea nitrogen (BUN).

Upper gastrointestinal tract endoscopy should be considered in selected cases since GI tract involvement is frequent in aggressive ATLL.[690] CNS evaluation using CT scan, MRI and/or lumbar puncture is also recommended for all patients with acute or lymphoma subtypes or in patients with neurological manifestations.[691]

Response Criteria

The current response criteria for ATLL are the modification of the JCOG response criteria as suggested at the international consensus meetings. The modified response criteria reflect the criteria for CLL and NHL which were published in 1996 and 1999. These response criteria are based on the reduction in the size of the enlarged lymph nodes and extranodal masses (as calculated by the sum of the products of the greatest diameters of measurable disease), reduction in the size of spleen or liver and the extent of involvement of bone marrow and skin.[687] The response is categorized as CR (complete disappearance of all clinical, microscopic, and radiographic evidence of disease and absolute lymphocyte count including the flower cells in the peripheral blood is less than 4 x 10^9/L), PR (defined as 50% or greater reduction in the sum of the products of the greatest diameters of measurable disease without the appearance of new lesions and 50% or greater reduction in absolute abnormal lymphocyte counts in peripheral blood),

stable disease (SD; failure to achieve CR or PR with no progressive disease) and relapsed disease or progressive disease (PD; 50% increase from nadir in the count of flower cells and an increase in absolute lymphocyte count including flower cells of 4 x 10^9/L or more). The response criteria also includes a category for unconfirmed CR defined as 75% or more reduction in tumor size but with a residual mass after treatment with an absolute lymphocyte count, including flower cells, of less than 4 x 10^9/L. The usefulness of PET or PET-CT has not been evaluated in the response assessment of ATLL.

Treatment Options

The ATLL subtype is an important factor for predicting prognosis and deciding appropriate treatment strategies. Smoldering and chronic subtypes are considered indolent and are usually managed as indolent NHL with watchful waiting until disease progression, whereas acute and lymphoma subtypes require immediate therapy.

Several small phase II studies have reported responses with the combination of AZT and interferon in patients with ATLL.[692-697] The results of a worldwide meta-analysis on the use of zidovudine and interferon for patients with ATLL were recently reported by Bazarbachi et al.[698] In 231 patients with available survival data, first-line therapy was recorded in 207 patients. Five year OS rates were 46%, 20% and 12% respectively for patients who received antiviral therapy alone, chemotherapy alone and chemotherapy followed by antiviral therapy. Of the 62 patients who received first-line antiviral therapy, CR and PR were achieved in 35% and 31% of patients respectively. Of the 48 patients who received first-line chemotherapy, 25% achieved CR and 56% achieved PR. Of the 14 patients who received chemotherapy followed by antiviral therapy and for whom response data were available, CR and PR were achieved in 50% and 43% of patients respectively. In patients with acute subtype, achievement of complete remission with first line antiviral therapy resulted in a significantly improved survival (5-year OS of 82%) compared with patients who did not achieve CR (5-year OS 12%). In the OS analysis by subtype, patients with acute, chronic, and smoldering subtypes significantly benefited from first line antiviral therapy, whereas patients with lymphoma subtype had a better outcome with first line chemotherapy. Patients with chronic and smoldering subtypes who received first line antiviral therapy had an excellent survival (100% OS beyond 5 years) compared to those who received first-line chemotherapy with or without maintenance antiviral therapy (5-year OS of 42%). In patients with acute subtype, the corresponding survival rates were 28% and 10% respectively for antiviral therapy and chemotherapy with or without maintenance antiviral therapy. In patients with lymphoma subtype, first-antiviral therapy resulted in a significant survival disadvantage (median and 5-year OS were 7 months and 0%, respectively) compared with first-line chemotherapy with or without maintenance antiviral therapy (median and 5-year OS were 16 months and 18%). These results confirm that treatment of patients with ATLL using zidovudine and interferon results in a high response and complete remission rates particularly in acute, chronic and smoldering subtypes, but not in lymphoma subtype.

In the clinical trials for advanced NHL conducted by the Japan Clinical Oncology Group (JCOG), the CR rate and OS were poorer in ATLL treated with CHOP-like regimens compared to those with aggressive NHL.[699] More intensive multidrug combination chemotherapy regimen [vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP)] has been reported to be more effective for patients with newly diagnosed aggressive

ATLL.[700] The 3-year OS rates were 24% and 13% respectively for VCAP-AMP-VECP arm and CHOP. However, VCAP-AMP-VECP regimen was also associated with significantly higher grade 3 or 4 toxicities neutropenia: 98% vs. 83%; thrombocytopenia: 74% vs. 17%) and infections rates (32% vs. 15%) than biweekly CHOP.

In small series of patients, doxorubicin-based chemotherapy with or without antiretroviral therapy and interferon has been shown to be effective in patients with ATLL.[701-703] In a retrospective analysis of 36 consecutive patients diagnosed with HTLV-1 ATLL, Shapira et al reported that CHOP chemotherapy consistently improved survival compared to non-CHOP therapy (40-47 weeks vs. 6-11 weeks respectively in patients without hypercalcemia and 25-30 weeks vs. 10-12 weeks respectively in those with hypercalcemia).[701] In another report, the overall median survival was 8 months for 29 patients diagnosed with an ATLL who received initial treatment with two cycles of CHOP followed by antiretroviral therapy.[702] In a phase II trial conducted by the AIDS Malignancy Consortium, EPOCH chemotherapy followed by antiretroviral therapy was also found to be an active therapeutic regimen for ATLL, although it was associated with viral reactivation during induction chemotherapy.[703]

Allogeneic HSCT (myeloablative and non-myeloablative) has been shown to improve the outcome suggesting a graft-versus-ATLL effect.[704-710] In a retrospective analysis that included 40 patients who received myeloablative allogeneic HSCT, the median survival time of all cases after transplantation was 9.6 months.[704] The estimated 3-year OS and RFS, and risk of disease relapse were 45.3, 33.8 and 39.3% respectively. There were 21 deaths after transplantation, and 16 were related to adverse events of transplantation. Acute and chronic graft-versus-host disease developed in 26 and 15 patients respectively. In this study, among 10 patients relapsed after transplantation, five patients achieved second CR; three achieved CR only by the reduction or cessation of immunosuppressive agents suggesting graft-versus-ATLL effect. In a recent retrospective analysis of 386 patients undergoing allogeneic HSCT, patient's age (greater than 50 years), male sex, lack of complete remission at the time of transplant and the use of unrelated or cord blood were identified as adverse prognostic factors for OS.[711]

NCCN Recommendations

Since there are no optimal treatment options, the guidelines have included enrollment in clinical trials as one of the options for all patients with ATLL. Prophylaxis with anti-Strongyloides agents and anti-infectious prophylaxis with sulfamethoxazole-trimethoprim are recommended for all patients.[687]

Primary Therapy

Observation is an option for patients with chronic or smoldering subtypes since both these are considered indolent. Alternatively, these patients can be managed with skin-directed therapies (as recommend for patients with MFSS) or a combination of zidovudine and interferon.

For patients with acute or lymphoma subtype, there are no defined treatment options and efficacy of long-term treatment is limited. In a small series allogeneic transplant has been beneficial. The guidelines have included zidovudine and interferon or chemotherapy as options for patients with acute subtype. For patients with the lymphoma subtype, combination chemotherapy should be considered for primary therapy, since antiviral therapy is not effective for this group of patients.[698] CNS prophylaxis (intrathecal methotrexate and cytarabine and corticosteroids) is recommended.

Outside of a clinical trial, if a patient is not responding or is progressing, on zidovudine and interferon, treatment should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. The duration of initial therapy is usually 2 months. If life threatening manifestations occur, treatment can be discontinued before the two months period.

The optimal chemotherapy for patients with ATLL is not yet established. The regimens listed in the guidelines are based on institutional preferences and these include CHOP, EPOCH or hyper-CVAD.

Response Assessment and Additional Therapy

If there is CR after 2 months, continuation of zidovudine and interferon is recommended for patients with chronic or smoldering or acute subtype. Allogeneic HSCT should be considered for patients with acute or lymphoma subtype.

Patients with persistent or progressive disease following primary therapy should be treated with chemotherapy, clinical trial or best supportive care. Allogeneic HSCT should be considered for patients with acute or lymphoma subtype.

Extranodal NK/T-Cell lymphomas, nasal type

Mature NK/T-cell lymphomas are a rare and distinct subtype of NHL. NK/T-cell lymphomas are predominantly extranodal and majority of these are of nasal type. In the International PTCL project, among 1153 new adult cases of PTCL, extranodal NK/T-cell lymphomas (ENKL) were identified in 12% of patients (nasal 68%, extranasal 26%, aggressive or unclassifiable 6%).[712] The frequency was higher in Asia than in Western countries. In the USA, the data from the Surveillance Epidemiology and End Results (SEER) registry database reported an increase in the incidence of ENKL, nasal type, from 1992 through 2005, with an annual percentage change of 11%.[713] The incidences were also found to be higher in men and in people of Asian and Pacific Island descent.

In the 2008 WHO classification, mature NK-cell neoplasms are classified into 2 subtypes: ENKL, nasal type and aggressive NK-cell leukemia.[17] However, ENKL may also have an extranasal presentation.[714] ENKL, nasal type is often localized to the upper aerodigestive tract including the nasal cavity, nasopharynx, paranasal sinuses, hypopharynx, and larynx. The most common sites of involvement for extranasal subtype are skin, testis, gastrointestinal tract, soft tissues, and spleen. Majority of the patients with extranasal disease present with advanced stage (68%) and B symptoms (54%) compared to 27% and 39% respectively among patients with nasal type.[712] ENKL, nasal type has a better median overall survival compared to the extranasal type both in patients with early stage (2.96 vs 0.36 years) and advanced stage disease (0.8 vs 0.28 years).[712]

Diagnosis

Most of the ENKL are characterized significant angiocentricity, necrosis and ulceration. Necrosis is thus very common in diagnostic biopsies and may delay diagnosis significantly. Biopsy specimen should include edges of the lesions, to increase the odds of having a viable tissue. It may be useful to perform multiple nasopharyngeal biopsies even in areas not clearly involved.

The most typical immunophenotype is CD20-, CD2+, CD56+, CD7+, CD8+, CD43+, CD45RO+, and cytoplasmic CD3ε+(surface CD3).[715] ENKL usually lack the *TCR* and immunoglobulin gene rearrangements. Ki-67 expression is predictive of prognosis in patients with stage I/II ENKL, nasal type.[716, 717] High Ki-67 expression (65% or more) was associated with a shorter overall and disease-free survival. In

multivariate analysis, Ki-67 expression and primary site of involvement were found to be independent prognostic factors for overall survival (OS) and disease-free-survival (DFS).[716]

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis. The recommended panel for immunohistochemistry includes CD3, CD5, CD10, BCL6, BCL2, CD20, CD2, CD7, CD8, CD4, cytoplasmic CD3ε, CD56 and Ki67. EBV infection is always present and can be determined by EBV-encoded RNA in situ hybridization (EBER-ISH).

Workup

The workup should include complete ENT evaluation of nasopharynx involvement (including Waldeyer's ring), testicles and skin, performance statues, B symptoms, CBC with differential, platelets, comprehensive metabolic panel, measurement of serum uric acid, lactate dehydrogenase (LDH), CT scans with contrast of chest, abdomen and pelvis PET-CT scan with a diagnostic quality CT and dedicated CT of the nasal cavity, hard palate, anterior fossa or MRI of the nasopharynx. Bone marrow biopsy is recommended as part of the initial work up. Bone marrow involvement is uncommon at diagnosis and occurs in less than 10% of patients.[718] Morphologically negative biopsies need evaluation by EBER-ISH and if positive considered involved.[718-721]

Measurement of EBV-DNA viral load is useful in the diagnosis and possibly in the monitoring of the disease. EBV DNA viral load correlates well with clinical stage, response to therapy and poor survival.[722, 723] In multivariate analysis, EBV DNA 6.1 x 10^7copies/mL or more at presentation was significantly associated with an inferior disease-free survival (27 months for those with less than 6.1 x 10^7copies/ml compared to 0.5 months for patients with at least 6.1 x 10^7copies/ml).[722] Patients with undetectable trough EBV DNA during the clinical course had a significantly higher median OS (25 months) compared with patients with lack of normalization of EBV viremia.

IPI is most commonly used for patients with aggressive lymphomas. However, the use IPI in patients with ENKL is limited because most patients present with localized disease, rare involvement of bone marrow and the presence of constitutional symptoms even with localized disease. Recently, Lee et al have proposed a prognostic model specifically for patients with ENKL, nasal type, based on a large, retrospective, multicenter study that included 262 patients.[724] This model identified 4 different risk groups with different survival outcomes based on the presence or absence of 4 prognostic factors (B symptoms, stage of the disease, LDH and regional lymph node involvement). The 5-year OS rates were 81% and 64% respectively for patients with no risk factors (Group 1-low risk) and one risk factor (Group 2-low-intermediate risk). The corresponding survival rates were 34% and 7% respectively for patients with 2 risk factors (Group 3-intermediate high risk) and 3 or 4 risk factors (Group 4-high risk). Local tumor invasion (LTI), defined as bony invasion and/or perforation or invasion of the skin, has also been associated with a low probability of complete response, reduced DFS and a high frequency (65%) of systemic failure in patients with stage I/II disease.[725]

The guidelines recommend measurement of EBV DNA load and calculation of NK/T-cell prognostic index as part of initial work up.

Treatment

Initial treatment with RT alone has been effective in achieving favorable complete response rates compared to chemotherapy alone in patients with localized disease.[726-733] RT doses of 50 Gy or more resulted in better overall and disease free survival. The 5-year OS and DFS rates

were 75.5% and 60% respectively, compared to 46 % and 33%, respectively for patients receiving RT doses of less than 54 Gy.[733] In a retrospective review of 46 patients with localized disease, overall survival and failure-free survival was superior for patients treated with RT alone.[730] The 5-year OS rates were 83% and 29% respectively for RT and chemotherapy; the 5-year failure-free survival (FFS) rates were 83.3% and 27%. In the chemotherapy group, salvage RT was superior to chemotherapy alone for OS (5-year OS rates were 42% and 20% respectively) or FFS (5-year FFS rates were 41% and 20%). Combined chemotherapy and RT was also superior to chemotherapy alone in terms of OS and FFS; the 5-year OS rates were 37.5% and 23% and the 5-year FFS rates were 27% and 23%.[730] The benefit of adding RT to chemotherapy was also confirmed in the International Peripheral T-cell lymphoma Project that retrospectively reviewed the clinical outcome of 136 patients with early-stage ENKL, nasal type.[712] The 3-year OS rate was 57% compared to 30% for patients who received chemotherapy alone. Extranasal disease, however, was less amenable to RT.

Recently, concurrent chemoradiation has been reported to be a safe and effective treatment for the treatment of localized disease.[734, 735] In the phase I/II study conducted by the Japanese Clinical Oncology Group (JCOG0211), high risk patients with stage I/II nasal disease (lymph node involvement, B symptoms and elevated LDH) were treated with concurrent RT (50 Gy) and 3 courses of chemotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC).[735] With a median follow-up of 32 months, the 2-year OS was 78% and the overall response rate was 81%. Similar results were reported by a Korean study group which evaluated concurrent chemoradiotherapy (CCRT) with cisplatin and RT (40-53 Gy) followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD).[734] Majority of the patients had stage I/II disease (21 patients) and 9 patients had stage III/IV disease, as determined by the NK-cell prognostic index. The complete response rate was 73% after CCRT which increased to 80% after VIPD chemotherapy. The estimated 3-year, PFS and OS rates were 85% and 86% respectively. The results of these two studies support the use of concurrent chemoradiotherapy for patients with stage I/II disease.

Concurrent chemoradiation therapy is also the primary treatment option for patients with advanced stage disease and local RT an essential adjunct for local control. NK-cells are associated with a high expression of P-glycoprotein leading to multidrug resistance that is responsible for poor response to conventional chemotherapy.[736] Several studies have confirmed the efficacy of L-asparaginase-based regimens for patients with advanced, relapsed or refractory disease.[737-740] In a series of 45 patients with refractory and relapsed ENKL, nasal type treated with L-asparaginase-based chemotherapy followed by involved-field RT, the overall response rate was 82% (55% CR and 27% PR). Both 3-year and 5-year OS rates were 67%.[739] The efficacy of L-asparaginase in combination with methotrexate and dexamethasone (AspaMetDex regimen) was evaluated in a phase II intergroup study in patients with refractory or relapsed ENKL.[737] After 3 cycles, patients with localized disease were treated with consolidative RT, if not received previously and those with disseminated disease received high-dose therapy with peripheral blood stem cell infusion. Objective responses were achieved in 14 of the 18 evaluable patients after 3 cycles. Eleven patients had complete remission (61%). The median OS was 1 year, with median response duration of 12 months. The absence of anti asparaginase antibodies and the disappearance of EBV-DNA were significantly associated with a better outcome.

More recently, in a phase I study, Yamaguchi et al demonstrated the safety and efficacy of new L-asparaginase-based combination chemotherapy regimen called SMILE (steroid = dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) in patients with newly diagnosed stage IV, relapsed or refractory disease.[740] After 2 cycles, the overall response rate was 67% and the complete response rate was 50%. Based on these results a larger phase II study evaluated SMILE regimen with growth factor support in 39 patients including 21 with newly diagnosed stage IV disease, 13 in first relapse and 5 with primary refractory disease. A total of 29 patients (74%) completed the planned treatment with overall and complete response rates of 74% and 38%, respectively.[740] EBV-DNA copy number was also predictive for response and adverse events after SMILE chemotherapy. The overall response rate was 88% in patients with less than 10^5 copies/mL EBV-DNA in whole blood, but was 44% in patients with more than 10^5 copies/mL; grade 4 non-hematologic toxicity was significantly higher in patients with more than 10^4 copies/mL of EBV-DNA in plasma (55% vs. 14%).[741] Although preliminary, these data indicate that L-asparaginase-based regimen is a reasonable option for patients with advanced, relapsed or refractory disease. Long-term benefit needs to be confirmed in larger randomized clinical trials.

High-dose therapy with autologous stem cell rescue (HDT/ASCR) has been evaluated as a consolidation therapy for patients with early and advanced-stage disease responding to primary therapy. In retrospective analyses disease status at the time of HDT/ASCR was the most important prognostic factor for survival and relapse free survival in patients with early-stage as well as advanced stage disease.[742-744] In patients who were in complete response at the time of HDT/ASCR, 5-year disease-specific survival rates were significantly higher in the transplant group compared with the control group (87% and 68% respectively).[744] When stratified by risk based on NK/T-cell prognostic index, there was no significant difference in survival between the transplant and control groups for patients with low risk (disease-specific 5-year survival rate were 87% for transplant vs 69% for the control group), whereas among patients in the high-risk group, the survival benefit was statistically significant between the 2 groups (disease-specific 5-year survival rates were 100% vs. 52% respectively).[744]

NCCN Recommendations

Since ENKL are rare and there has been no randomized trials comparing different regimens, there is no standard therapy for patients with ENKL. Most of the available data are from retrospective analyses and small prospective series. It is preferred that patients with ENKL are treated at centers with expertise in the management of this disease and enrolled on clinical trials.

Induction Therapy

In the NCCN guidelines, patients are stratified by nasal versus extranasal disease at presentation and then by the stage of the disease.[745] Patients with stage I disease are further stratified based on risk factors (60 years or older, B symptoms, ECOG performance status of 2 or more, regional lymph node involvement, LTI, LDH, histological evidence of high Ki-67 staining and EBV DNA 6.1 x 10^7copies/mL or more).

Enrolment on a clinical trial is the preferred option for all patients with any stage disease. Selected patients with stage I nasal disease without risk factors can be treated with RT (50 Gy or more) alone. Alternatively, they can be treated similar to patients with stage I disease with risk factors or stage II disease, with concurrent chemoradiation therapy [RT (50 Gy) and 3 courses of DeVIC or concurrent RT(40-53 Gy) and

cisplatin followed by 3 cycles of VIPD]. L-asparaginase-based combination chemotherapy (SMILE regimen) with or without RT or concurrent chemoradiation therapy [RT (50 Gy) and 3 courses of DeVIC or concurrent RT(40-53Gy) and cisplatin followed by 3 cycles of VIPD] are included as options for patients with stage III-IV nasal disease and stage I-IV extranasal disease.

Response Assessment and Additional Therapy

Patients are restaged after induction therapy. Restaging should include appropriate imaging studies (CT, MRI or PET-CT), endoscopy with visual inspection, repeat biopsies and measurement of EBV DNA. The role of PET scan is not well established.

No further treatment is necessary for patients with stage I nasal disease achieving complete response to induction therapy. Hematopoietic stem cell transplant (HSCT) is a reasonable option for patients with stage I nasal disease achieving a partial response If eligible, HSCT should be considered for all patients with stage II-IV nasal disease and stage I-IV extranasal disease achieving complete or partial response to induction therapy.

For patients with refractory disease, L-asparaginase-based chemotherapy, as described for induction therapy may offer benefit. There is limited data regarding the role of HSCT in this patient population. Allogeneic HSCT has been evaluated[746, 747] and in a series of 25 patients, at a median follow-up of 34 months, the 2-year progression-free and overall survival rates were 34% and 40%, respectively.[746] Reduced-intensity non-myeloablative allogeneic transplant is associated with lower transplant-related mortality (20% vs. 30% for myeloablative HSCT) with an equivalent overall response rate (52% and 60% respectively).[746] Salvage chemotherapy or best supportive care is recommended for all patients with refractory disease.

Post-transplant lymphoproliferative disorders

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphoid neoplasms following solid organ transplantation (SOT) and allogeneic HSCT.[748, 749] PTLD following autologous HSCT is very rare. The majority of PTLD following both allogeneic HSCT and SOT are of B-cell origin and are usually associated with Epstein-Barr virus (EBV).[750] EBV-negative PTLD has been shown to be a late serious complication of transplantation.[751, 752] Gene expression profiling studies have shown that EBV-negative PTLD are biologically distinct from their EBV-associated counterparts.[753] PTLD following HSCT are usually of donor B-cell origin, whereas PTLD following SOT are of recipient B-cell origin in the majority of cases, though donor-derived cases typically involving the grafted organ have been reported.[754, 755]

In EBV-PTLD following SOT, clinical stage, poor performance status, EBV seronegativity, elevated lactate dehydrogenase (LDH) ratio, organ dysfunction, and multi-organ involvement by PTLD were identified as poor prognostic factors.[756-758] In contrast to PTLD following SOT, EBV seronegativity and graft organ involvement were not of any predictive value in patients with PTLD following allogeneic HSCT. Major risk factors for the development of PTLD in this group of patients include the use of unrelated or HLA-mismatched related donors, T-cell depletion of the donor graft and the use immunosuppressive therapy for the prophylaxis and treatment of acute graft-versus-host disease.[759]

In the WHO classification, PTLD are classified into 4 major categories: early lesions, monomorphic PTLD, polymorphic PTLD and classical Hodgkin lymphoma (CHL)-type PTLD.[17] Early lesions develop within a year of transplantation and are more common in transplant recipients

that are EBV naive. Early lesions consist of 2 histological subtypes, plasmacytic hyperplasia and infectious mononucleosis-like PTLD. Monomorphic PTLD most commonly resembles diffuse large B-cell lymphoma (DLBCL) but some lesions, although less common, can resemble Burkitt lymphoma, plasma cell myeloma or plasmacytoma. Unlike the EBV-positive PTLD, monomorphic lesions are more common among patients with EBV-negative PTLD. Polymorphic PTLD can be either polyclonal or monoclonal, although the former subtype is very rare.[17]

Diagnosis

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis.[760, 761] BCL6, MUM-1 and CD138 can be useful in distinguishing between the histological subtypes of PTLD.[762, 763] BCL-6 expression was detected in majority of monomorphic PTLD (71%) whereas it was consistently absent in polymorphic PTLD. MUM1 was preferentially expressed in 92% of polymorphic PTLD.[762] Overall, BCL6-, MUM1(+) and CD138(-) phenotype is associated with polymorphic PTLD whereas BCL6(+), MUM1(+/-) and CD138(-) is associated with monomorphic PTLD. The recommended panel for immunohistochemistry includes CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, and Ki67. Cell surface markers CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, kappa and lambda are recommended analysis by flow cytometric analysis.

EBV detection can be done either by immunohistochemistry for latent membrane protein-1 (LMP-1) or EBV-encoded RNA in situ hybridization (EBER-ISH). EBER-ISH is more sensitive than immunohistochemistry, but it not required in most cases.[760] If immunostaining for LMP-1 is positive, EBER-ISH is not required.

Immunoglobulin heavy chain variable (*IGHV*) gene mutations are seen in majority of PTLD, with the exception of early lesions.[764] Genetic alterations in *MYC*, *NRAS* and *TP53* are seen only in monomorphic PTLD.[763] *BCL6* mutations have been associated with shorter survival and poor response to therapy.[765] Molecular genetic analysis to detect *IGHV* rearrangements and *BCL6* mutations could be useful in selected cases.

Workup

The workup should include evaluation of performance status, prior history of immunosuppressive therapy, complete blood count, measurement of serum albumin, LDH and other electrolytes, CT scans of chest, abdomen and pelvis. PET-CT scan, bone marrow evaluation and brain MRI may be useful in selected cases. EBV-DNA viral load by quantitative PCR can aid in the diagnosis as well as monitoring treatment responses in patients with PTLD. Plasma or peripheral blood mononuclear cells (PBMC) are useful for measuring EB viral load, some studies have shown that viral load in plasma is more sensitive than PBMC in the diagnosis of PTLD.[766,767] Cytomegalovirus (CMV) has also been associated with an increased risk of PTLD in EBV-seronegative patients.[768] PCR for the measurement of EBV and CMV can be useful for selected patients. PTLD tends to involve extranodal sites including the central nervous system. In such cases, cerebrospinal fluid (CSF) analysis for EBV-DNA viral load by quantitative PCR is diagnostic.

Treatment

While guidelines have been published, the optimal treatment for PTLD is not defined due to lack of randomized controlled trials.[769] Reduction in immunosuppression (RIS) remains the first step in the management of nearly all cases of PTLD.[758, 770, 771] The role of antiviral therapy has

been controversial since the majority of PTLD are associated with latent EBV. Replicating EBV DNA has been reported in about 40% of EBV-associated lymphoproliferative disorders in immunocompromised patients.[772] Antiviral drugs targeting EBV replication may be beneficial in this subset of patients with early or polymorphic PTLD.[773]

Several phase II studies and retrospective analyses have confirmed the efficacy of rituximab monotherapy in the treatment of patients with PTLD.[774-779] In a prospective multicenter study, rituximab induced responses 44% of patients with an overall survival rate of 67% at one year.[774] Another prospective multicenter phase II study demonstrated that extended treatment with rituximab induced a high rate of CR in patients with PTLD after solid organ transplantation without increasing toxicity.[780] In a recent multicenter retrospective analysis, rituximab significantly improved PFS and OS in patients with PTLD.[776] With a median follow-up of 40 months, the 3-year PFS and OS rates were 70% and 73% respectively for patients who received rituximab-based therapy as part of initial treatment. The corresponding survival rates were 21% and 33%, respectively, for patients who received initial treatment without rituximab. This study identified hypoalbuminemia, CNS and bone marrow involvement as prognostic indicator for progression and survival. The 3-year PFS rates were 84%, 66% and 7%, respectively for patients with 0, 1 and 2 or more adverse factors. The corresponding 3-year OS rates were 93%, 68% and 11%, respectively.

Anthracycline-based chemotherapy with or without rituximab has also been effective in the treatment of patients with PTLD.[775, 781-785] In a retrospective analysis, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) induced an overall response rate of 65%, with a median follow-up of 9 years.[783] Median overall and progression-free survivals were 14 and 42 months, respectively. Chemotherapy and RIS, with or without rituximab has also been reported to induce durable complete remission with reduced the risk of graft impairment, when used as first-line treatment.[786, 787]

Adoptive immunotherapy using autologous or allogeneic EBV-specific cytotoxic T-lymphocytes (EBV-CTL) has been investigated.[788-790] In a long-term follow-up study, EBV-CTL therapy was very effective as a prophylaxis or treatment of patients with PTLD following HSCT.[790] In a recent retrospective analysis, the use of EBV-CTL significantly reduced the risk of death due to EBV-PTLD in HSCT recipients.[789] Partially HLA-matched allogeneic EBV-CTL therapy has also been reported to be a safe and effective option for PTLD.[791, 792] However, further studies are needed to confirm these findings.

NCCN Recommendations

Primary Treatment

Treatment options for PTLD depend on the histological subtype and should be individualized. RIS is the primary treatment for patients with early lesions. EBV-positive patients could be treated with ganciclovir.

For patients with localized polymorphic PTLD, options include surgery, RT or rituximab, whereas chemoimmunotherapy or rituximab is recommended for patients with systemic polymorphic PTLD. Alternatively, this group of patients can be treated with RIS or with ganciclovir, if EBV-positive.

RIS or chemoimmunotherapy are recommended for patients with monomorphic PTLD. However, response to RIS is variable and patients should be closely monitored. Patients unable to tolerate chemotherapy could be treated with single agent rituximab.

Second-line treatment

Treatment options are dependent on response to primary treatment and histological subtype. The guidelines recommend continuation of RIS for patients with early lesions achieving complete response to primary treatment, whereas those with persistent or progressive disease should be treated with rituximab. Monitoring viral load with EBV-PCR is recommended for all patients receiving second-line therapy.

Continuation of RIS and monitoring viral load with EBV-PCR or maintenance rituximab are recommended for patients with polymorphic PTLD achieving complete response to primary treatment. Chemoimmunotherapy or EBV-CTL infusion (if EBV-positive) are included as options for patients with persistent or progressive disease.

Patients with monomorphic lesions achieving complete response to primary treatment should be managed according to the specific treatment guidelines based on their histology. For patients with persistent or progressive disease, second-line treatment options are dependent on prior therapy. Rituximab or chemoimmunotherapy are options for patients who received RIS as primary treatment, whereas patients who received rituximab alone as initial therapy should be treated with chemoimmunotherapy. EBV-CTL infusion is an option for EBV-positive patients.

The guidelines recommend clinical trial as an option for patients with persistent or progressive polymorphic and monomorphic lesions following initial treatment.

The following sections of the discussion are being updated to correspond with the newly updated algorithm.
Last updated on 04/10/2008.

Marginal Zone Lymphomas

Marginal zone lymphomas (MZL) are a heterogeneous group of disorders consisting of extranodal marginal zone lymphoma (MALT lymphoma), nodal MZL, and splenic MZL. MALT lymphomas are subdivided into the gastric and non-gastric lymphomas. Splenic MZL involves the spleen and bone marrow, whereas nodal MZL occurs primarily in the lymph nodes though additional extra nodal sites are common.

Adequate hematopathology and immunophenotyping are needed to establish a diagnosis. The typical immunophenotype of MZL is CD5-, CD10-, CD20+, CD23-/+, CD43-/+, cyclin D1-, bcl-2 follicles-. In addition splenic marginal zone lymphoma is characterized by annexin-1- and CD103-. Immunophenotyping is useful in distinguishing MZLs from CLL (CD5+) and MCL (CD5+) and hairy cell leukemia (annexin-1+ and CD103+). Molecular, cytogenetics or FISH evaluation for the t(11;18) chromosomal translocation, is recommended. The t(11:18) is the most common genetic abnormality found in patients with gastric MALT lymphomas. It is associated with disseminated disease and resistance to antibiotic treatment in patients with gastric MALT lymphoma.[793, 794] In some cases cytogenetic evaluation should include evaluation for t(3;14)(p14.1;q32) [IGH-FOXP1]; t(1;14)(p22;q32) [IgH-BCL10]; t(14;18)(q32;q21) [IGH-MALT1] and del (7q31-32).

Gastric MALT Lymphoma

Gastric MALT lymphomas develop in the stomach. *Helicobacter pylori* (*H. pylori*) infection has a critical role in the pathogenesis of this disease and its eradication can lead to tumor remission.[795] Other MZLs have been shown to be associated with infectious agents, but this association has not been validated.[796-798]

Workup

The workup for gastric MALT lymphoma is similar to the workup for other NHLs. Special aspects of the workup for gastric MALT lymphoma include direct endoscopic assessment of the gastrointestinal tract and additional evaluation of the tumor specimen for the presence of *H.pylori.* The presence of H.pylori infection must be confirmed by biopsy with PCR (polymerase chain reaction) and urea breath test. Nondiagnostic atypical lymphoid infiltrates that are *H.pylori* positive should be re-biopsied to confirm or exclude lymphoma prior to treatment of *H.pylori*. Appropriate imaging studies include CT of the chest, abdomen and pelvis, and in select cases, bone marrow biopsy. At some NCCN institutions, endoscopic ultrasound (EUS) is used to complement conventional endoscopy at the time of the initial workup and at follow-up. EUS also provides information regarding the depth of involvement in the gastric wall that is essential information in some of the currently used staging systems.

Staging

Several different staging systems have been for gastric MALT lymphomas. In the Lugano staging system, Ann Arbor stage III has been removed and supradiaphragmatic nodal disease is included under stage IV. TNM (Tumor-Node-Metastasis) staging system corresponds to the staging in gastric cancer and the depth of the lymphoma infiltration is measured by EUS. Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvements in other lymphomas, and these patients may be managed by treating each site separately with excision or RT. In contrast, cases with disseminated nodal involvement appear to behave more like nodal MZL or like disseminated FL.

Treatment

H.pylori infection plays a central role in the pathogenesis of some cases of gastric MALT lymphoma. The efficacy of antibiotic therapy for the treatment for gastric MALT lymphoma has been evaluated in numerous trials.[799-801] Approximately two thirds of patients with localized gastric MALT lymphoma have a complete tumor remission after eradication of *H.pylori* infection with antibiotic therapy.[802]However, there is increasing evidence that late relapses occur after antibiotic management and a long duration of follow-up is appropriate.[803]

For disease confined to the stomach (stage IE, H.pylori positive), treatment begins with antibiotics in combination with a proton pump inhibitor to block gastric acid secretion. The tumor response may be slow, and re-evaluation with endoscopy should not be done until 3 months post treatment unless clinical deterioration is evident. If there is evidence of the t(11;18) t(1;14), t(14;18)(q32;q21), treatment of the *H.pylori* infection with antibiotics may be ineffective and these patients should be considered for alternative therapy. H. Pylori infection is not evident in approximately 10-40% of patients with gastric MALT lymphomas.[804] IFRT is preferred for patients with disease that is extending to the muscularis or disease extending from the GI tract to adjacent organs (stages IE [T2 or T3] or IIE H.pylori negative), particularly if one of the t(11;18), t(1;10), or t(14;18)(q32;q21) translocations is present.[805] Rituximab or chemoimmunotherapy are other treatment options.[806]

In patients with disseminated disease (stage III or IV), treatment is similar to that described for other advanced-stage indolent lymphomas. As with other indolent lymphoma, asymptomatic patients without indications for treatment are monitored without therapy. The decision to treat is guided by end-organ dysfunction or the presence of symptoms (such as bleeding, early satiety), bulky disease at presentation, steady progression of disease, or patient preference. Treatment may include single-agent or combination chemotherapy, or locoregional RT. If there is evidence of recurrence, patients are managed according to the FL guidelines. Surgical resection is generally limited to specific clinical situations. Though disease control is excellent with total gastrectomy, the long-term morbidity has precluded routine surgical resection. Total gastrectomy is necessary because of the multi-focal nature of the disease.

Follow-Up Endoscopy

Following primary antibiotic therapy, patients are restaged with endoscopy and biopsy after 3-months. Patients with responsive disease (microbiologic and tumor response) are just observed. Patients with persistent lymphoma with no evidence of *H.pylori* are treated with RT, if they are symptomatic or if there is significant disease progression. Asymptomatic patients can be observed for 3 months. Locoregional RT can be considered as early as 3 months after observation but observation can be prolonged for up to 18 months (category 2B). Patients with persistent *H.pylori* and regressing or stable lymphoma are treated with second-line antibiotics. Lastly, patients who are *H.pylori* positive with persistent lymphoma are treated with RT, if they have progressive disease. Those with stable disease are treated with second-line antibiotics.

Follow-up surveillance at 6 months consists of repeat endoscopy and biopsy. Patients can be subdivided into the same four groups, as above. Patients with complete tumor response continue to be observed if the *H. pylori* is negative, or they can be treated with other antibiotic therapy if *H. pylori* remains positive. Patients with persistent or recurrent lymphoma after antibiotic therapy, irrespective of their H.Pylori status, are treated with locoregional RT if not previously

treated. Patients whose disease does not respond to radiation are managed with single-agent or combination chemotherapy similar to FL. Following second-line antibiotic therapy or RT, patients are again evaluated with endoscopy and biopsy to rule out large cell lymphoma. Systemic therapy as indicated for follicular lymphoma is recommended for recurrence following CR to RT or antibiotic therapy, or for patients with no response to prior RT.

Non-gastric MALT Lymphomas

Nongastric MALT lymphomas can arise from a large number of non-gastric sites such as lung, thyroid, salivary glands, breast, and tissues surrounding the eye. For patients with stage IE -II disease or extranodal disease involving multiple sites, locoregional RT (20-30 Gy) is appropriate. Surgery may be considered for certain sites of disease (eg, lung, skin, thyroid, colon, small intestine, and breast). If there is no residual disease following surgery, patients are observed, whereas those with positive surgical margins are treated with locoregional RT. Recurrence following primary treatment is managed similar to advanced stage FL. RT is an option for those with local recurrence. Patients with advanced-stage disease (stage III-IV) are managed the same as patients with FL. Aggressive histologies, in which MALT lymphomas coexist with large cell lymphoma, should be managed according to the diffuse large B-cell practice guidelines.

Nodal Marginal Zone Lymphoma

Nodal MZL is rare and often presents concurrently with extranodal sites of disease. The diagnosis of nodal MZL requires careful evaluation to rule out extranodal sites of disease and it must be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma and CLL, all of which are more common. Nodal MZL is managed as per FL.

Splenic Marginal Zone Lymphoma

Diagnosis

Splenic MZL is often presumptive based on the findings of splenomegaly with peripheral blood flow cytometry usually revealing a monoclonal B cell population.[807] Involvement of the bone marrow is also common. This lymphoma is distinguished from CLL by the absence of CD5 expression, strong CD20 expression and variable CD23 expression. In some cases, the diagnosis can be established by the finding of villous projections on the circulating lymphocytes. Splenectomy can definitively establish the diagnosis and in many cases is therapeutic as well.

Workup

The workup is similar to the other indolent lymphomas. Flow cytometry of peripheral blood and bone marrow is essential in identification of a monoclonal B cell population. CT of the chest, abdomen, and pelvis will help in establishing the extent of disease. Hepatitis C has been associated with and implicated in the pathogenesis of splenic MZL and should be evaluated for all patients suspected of having this diagnosis.[808]

Treatment

Most of the patients with no splenomegaly, cytopenia or other symptoms can be observed. Patients presenting with splenomegaly are treated depending on their hepatitis C status. Hepatology evaluation is recommended for hepatitis C positive patients; anecdotal tumor regressions have been reported in responses to hepatitis therapy. In all other patients, in the absence of cytopenias or other symptoms, patients should be observed.

In a retrospective study, rituximab-based treatments resulted in longer failure free survival in patients with splenic MZL compared to patients treated with chemotherapy alone.[809] Rituximab was superior to splenectomy in normalizing white blood cell and absolute lymphocyte counts. Splenomegaly also disappeared in 92% of the patients treated with rituximab alone.

Splenectomy is the preferred option for patients with cytopenias or symptoms of weight loss, early satiety or abdominal pain. Rituximab is another treatment option for this group of patients. Patients should be monitored on a regular basis. If there is disease progression, patients are managed similar to advanced stage FL.

Mantle Cell Lymphoma

Diagnosis

Mantle cell lymphoma can be readily distinguished from other small lymphocytic lymphomas due to the widespread availability of appropriated diagnostic reagents.[810] The diagnosis can be established by histological examination in combination with immunohistochemistry with a profile consisting of CD5+, CD10-/+, CD20+, CD23-, CD43+, and cyclin D1+. Rare cases of MCL may include CD5- or CD 23+ immunophenotype. The diagnosis of MCL requires the expression of cyclin D1, an opinion shared by the panel.[811] However, recent gene profiling data suggests that cyclin D1 expression may not be required for the molecular signature of MCL; in these cases, over-expression of cyclin D2 or D3 can be observed.[812] Cases with a typical immunophenotype, CD5+, CD23-, CD20+ that are cyclin D1- should be evaluated for cyclin D2 and D3 expression; positive cases should be classified as MCL with a variant immunophenotype, negative cases should be classified as variant SLL/CLL. Currently available reagent for immunohistochemistry of cyclin D1 are robust and yield good staining; however, in some cases cytogenetics or FISH for the t(11;14), juxtaposing the cyclin D1 locus with the IgH locus can be diagnostically helpful.[813]

Workup

The workup for MCL is similar to the workup for many indolent lymphomas and certain aggressive lymphomas. MCL is a systemic disease with frequent involvement of the bone marrow, gastrointestinal tract and frequently a leukemic phase. For this reason, both the peripheral blood and bone marrow must be carefully evaluated for the presence of malignant cells. Chest, abdominal, and pelvic CT scans are routinely performed. MCL may present as lymphomatous polyposis coli and colon involvement is common.[814] In the current guideline, colonoscopy is now considered a routine part of the evaluation of MCL. Post treatment colonoscopy is necessary to confirm a CR, if it was not done previously. Upper endoscopy and neck CT scan may be helpful in selected cases. In patients with the blastic variant, lumbar puncture is done to evaluate the spinal fluid for involvement.

Treatment

It has generally been thought that MCL has the worst characteristics of both indolent and aggressive non-Hodgkin's lymphomas owing to the incurability with conventional chemotherapy and it more aggressive growth pattern. However, emerging data suggests that the long-term outcome of patient with MCL may be improving.[815] There remains no established standard of care. In the absence of standard management for MCL, patients with this disease should be referred for participation in prospective clinical trials. Like the management of patients with indolent lymphoma patients with MCL often have highly individualized course of care.

Several regimens have shown significant activity in newly diagnosed MCL, but none of these regimens are curative in patients with advanced disease.[816, 817] Recent metal analysis has shown that the addition of rituximab to chemotherapy increases response rates but it has not yet been proven to extend either progression-free or OS.[416] R-CHOP was significantly superior to CHOP in terms of overall response rate (94% v 75%), complete remission rate (34% v 7%).[818, 819]No differences were observed for PFS. In patients with newly diagnosed MCL, R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with R-MA (rituximab plus high-dose methotrexate and cytarabine) produced a 3-year failure-free survival (FFS) rate of 64% and OS rate of 82%.[820] However, in a subset of patients more than 65 years of age, this regimen was associated with shorter FFS and significant toxicity. R-HyperCVAD was evaluated in a multicenter SWOG study that reported a CR/CRu rate of 58% and 2-year PFS of only 63%.[821] Modified R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen developed by the Wisconsin Oncology Network, produced favorable overall response rate (77%) and CR rate (64%) with acceptable toxicity in patients with untreated MCL.[822] This is being tested more widely in an ongoing ECOG trial. RIT has also been investigated as initial therapy as well as second-line treatment for refractory or relapsed MCL as reviewed by Zelenetz.[817]

Few patients present with localized MCL and the available published literature on management is retrospective and anecdotal. In a retrospective analysis of 26 patients with early stage MCL, inclusion of RT was associated with an improved PFS and a trend towards improved OS.[823] Outside of a clinical trial, the panel recommended IFRT with or without combination chemotherapy. These recommendations are based on treatment principles in the absence of more definitive data.

Majority of patients with MCL will have advanced stage disease and require systemic therapy. Highly selected patients who are asymptomatic with stable adenopathy and non-bulky disease are observed; these patients usually have low bulk, nodular morphology variant and a low proliferation fraction. Based on the available data, the panel has included R-HyperCVAD and R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)[351] as options for first-line therapy. In patients older than 65 years of age, the panel recommends the use of modified HyperCVAD regimen with rituximab maintenance. CHOP (with or without rituximab) is recommended for selected older patients who cannot tolerate intensive therapy.

Initial remission should be followed by HDT/ASCR in eligible patients, as this has been associated with some evidence of durable remission. In a study conducted by M.D. Anderson Cancer Center, ASCR following treatment with hyperCVAD regimen for cytoreduction prolonged OS in patients with MCL in first disease remission, especially in those with a low beta-2-microglobulin level.[824] In a randomized trial conducted by European MCL network, patients 65 years of age or younger with advanced-stage MCL were randomized to ASCR or maintenance with interferon-alpha after achieving of complete or partial remission by CHOP-like chemotherapy. Three-year OS was 83% after ASCR versus 77% in the IFN group.[825]

The optimal approach to recurrent disease remains to be defined. Fludarabine-based combination regimens such as fludarabine in combination with cyclophosphamide[826] and FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) have shown activity in

MCL. In a prospective randomized study of the GLSG, addition of rituximab to the combination of fludarabine, cyclophosphamide, mitoxantrone, produced significantly longer OS in patients with relapsed and refractory MCL.[424] Cladribine also has shown activity in patients with untreated or relapsed MCL, achieving a response rate of 58%.[827] In a phase II trial, the proteosome inhibitor bortezomib induced 33% response rate including 8% CR in patients with relapsed or refractory MCL.[828] Median time to progression was 6.2 months. Based in these data, bortezomib received FDA approval for the treatment of patients with MCL who have received at least one prior therapy. Studies of bortezomib-based combinations in MCL are ongoing. Marked anti-tumor activity has been shown for rituximab plus thalidomide in patients with relapsed or refractory MCL.[829] Lenalidomide, an immunomodulator related to thalidomide also has activity in MCL either alone or in combination with rituximab.

Bendamustine is an emerging agent (recently approved for the treatment of CLL) that has well-documented activity in patients with MCL. In a phase II study conducted by the German study group (which included low grade NHL and MCL patients), the subset of patients with relapsed or refractory MCL treated with the combination of bendamustine and rituximab has an overall response rate of 75% with a CR rate of 50%.[830] Median follow-up duration was 20 months. The median PFS for MCL patients was 18 months whereas the median PFS for patients with FL had not been reached. Further studies are needed to confirm these findings.

Based on the efficacy data available in the literature, the combination of bendamustine with or without rituximab is included in the guidelines as an option for second-line therapy for patients with relapsed or refractory MCL, with a category 2B recommendation since no data is available yet from randomized studies and there was not uniform consensus among the panel. Ongoing phase III studies are evaluating the efficacy of bendamustine plus rituximab vs. R-CHOP in previously untreated MCL patients. The panel felt that additional follow-up from this study was necessary prior to making recommendations regarding initial therapy. The same combination is also being compared to fludarabine with rituximab in relapsed MCL.

Patients with relapsed disease following CR to induction therapy, those who obtain only a PR to induction therapy or those with progressive disease are appropriate candidates for clinical trials of high-dose therapy with autologous or allogeneic stem cell rescue.[831] Alternatively, these patients can also be treated with second-line chemotherapy.

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