National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Acute Lymphoblastic Leukemia

Version 1.2012

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NCCN Guidelines Version 1.2012 Panel Members
Acute Lymphoblastic Leukemia

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NCCN Guidelines Panel Disclosures

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Acute Lymphoblastic Leukemia

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.

DIAGNOSIS

Acute lymphoblastic leukemia (ALL)[a,b,c]

The diagnosis of ALL generally requires demonstration of ≥ 20% bone marrow lymphoblasts[d] upon hematopathology review of bone marrow aspirate and biopsy materials, which includes:

- **Morphologic assessment of Wright-Giemsa stained bone marrow aspirate smears, and H&E stained core biopsy and clot sections**
- **Comprehensive flow cytometric immunophenotyping[e]**

GENETIC CHARACTERIZATION

Optimal risk stratification and treatment planning requires testing marrow or peripheral blood lymphoblasts for specific recurrent genetic abnormalities using:

- **Karyotyping of G-banded metaphase chromosomes (cytogenetics)**
- **Interphase FISH testing including probes capable of detecting the major recurrent genetic abnormalities[a]**
- **RT-PCR testing for fusion genes (eg, BCR-ABL)**

Additional optional tests include:

- **Flow cytometric DNA index/ploidy testing (additional assessment for hyperdiploidy and hypodiploidy)**

CLASSIFICATION

Together, these studies allow determination of the WHO ALL subtype[a] and cytogenetic risk group[f]

Strongly recommend that patients be treated in specialized centers

See Workup and Risk Stratification ALL-2

[a] Subtypes: B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities include hyperdiploidy, hypodiploidy, and commonly occurring translocations: t(9;22)(q34;q11.2)[BCR-ABL1]; t(v;11q23)[MLL rearranged]; t(12;21)(p13;q22)[TEL-AML1]; t(1;19)(q23;p13.3)[E2A-PBX1]; t(5;14)(q31;q32)[IL3-IGH;relatively rare]. B-cell lymphoblastic leukemia/lymphoma, not otherwise specified. T-cell lymphoblastic leukemia/lymphoma.

[b] Criteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO 2008 criteria. Note that in ALL, myeloid-associated antigens such as CD13 and CD33 may be expressed, and the presence of these myeloid markers does not exclude the diagnosis of ALL.

[c] Treatment of Burkitt leukemia/lymphoma – see NCCN Guidelines for Non-Hodgkins Lymphoma.

[d] While these Guidelines pertain primarily to patients with leukemia, patients with lymphoblastic lymphoma (B- or T-cell) would likely also benefit from ALL-like regimens.

[e] See Typical Immunophenotype by Major ALL Subtypes ALL-A.

[f] Cytogenetic risk groups are defined as follows:
Good risk: Hyperdiploidy (51-65 chromosomes and/or DNA index > 1.16; cases with trisomy of chromosomes 4,10 and 17 appear to have the most favorable outcome); t(12;21)(p13;q22): TEL-AML1;
Poor risk: Hypodiploidy (<44 chromosomes and/or DNA index < 0.81); t(v;11q23): MLL rearranged; t(9;22)(q34;q11.2): BCR-ABL; Complex karyotype (5 or more chromosomal abnormalities).

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WORKUP

- H&P
- CBC, platelets, differential, chemistry profile
- DIC panel: d-dimer, fibrinogen, PT, PTT
- Tumor lysis syndrome panel: LDH, uric acid, K, Ca, Phos (See Tumor Lysis Syndrome in the NCCN Guidelines for Non-Hodgkin Lymphoma Guidelines)
- CT/MRI of head, if neurologic symptoms[g]
- Lumbar puncture (LP)[g,h]
  - See Evaluation and Treatment of Extramedullary Involvement (ALL-C)
  - Consider intrathecal (IT) chemotherapy
- CT of chest (for T-ALL patients)
- Testicular exam (testicular involvement is especially common in T-ALL)
- Infection evaluation:
  - Screen for active infections if febrile or for symptomatic opportunistic infections
  - Initiate empirical treatment, as appropriate (See NCCN Guidelines for Prevention and Treatment of Cancer-related Infections)
- Echocardiogram or cardiac scan should be considered in all patients, since anthracyclines are important components of ALL therapy, but especially in patients with prior cardiac history, prior anthracycline exposure of clinical symptoms suggestive of cardiac dysfunction.
- Central venous access device of choice
- HLA typing (except for patients with a major contraindication to HSCT)
- In patients with poor risk features who lack a sibling donor, consider early evaluation for alternative donor search

RISK STRATIFICATION

[g] For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or CNS bleeding. See Evaluation and Treatment of Extramedullary Involvement (ALL-C)

[h] Timing of LP should be consistent with the chosen treatment regimen. Pediatric-inspired regimens typically include LP at the time of diagnostic workup. The Panel recommends that LP, if performed, be done concurrently with initial intrathecal therapy.

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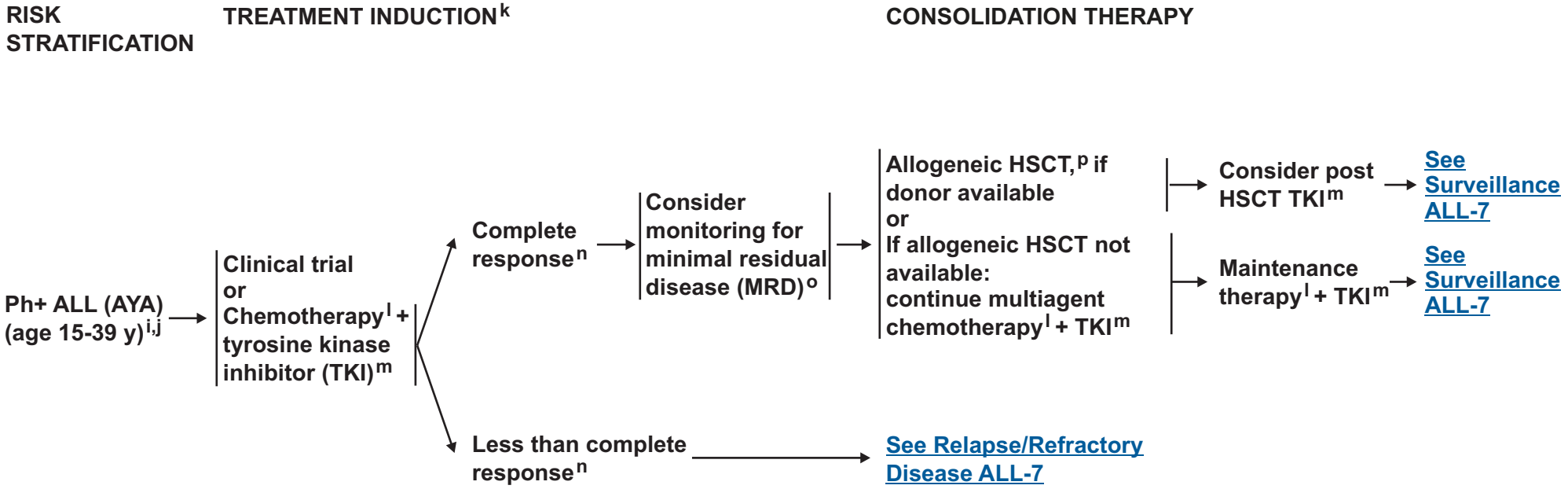

[i] Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including the following factors: end-organ reserve, end-organ dysfunction, performance status.

[j] For additional considerations in the management of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult Oncology.

[k] All ALL treatment regimens include CNS prophylaxis.

[l] See Principles of Chemotherapy (ALL-D).

[m] See Discussion section for use of different TKIs in front-line therapy.

[n] See Response Criteria (ALL-E).

[o] See Minimal Residual Disease Assessment (ALL-F).

[p] Emerging data suggests that for younger patients (age ≤ 21 y), allogeneic HSCT may not offer an advantage over chemotherapy + TKIs; Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009;27:5175-5181.

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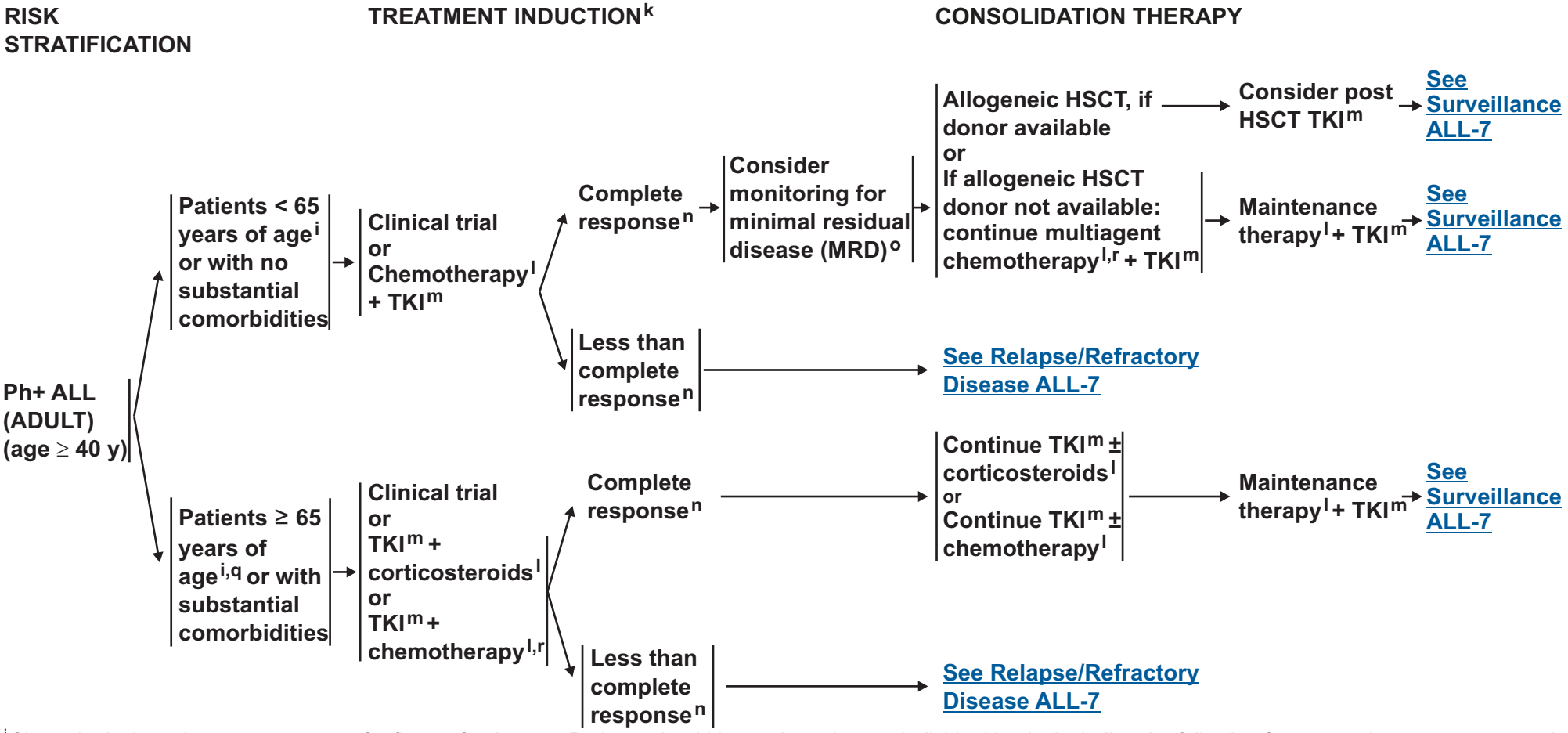

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[o] See Minimal Residual Disease Assessment (ALL-F).

[q] For additional considerations in the management of senior adult patients with ALL, see the NCCN Guidelines for Senior Adult Oncology.

[r] Consider dose modifications appropriate for patients age and performance status.

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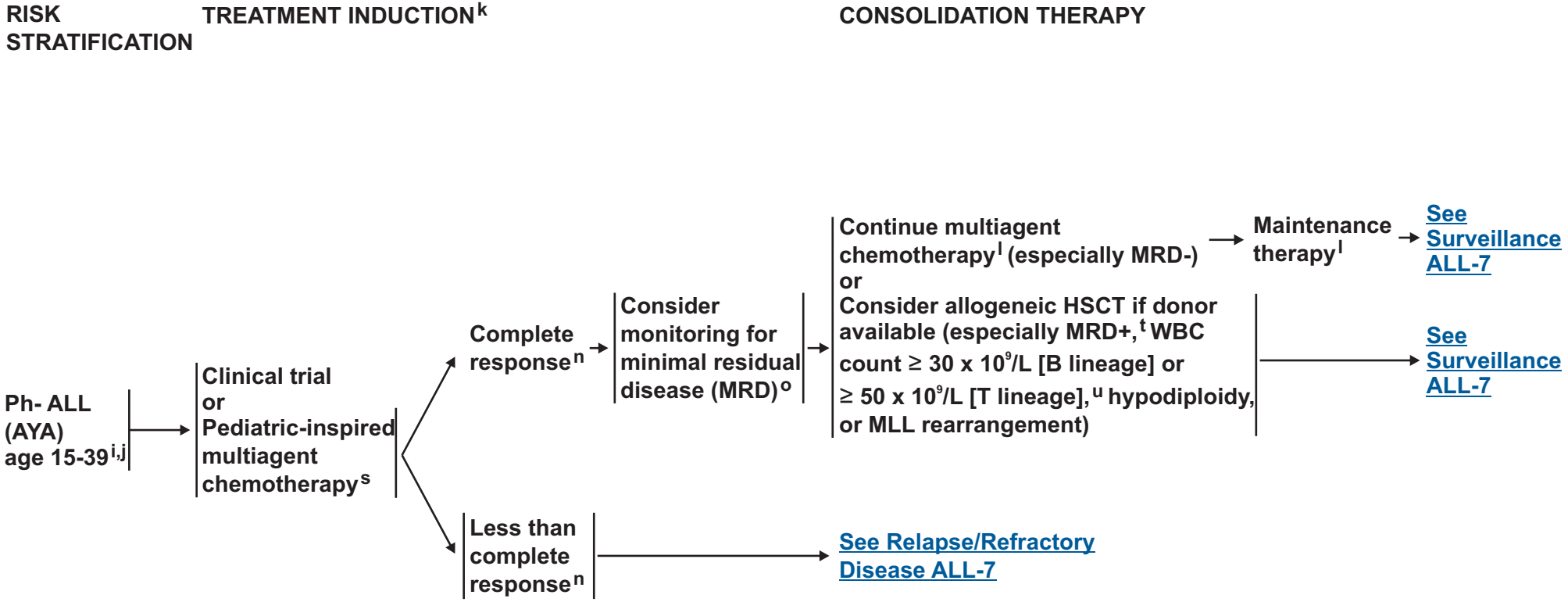

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[o] See Minimal Residual Disease Assessment (ALL-F).

[s] See Principles of Chemotherapy (ALL-D). All regimens include induction/delayed intensification (especially for pediatric-inspired regimens), and maintenance therapy.

[t] Benefit with allogeneic HSCT is unclear in this setting.

[u] Data demonstrating the effect of WBC counts on prognosis is less firmly established for adults than for the pediatric population.

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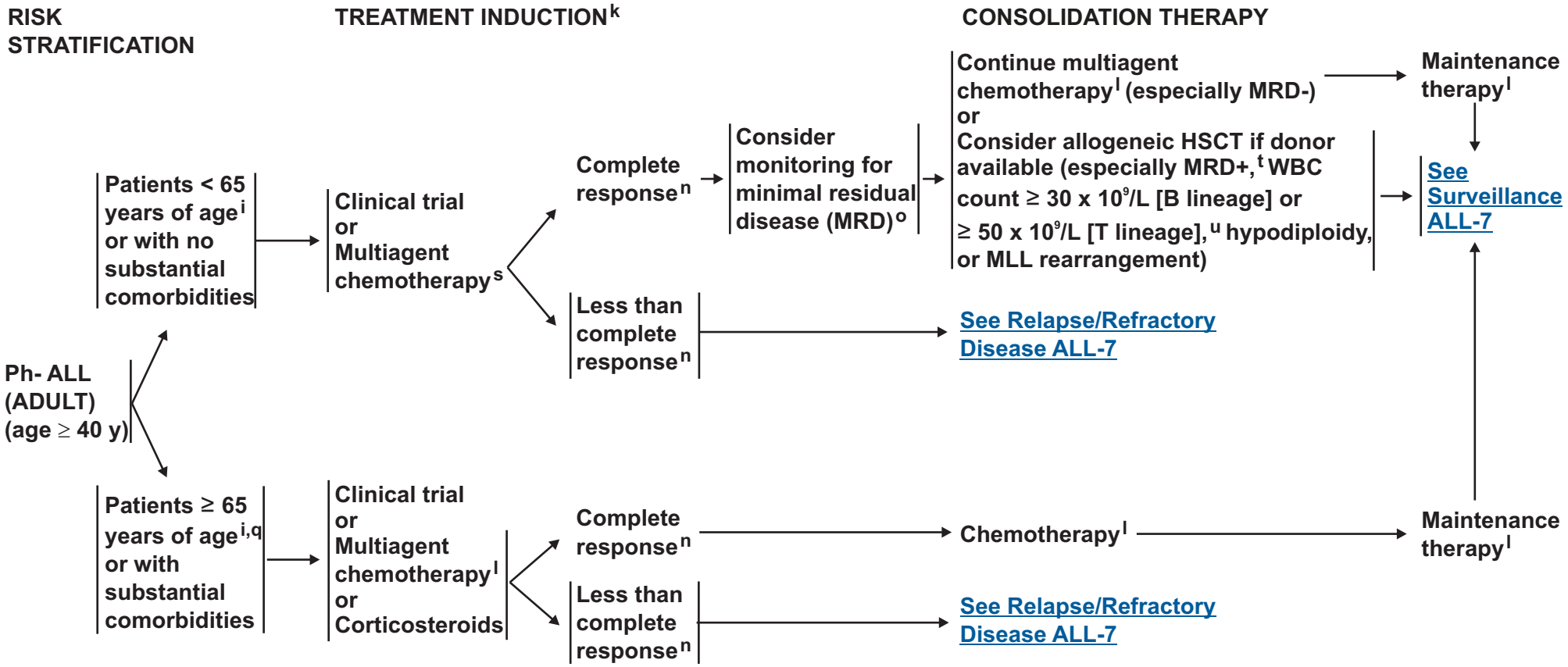

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SURVEILLANCE[v]

Year 1 (every 1-2 months):
- Physical exam, CBC with differential every month
- LFTs every 2 months until normal
- Bone marrow aspirate, CSF and echocardiogram as indicated
  - If bone marrow aspirate done: Comprehensive cytogenetics, FISH, flow cytometry and consider molecular tests

Year 2:
- Physical exam including testicular exam, CBC with differential every 3 months

Year 3+:
- Physical exam including testicular exam, CBC with differential every 6 months or as indicated

Refer to Survivorship recommendations in the NCCN Guidelines for Adolescent and Young Adult Oncology

Refer to the ALL Long-term Follow-up Guidelines from COG: http://www.childrensoncologygroup.org/disc/le/

RELAPSE/REFRACTORY

Relapse/ refractory[w]

- Ph+ ALL (AYA) → Consider *ABL* gene mutation testing[x] → Consider clinical trial or TKI[m] ± chemotherapy[y] or Allogeneic HSCT (if remission achieved) or DLI (if prior allogeneic HSCT)
- Ph+ ALL (Adults) → Consider *ABL* gene mutation testing[x] → Consider clinical trial or Allogeneic HSCT (if remission achieved) or TKI[m] ± corticosteroids or TKI[m] ± chemotherapy[y]
- Ph- ALL (AYA) → Consider clinical trial or Allogeneic HSCT (if remission achieved) or Chemotherapy[y,z]
- Ph- ALL (Adults) → Consider clinical trial or Consider allogeneic HSCT (if remission achieved) or Chemotherapy[y]

[m] See Discussion section for use of different TKIs in this setting.

[v] Surveillance recommendations apply after completion of chemotherapy, including maintenance.

[w] Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent replase in marrow.

[x] See Treatment Options Based on BCR-ABL KD Mutation Status ALL-G.

[y] See Principles of Chemotherapy (ALL-D 1 of 4 or ALL-D 2 of 4 for regimens not previously used for induction therapy or ALL-D 3 of 4 for salvage regimens).
Nelarabine is available for patients with relapsed T-ALL.
Clofarabine is available for relapsed pre-B-ALL in patients age ≤ 21 y.

[z] For late relapse (> 3 years from initial diagnosis), consider treatment with same induction regimen (See ALL-D 2 of 4).

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TYPICAL IMMUNOPHENOTYPE BY MAJOR ALL SUBTYPES

The initial immunophenotyping panel should be sufficiently comprehensive to establish a leukemia-associated phenotype (LAP) that may include expression of non-lineage antigens. These LAP are useful in classification, particularly mixed-lineage leukemias, and as a signature for minimal residual disease (MRD) detection.

B-ALL, not otherwise specified: CD10+, CD19+, CD79a+, cCD22+, sCD22+, CD24+, PAX5+, TdT+, variable CD20, variable CD34.
- **Early precursor B-ALL (pro-B-ALL): CD10-, CD19+, cCD79a, cCD22+, TdT+.**
- **Common B-ALL: CD10+.**
- **Precursor B-ALL (pre-B-ALL): cytoplasmic μ+, sIg-, CD10+/-.**

B-ALL with recurrent genetic abnormalities:
- **Hyperdiploidy (DNA index >1.16; 51-65 chromosomes without structural abnormalities): CD10+, CD19+, CD34+, CD45**
- **Hypodiploidy (<46 chromosomes): CD10+, CD19+, CD34+**
- **t(9;22)(q34;q11.2); BCR-ABL1: CD10+, CD19+, TdT+, CD13+, CD33+, CD117-**
- **t(v;11q23); MLL rearranged: CD10-, CD19+, CD24-, CD15+**
- **t(12;21)(p13;q22); TEL-AML1: CD10+, CD19+, TdT+, CD13+, CD34+**
- **t(1;19)(q23;p13.3); E2A-PBX1: CD10+, CD19+, CD20 variable, CD34 -/+, cytoplasmic μ+**
- **t(5;14)(q31;q32); IL3-IGH: CD10+, CD19+**

T-ALL: TdT+, variable for all of the following: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD34.
- **Pro-T-ALL: cCD3+, CD7+, CD1a-, CD2-, CD4-, CD8-, CD34+/-.**
- **Pre-T-ALL: cCD3+, CD7+, CD1a-, CD2+, CD4-, CD8-, CD34+/-.**
- **Cortical T-ALL: cCD3+, CD7+, CD1a+, CD2+, CD4+, CD8+, CD34-.**
- **Medullary T-ALL: cCD3+, sCD3+, CD7+, CD1a-, CD2+, CD4+ or CD8+, CD34-.**

Borowitz MJ, Chan JKC. B lymphoblastic leukaemia/lymphoma, not otherwise specified In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon: IARC; 2008:168-170.

Borowitz MJ, Chan JKC. B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon: IARC; 2008:171-175.

Borowitz MJ, Chan JKC. T lymphoblastic leukaemia/lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon: IARC; 2008 176-178.

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SUPPORTIVE CARE (1 of 3)

Best supportive care

- Infection control (See NCCN Guidelines for Prevention and Treatment of Cancer-related Infections)
  - ♦ Prophylactic antibiotics
    - → Antibacterial prophylaxis: consider fluoroquinolones
    - → Antiviral prophylaxis: During periods of neutropenia (and at least 30 days after HSCT for transplant recipients), HSV prophylaxis (eg, acyclovir, famciclovir, or valacyclovir)
    - → CMV infection management: Consider CMV monitoring and pre-emptive therapy with IV ganciclovir, IV foscarnet or oral valganciclovir for all patients; for patients undergoing allogeneic HSCT, CMV monitoring and pre-emptive therapy strongly recommended until at least 6 months after transplantation.
    - → Antifungal prophylaxis: Consider prophylaxis with fluconazole or amphotericin B agents for all patients treated with chemotherapy; for patients undergoing allogeneic HSCT, antifungal prophylaxis with fluconazole or micafungin strongly recommended until at least day 75 after transplantation.
    - → PCP prophylaxis: TMP-SMX
- Infection control
  - ♦ Heightened awareness for risk of sepsis/death due to steroid therapy and neutropenia
  - ♦ Febrile neutropenia management
    - → Fever is defined as a single temperature ≥38.3 °C (101°F) or ≥ 38.0 °C (100.4°F) over a 1-hour period
    - → IV antibiotics/inpatient admission
- Acute tumor lysis syndrome (See Tumor Lysis Syndrome in the NCCN Guidelines for Non-Hodgkin Lymphoma Guidelines)
- Asparaginase Toxicity Management - see ALL-B 2 of 3 and ALL-B 3 of 3
- Steroid management
  - ♦ Acute side effects
    - → Steroid induced Diabetes Mellitus
      Tight glucose control using Insulin Sliding Scale (ISS) to decrease infection complications
    - → Use of histamine 2 antagonist (PPI) recommended during steroid therapy
- Long term side effects of steroids
  - ♦ Osteonecrosis/avascular necrosis
    - → Obtain vitamin D and calcium status and replete as needed
    - → Consider radiographic evaluation with plain films or MRI
- Transfusions
  - ♦ Products should be irradiated
- Use of filgrastim (G-CSF)
  - ♦ 5 mcg/kg/day SC (recommended for myelosuppressive blocks of therapy or as directed by treatment protocol)
- Hyperleukocytosis
  - ♦ Although uncommon in patients with ALL, symptomatic hyperleukocytosis may require emergent treatment (See Symptomatic Leukocytosis in the NCCN Guidelines for Acute Myeloid Leukemia)
- Anti-emetics (See NCCN Guidelines for Antiemesis)
  - ♦ Given as needed prior to chemotherapy and post chemotherapy
  - ♦ Routine use of corticosteroids as anti-emetic avoided
- Gastroenterology
  - ♦ Consider starting a bowel regimen to avoid constipation
    - → Docusate sodium daily
    - → Laxatives promptly considered and used if symptoms arise
- Nutritional support
  - ♦ Consider enteral or parenteral support for >10% weight loss
- Palliative treatment for pain (See NCCN Guidelines for Cancer Pain)

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SUPPORTIVE CARE (2 of 3)

Asparaginase Toxicity Management

	Toxicity Grade		
Toxicity	**2**	**3**	**4**
Systemic Allergic Reaction/ Anaphylaxis	**Permanently discontinue pegasparaginase or native E. coli asparaginase; substitute asparaginase Erwinia chrysanthemi as follows: To substitute for a dose of pegasparaginase: the recommended dose is 25,000 IU/m^2 IM three times per week (Monday/Wednesday/Friday) for six doses for each planned dose of pegasparaginase. To substitute for a dose of native E. coli asparaginase: the recommended dose is 25,000 IU/m^2 IM for each scheduled dose.**		
Pancreatitis	**Continue asparaginase for asymptomatic amylase or lipase elevation > 3.0 x ULN (chemical pancreatitis) or only radiologic abnormalities; observe closely for rising amylase or lipase levels.**	**Continue pegasparaginase for non-symptomatic chemical pancreatitis but observe patient closely for development of symptomatic pancreatitis for early treatment. Hold native asparaginase for amylase or lipase elevation > 3.0 x ULN until enzyme levels stabilize or are declining. Permanently discontinue asparaginase for symptomatic pancreatitis.**	**Permanently discontinue all asparaginase for clinical pancreatitis (vomiting, severe abdominal pain) with amylase or lipase elevation > 3 x ULN for > 3 days and/or development of pancreatic pseudocyst.**
Hepatic transferasemia	**For alanine or glutamine aminotransferase elevation > 3.0 - 5.0 x ULN, continue asparaginase.**	**For alanine or glutamine aminotransferase elevation > 5.0 - 20.0 x ULN, delay next dose of asparaginase until grade < 2.**	**For alanine or glutamine aminotransferase elevation > 20.0 x ULN, discontinue asparaginase if toxicity reduction to grade < 2 takes > 1 week.**
Hyper-bilirubinemia	**Continue asparaginase if direct bilirubin < 3.0 mg/dL.**	**If direct bilirubin 3.1 - 5.0 mg/dL, hold asparaginase and resume when direct bilirubin is < 2.0 mg/dL. Consider switching to native asparaginase.**	**If direct bilirubin > 5.0 mg/dL, discontinue all asparaginase and do not make up for missed doses.**

Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma 2011:52:2237-2253.

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SUPPORTIVE CARE (3 of 3)

Asparaginase Toxicity Management

Toxicity Grade

Toxicity	2	3	4
Non-CNS thrombosis	For abnormal laboratory findings without clinical correlates, continue asparaginase.	Withhold asparaginase until acute toxicity and clinical signs resolve and anticoagulant therapy stable or completed; do not withhold asparaginase for abnormal laboratory findings without a clinical correlate.	Withhold asparaginase until acute toxicity and clinical signs resolve and anticoagulant therapy stable or completed.
Non-CNS hemorrhage	For bleeding in conjunction with hypofibrinogenemia, withhold asparaginase until bleeding ≤ grade 1, do not withhold asparaginase for abnormal laboratory findings without a clinical correlate.	Withhold asparaginase until bleeding ≤ grade 1 ,until acute toxicity and clinical signs resolve, and coagulant replacement therapy stable or completed.	Withhold asparaginase until bleeding ≤ grade 1, until acute toxicity and clinical signs resolve, and coagulant replacement therapy stable or completed.
CNS thrombosis	For abnormal laboratory findings without a clinical correlate, continue asparaginase.	Discontinue all asparaginase; if CNS symptoms and signs are fully resolved and significant asparaginase remains to be administered, may resume asparaginase therapy at a lower dose and/or longer intervals between doses.	Permanently discontinue all asparaginase.
CNS hemorrhage	Discontinue asparaginase; do not withhold asparaginase for abnormal laboratory findings without a clinical correlate.	Discontinue all asparaginase; if CNS symptoms and signs are fully resolved and significant asparaginase remains to be administered, may resume asparaginase therapy at a lower dose and/or longer intervals between doses.	Permanently discontinue all asparaginase.

Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma 2011:52:2237-2253.

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EVALUATION AND TREATMENT OF EXTRAMEDULLARY INVOLVEMENT

- Given the risks of neurotoxicity associated with CNS-directed therapy, baseline and post-treatment comprehensive neuropsychological testing may be useful.
- The aim of CNS prophylaxis and/or treatment is to clear leukemic cells within sites that cannot be readily accessed by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse.
- Factors associated with increased risks for CNS leukemia in adults include mature B-cell immunophenotype, T-cell immunophenotype, high presenting WBC counts, and elevated serum lactate dehydrogenase levels.[1,2]
- CNS involvement should be evaluated (by lumbar puncture [LP]) at the appropriate timing:
  - Timing of LP should be consistent with the chosen treatment regimen.
  - Pediatric-inspired regimens typically include LP at the time of diagnostic workup.
  - Panel recommends that LP, if performed, be done concomitantly with initial intrathecal therapy.
- Classification of CNS status:
  - CNS-1: No lymphoblasts in cerebrospinal fluid (CSF) regardless of WBC count.
  - CNS-2: WBC < 5/mcL in CSF with presence of lymphoblasts.
  - CNS-3: WBC ≥ 5/mcL in CSF with presence of lymphoblasts.
  - If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC ≥ 5/mcL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.
- All patients with ALL should receive CNS prophylaxis. Although the presence of CNS involvement at the time of diagnosis is uncommon (about 3% to 7%), a substantial proportion of patients (> 50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.
- CNS-directed therapy may include cranial irradiation, intrathecal chemotherapy (e.g., methotrexate, cytarabine, corticosteroids) and/or high-dose systemic chemotherapy (e.g., methotrexate, cytarabine, mercaptopurine, L-asparaginase).
- CNS leukemia (CNS-3) at diagnosis typically warrants treatment with cranial irradiation of 18 Gy. The recommended dose of radiation, where given, is highly dependent on the intensity of systemic chemotherapy; thus, it is critical to adhere to a given treatment protocol in its entirety.
- Note that areas of the brain targeted by the radiation field in the management of ALL are different from areas targeted for brain metastases of solid tumors.
- With the incorporation of adequate systemic chemotherapy (e.g., high-dose methotrexate and cytarabine) and intrathecal chemotherapy regimens (e.g., methotrexate alone or with cytarabine and corticosteroid, which constitutes the triple intrathecal regimen), it may be possible to avoid the use of upfront cranial irradiation except in cases of overt CNS leukemia at diagnosis, and to reserve the use of irradiation for salvage therapy settings.
- Adequate systemic therapy should be given in the management of isolated CNS relapse.
- Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of the induction therapy should be considered for radiation to the testes, which is typically done concurrently with the first cycle of maintenance chemotherapy.

[1] Gokbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2006:133-141;
[2] Lazarus HM, Richards SM, Chopra R, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: results from the international ALL trial MRC UKALL XII/ECOG E2993. Blood 2006;108:465-472.

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 CHEMOTHERAPY (1 of 4)

Induction Regimens* for Ph-positive ALL

Adult patients age ≥ 40 years:

- **TKIs + hyper-CVAD: imatinib or dasatinib; and hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, cytarabine.[1-4]**
- **TKIs + multiagent chemotherapy: imatinib; and daunorubicin, vincristine, prednisone, cyclophosphamide[5,6]**
- **TKIs + corticosteroids: imatinib and prednisone (for this study, patients were aged >60 years)[7]**
- **Dasatinib[8,9]**

Pediatric-inspired Protocols for AYA patients age 15-39 years:

- **COG AALL-0031 regimen: vincristine, prednisone (or dexamethasone), asparaginase, with or without daunomycin; or prednisone (or dexamethasone) and asparaginase with or without daunomycin; imatinib added during consolidation blocks.[10]**

Maintenance Regimens:

- **Weekly methotrexate + daily 6-mercaptopurine (6-MP)** + monthly vincristine/prednisone pulses (for 2-3 years)**
- **Add TKIs (imatinib or dasatinib) to above maintenance regimen.**

Induction Regimens for Ph-negative ALL ALL-D 2 of 4

Salvage Regimens for Relapsed/Refractory ALL ALL-D 3 of 4

References ALL-D 4 of 4

*All regimens include CNS prophylaxis with systemic therapy (e.g., methotrexate, cytarabine, 6-mercaptopurine) and/or intrathecal therapy (e.g., IT methotrexate , IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

**For patients receiving 6-MP, consider testing for TPMT gene polymorphisms, particularly in patients that develop severe neutropenia after starting 6-MP.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF CHEMOTHERAPY (2 of 4)

Induction Regimens* for Ph-negative ALL

Adult patients age ≥40 years:

- **CALGB 8811 Larson regimen: daunorubicin, vincristine, prednisone, asparaginase, cyclophosphamide; for patients aged ≥60 years, reduced doses for cyclophosphamide, daunorubicin, prednisone[11]**
- **Linker 4-drug regimen: daunorubicin, vincristine, prednisone, asparaginase[12]**
- **Hyper-CVAD +/- rituximab: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, cytarabine; with or without rituximab for CD20-positive disease[13,14]**
- **MRC UKALLXII/ECOG2993 regimen: daunorubicin, vincristine, prednisone, asparaginase (induction phase I); and cyclophosphamide, cytarabine, 6-mercaptopurine** (induction phase II)[15]**

Pediatric-inspired Protocols for AYA patients age 15-39 years:

- **GRAALL-2003 regimen: daunorubicin, vincristine, prednisone, asparaginase, cyclophosphamide (patients aged <60 years)[16]**
- **COG AALL-0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, asparaginase; nelarabine added to consolidation regimen (ongoing study)[17]**
- **CCG-1961 regimen: daunorubicin, vincristine, prednisone, asparaginase (patients aged ≤21 years)[18,19]**
- **PETHEMA ALL-96 regimen: daunorubicin, vincristine, prednisone, asparaginase, cyclophosphamide (patients aged <30 years)[20]**
- **CALGB 10403 regimen: daunorubicin, vincristine, prednisone, asparaginase (ongoing study in patients aged <40 years)**
- **DFCI ALL regimen based on DFCI Protocol 00-01: doxorubicin, vincristine, prednisone, high-dose methotrexate, asparaginase (ongoing study in patients aged<50 years)[21]**

Maintenance Regimen:

- **Weekly methotrexate + daily 6-mercaptopurine** + monthly vincristine/prednisone pulses (for 2-3 years)**

Induction Regimens for Ph-positive ALL ALL-D 1 of 4

Salvage Regimens for Relapsed/Refractory ALL ALL-D 3 of 4

References ALL-D 4 of 4

*All regimens include CNS prophylaxis with systemic therapy (e.g., methotrexate, cytarabine, 6-mercaptopurine) and/or intrathecal therapy (e.g., IT methotrexate , IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

**For patients receiving 6-MP, consider testing for TPMT gene polymorphisms, particularly in patients that develop severe neutropenia after starting 6-MP.

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PRINCIPLES OF CHEMOTHERAPY (3 of 4)

Salvage Regimens* for Relapsed/Refractory ALL

Ph-positive ALL:
- **Dasatinib[22,23]**
- **Nilotinib[24]**

Ph-negative ALL:
- **Clofarabine[25]**
- **Cytarabine-containing regimens[26]**
- **Alkylator combination regimens[27]**
- **Nelarabine (for T-ALL)[28]**
- **Augmented hyper-CVAD: hyper-fractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, asparaginase; alternating with high-dose methotrexate, cytarabine[29]**

Induction Regimens for Ph-positive ALL ALL-D 1 of 4

Induction Regimens for Ph-negative ALL ALL-D 2 of 4

References ALL-D 4 of 4

*All regimens include CNS prophylaxis with systemic therapy (e.g., methotrexate, cytarabine, 6-mercaptopurine) and/or intrathecal therapy (e.g., IT methotrexate , IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

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 CHEMOTHERAPY (4 of 4) - References

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RESPONSE CRITERIA

Response Criteria for Blood and Bone Marrow:

- Complete Response (CR)
  - ♦ No circulating blasts or extramedullary disease
    - → No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
  - ♦ Trilineage hematopoiesis (TLH) and <5% blasts
  - ♦ ANC > 1000/microL
  - ♦ Platelets > 100,000/microL
  - ♦ No recurrence for 4 weeks
- Complete response with incomplete recovery of counts (CRi)
  - ♦ Recovery of platelets but < 100,000 or ANC is < 1000/microL
- Overall response rate (ORR=CR + CRi)
- Refractory disease
  - ♦ Failure to achieve CR at the end of induction
- Progressive disease
  - ♦ Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
- Relapsed disease
  - ♦ Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR

Response Criteria for CNS Disease:

- CNS Remission: Achievement of CNS-1 status (see ALL-C) in a patient with CNS-2 or CNS-3 status at diagnosis.
- CNS Relapse: New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.

Response Criteria for Mediastinal Disease:

- Complete Response (CR): Complete resolution of mediastinal enlargement by CT.
- Complete Response Unconfirmed (CRu): Residual mediastinal enlargement that has regressed by > 75% in sum of the products of the greatest perpendicular diameters (SPD).
- Partial Response (PR): > 50% decrease in the SPD of the mediastinal enlargement.
- Progressive Disease (PD): > 25% increase in the SPD of the mediastinal enlargement.
- No Response (NR): Failure to qualify for PR or PD.
- Relapse: Recurrence of mediastinal enlargement after achieving CR or CRu.

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MINIMAL RESIDUAL DISEASE (MRD) ASSESSMENT

- **MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow.**
- **Studies in both children and adults with ALL have demonstrated the strong correlation between MRD and risks for relapse, and the prognostic significance of MRD measurements during and after initial induction therapy.**
- **The most frequently employed methods for MRD assessment include multicolor flow cytometry to detect abnormal immunophenotypes and real-time quantitative polymerase chain reaction (RQ-PCR) assays to detect fusion genes (e.g., BCR-ABL1), clonal rearrangements in immunoglobulin (Ig) heavy chain genes and/or T-cell receptor (TCR) genes.**
- **Current multicolor flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ (<0.01%) bone marrow mononuclear cells.[1,2] The concordance rate for detecting MRD between these methods is generally high. The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.**
  - **Timing of MRD assessment:**
    - → **Upon completion of initial induction.**
    - → **Additional time points may be useful depending on the regimen used.**
  - **Multicolor flow cytometry: sampling of bone marrow mononuclear cells (MNC) preferred over peripheral blood samples; requires at least 1×10^6 MNCs for analysis (about 2 mL of bone marrow or 5-10 mL of peripheral blood provides sufficient number of cells for multiple analysis).**
  - **RQ-PCR: sampling of bone marrow MNC preferred; requires at least 1×10^7 MNCs for initial marker characterization and generation of individual dilution series; 1×10^6 MNCs are sufficient for follow-up analysis.**
  - **The minimal limit of assay sensitivity (to declare MRD negativity) should be $<1 \times 10^{-4}$ (<0.01%).**
- **High-sensitivity PCR assays (for analysis of Ig or TCR gene rearrangements) require the identification of patient-specific markers that involve direct sequencing, and may therefore be labor- and resource-intensive for routine application in the clinical practice setting.**
- **Recommendations on the minimal technical requirements for MRD assessment (both for PCR and flow cytometry methods) and definitions for response based on MRD results (e.g., MRD negativity, non-quantifiable MRD positivity, quantifiable MRD positivity) have recently been published as a result of a consensus development meeting held by ALL study groups across Europe.[1] The recommendations were made in an effort to standardize MRD measurements and MRD data reporting within the context of clinical trials.**
- **MRD evaluations should be performed in reference laboratories with expertise in MRD assays; note that results from one lab to another may not be directly equivalent or comparable**

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TREATMENT OPTIONS BASED ON BCR-ABL KD MUTATION STATUS[1]

Mutation	Treatment Recommendation
T315I	HSCT or clinical trial
V299L, T315A, F317L/V/I/C	Consider nilotinib rather than dasatinib
Y253H, E255K/V, F359V/C/I	Consider dasatinib rather than nilotinib
Any other mutation	Consider high dose imatinib[2] or dasatinib or nilotinib

[1] This research was originally published in Blood. Soverini S, Hochhaus A, Nicolini FE, et al. Bcr-Abl kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood 2011;118:1208-1215. © the American Society of Hematology.

[2] There are not sufficient data on dose escalation available to indicate if mutations with lower IC_{50} values are sensitive to high dose imatinib.

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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

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for ALL was developed as a result of meetings convened by a multidisciplinary panel of ALL experts, with the aim to provide recommendations on standard treatment approaches based on the current evidence. The NCCN Guidelines and the following discussions focus on the immunophenotypic classification and cytogenetic/molecular subtypes of ALL, risk assessment and stratification for risk-adapted therapy, treatment strategies for Philadelphia chromosome (Ph)-positive and Ph–negative ALL for both AYA and adult patients, and supportive care considerations. Given the complexity of ALL treatment regimens and the required supportive care measures, the NCCN Guidelines panel recommends that patients be treated at a specialized cancer center with expertise in the management of ALL.

The present discussion is divided into the following sections:

Acute lymphoblastic leukemia (ALL) is a heterogenous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs.[1] The age-adjusted incidence rate of ALL in the U.S. is 1.6 per 100,000 individuals per year, with approximately 6,050 new cases and 1,440 deaths estimated in 2012.[2, 3] The median age of diagnosis for ALL is 13 years; 61% of patients are diagnosed <20 years of age while 23% are diagnosed at 45 years of age or older.[2] ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents only about 20% of all leukemias among adults.[1, 4]

The cure rates and survival outcomes for patients with ALL have dramatically improved during the last several decades, primarily among children with ALL. Improvements are largely owed to advances in the understanding of the molecular genetics and pathogenesis of the disease, incorporation of risk-adapted therapy, and the advent of new targeted agents. With current treatment regimens, the cure rate among children with ALL is about 80%.[5-7] The long-term prognosis for adults

with ALL, however, remain poor, with cure rates of only 30% to 40%.[6, 8-15] This difference in long-term outcomes can be explained, in part, by differences in the frequency of certain cytogenetic subtypes of ALL among age groups. For example, ALL characterized by the presence of the *TEL-AML1* fusion gene is more frequently observed among children (22% of cases) compared with adults (2%), and is associated with a favorable prognosis.[16] In addition, hyperdiploidy (>50 chromosomes) is more common among children (25%) versus adults (7%), and is also associated with favorable outcomes. ALL characterized by the *BCR-ABL* fusion gene—resulting from chromosomal translocation t(9;22) (Philadelphia chromosome [Ph])—carries a poor prognosis and is much less common among children (3%) than in adults with ALL (25%).[16] The cure rates for adolescents and young adults (AYA) with ALL remain suboptimal (5- to 7-year event-free survival rates from 60% to 70%) in comparison to children, although these outcomes represent substantial improvements with the recent adoption of pediatric treatment regimens.[17] AYA patients represent a unique population, as these patients may receive treatment based on a pediatric or adult protocol depending upon local referral patterns and institutional practices. Favorable cytogenetic subtypes such as *TEL-AML1* ALL and hyperploidy occur less frequently among AYA patients compared with children whereas the incidence of ALL with *BCR-ABL* (Ph-positive ALL) is higher in AYA patients.[17]

Diagnosis

Clinical Presentation and Diagnosis

The clinical presentation of ALL is typically nonspecific, and may include fatigue or lethargy, constitutional symptoms (fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding.[1, 18] Among children, pain in the extremities or joints may be the only presenting symptoms. [1] The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly upon physical examination may be found in about 20% of patients. Abdominal masses due to gastrointestinal involvement, or chin numbness resulting from cranial nerve involvement are more suggestive of mature B-cell ALL.[1, 18]

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts upon hematopathology review of bone marrow aspirate and biopsy materials. The 2008 WHO classification lists ALL and lymphoblastic lymphoma as the same entity, distinguished only by the primary location of the disease. When the disease is restricted to a mass lesion primarily involving nodal or extranodal sites with no or minimal involvement in blood or bone marrow (generally defined as <20% lymphoblasts in the marrow), the case would be consistent with a diagnosis of lymphoblastic lymphoma. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens.

Hematopathology evaluations should include morphologic examination of malignant lymphocytes by Wright-Giemsa stained slides and hematoxylin and eosin (H&E) stained core biopsy and clot sections, comprehensive immunophenotyping by flow cytometry (see Discussion section below on 'Immunophenotyping'), and assessment of cytogenetic or molecular abnormalities. Identification of specific recurrent genetic abnormalities is critical for disease evaluation, optimal risk stratification and treatment planning (see Discussion section below on "Cytogenetic and Molecular Subtypes"). Subtypes of B-cell ALL with recurrent genetic abnormalities include the following: hyperdiploidy (DNA index >1.16; 51-65 chromosomes); hypodiploidy (<46 chromosomes); t(9;22)(q34;q11.2), *BCR-ABL1*; t(v;11q23), *MLL rearrangement*; t(12;21)(p13;q22), *TEL-AML1*; t(1;19)(q23;p13.3), *E2A-PBX1*; and t(5;14)(q31;q32), *IL3-IGH*.[19] Presence of recurrent genetic abnormalities should be evaluated using karyotyping of G-banded metaphase chromosomes (conventional cytogenetics) and/or by

interphase FISH assays that include probes capable of detecting the major genetic abnormalities.

Immunophenotyping

Immunophenotypic classification of ALL involves the use of flow cytometry to determine the presence of cell surface antigens on lymphocytes. ALL can be classified broadly into three distinct groups based on immunophenotyping, which include precursor-B-cell ALL, mature B-cell ALL, and T-cell ALL.[1, 9] Among children, B-cell lineage ALL comprise approximately 88% of cases[16]; in adult patients, subtypes of B-cell lineage ALL comprise approximately 75% of cases (including mature B-cell ALL comprising 5% of adult ALL) while the remaining 25% constitute T-cell lineage ALL.[16, 20] Within the B-cell lineage, the profile of cell surface markers differ by different stages of B-cell maturation. Pre-pre-B-cell (pro-B-cell) ALL is characterized by the presence of terminal deoxynucleotidyl transferase (TdT), expression of CD19/CD22/CD79a, while being negative for CD10 (formerly referred to as 'common ALL antigen') or surface immunoglobulins; common B-cell ALL is associated with the expression of CD10, and pre-B-cell ALL is characterized by the presence of cytoplasmic immunoglobulins and CD10/CD19/CD22/CD79a expression.[1, 18, 20] Mature B-cell ALL shows positivity for surface immunoglobulins and clonal lambda or kappa light chains, and is negative for TdT.[1] In addition, CD20 may be expressed in about 50% of B-cell lineage ALL in adults, with a higher frequency (>80%) observed in cases of mature B-cell ALL.[21, 22]

T-cell lineage ALL is typically associated with the presence of cytoplasmic CD3 (T-cell lineage blasts) or cell surface CD3 (mature T cells) in addition to CD1a/CD2/CD5/CD7 (variable expression for these markers) and TdT.[1, 18] Additionally, CD52 may be expressed in about 30% to 50% of T-cell lineage ALL in adults.[1] Early precursor T-cell ALL may represent a distinct biological subtype of T-cell lineage ALL, and is associated with poor clinical outcomes even with contemporary treatment regimens; this subtype is characterized by the absence of CD1a/CD8, weak expression of CD5 (<75% positive lymphoblasts), and presence of ≥1 myeloid or stem cell markers on at least 25% of lymphoblasts.[23]

Hematologic malignancies related to ALL include acute leukemias with ambiguous lineage, such as the mixed phenotype acute leukemias (MPAL). MPAL includes bi-lineage leukemias, in which two distinct populations of lymphoblasts are identified, with one meeting the criteria for acute myeloid leukemia; another type of MPAL is the bi-phenotypic type, in which a single population of lymphoblasts express markers consistent with B-cell or T-cell ALL, in addition to expressing myeloid or monocytic markers. It should be noted that in ALL, myeloid-associated markers such as CD13 and CD33 may be expressed, and that the presence of these markers does not exclude the diagnosis of ALL. The identification of mixed lineage leukemias should follow the criteria set forth within the 2008 WHO classification of neoplasms.[19, 24] The initial immunophenotyping panel should be sufficiently comprehensive to establish a leukemia-associated phenotype that may include expression of non-lineage antigens; these are useful in classification, particularly for MPAL.

Cytogenetic and Molecular Subtypes

Recurrent chromosomal and molecular abnormalities characterize ALL subtypes in both adults and children (Table 1), and often provide prognostic information that may weigh into risk stratification and treatment decisions. As previously mentioned, the frequency of certain subtypes differ between adult and childhood ALL, which partially explains the difference in clinical outcomes between patient populations. Among children with ALL, the most common chromosomal abnormality is hyperdiploidy (>50 chromosomes; 25% of cases) seen in B-cell lineage ALL.[16, 25] The *TEL-AML1* subtype (also within the B-cell

lineage) resulting from chromosomal translocation t(12;21) is also among the most commonly occurring subtypes (22%) in childhood ALL.[16] Both hyperdiploidy and *TEL-AML1* subtypes are associated with favorable outcomes in ALL.[25, 26] Philadelphia chromosome (Ph)-positive ALL, associated with poor prognosis, is relatively uncommon among childhood ALL (3%) whereas this abnormality is the most common subtype among adults (25%).[16] The frequency of Ph-positive ALL increases with age (e.g., 40% in patients >50 years of age).[27-29] Moreover, younger children (1 to 9 years of age) with Ph-positive ALL have a better prognosis compared with adolescents with this subtype.[30] Although not as common, subtypes associated with translocations in the *MLL* gene (in particular, cases with t(4;11) translocation) are known to have poor prognosis.[17, 21] Hypodiploidy is only observed in 1% to 2% of patients, and is also associated with poor prognosis.[17, 31]

Table 1. Common chromosomal and molecular abnormalities in ALL

Cytogenetics	*Gene*	*Frequency in adults*	*Frequency in children*
Hyperdiploidy	--	7%	25%
Hypodiploidy	--	2%	1%
t(9;22)(q34;q11): Philadelphia chromosome (Ph)	*BCR-ABL1*	25%	3%
t(12;21)(p13;q22)	*TEL-AML1*	2%	22%
t(v;11q23), e.g., t(4;11), t(9;11), t(11;19)	*MLL*	10%	8%
t(1;19)	*E2A-PBX1*	3%	5%
t(5;14)(q31;q32)	*IL3-IGH*	<1%	<1%
t(8;14), t(2;8), t(8;22)	*c-MYC*	4%	2%
t(1;14)(p32;q11)	*TAL-1**	12%	7%
t(10;14)(q24;q11)	*HOX11**	8%	1%
t(5;14)(q35;q32)	*HOX11L2**	1%	3%

*Abnormalities observed exclusively in T-cell lineage ALL; all others occur exclusively or predominantly in B-cell lineage ALL.

Workup

The initial workup for patients with ALL should include a thorough medical history and physical examination, along with laboratory and imaging studies (where applicable). Laboratory studies include a complete blood count with platelets and differential, blood chemistry profile, disseminated intravascular coagulation (DIC) panel (that includes measurements for d-dimer, fibrinogen, prothrombin time [PT], and partial thromboplastin time [PPT]), and tumor lysis syndrome (TLS) panel (that includes measurements for serum LDH, uric acid, potassium, phosphates, and calcium). Procurement of cells should be considered for purposes of future research (in accordance with institutional practices or policies). All male patients should be evaluated for testicular involvement of disease; testicular involvement is especially common in cases of T-cell ALL. In addition, for patients with T-cell ALL, CT scans of the chest are warranted. All patients should be evaluated for infections, including screening for active infections if febrile or for symptomatic opportunistic infections. Empirical antiinfective therapy should be initiated, as appropriate (see NCCN Guidelines on Prevention and Treatment of Cancer-related Infections). In addition, echocardiogram or cardiac scans should be considered for all patients given that anthracyclines are included in the backbone of nearly all treatment regimens. Assessment of cardiac function is particularly important for patients with prior cardiac history, prior anthracycline exposure, or clinical symptoms suggestive of cardiac dysfunction, and for elderly patients. With the exception of patients with major contraindications for hematopoietic stem cell transplantation (HSCT), HLA typing should be performed at the time of workup. In patients with poor-risk features who lack a sibling donor, an early evaluation and search for alternative donors should be considered.

For patients with major neurologic signs or symptoms at the time of diagnosis, appropriate imaging studies (e.g., CT/MRI scan of the head) should be performed to detect meningeal disease, chloromas, or CNS bleeding. CNS involvement should be evaluated by lumbar puncture at the appropriate timing that is consistent with the treatment protocol being used. Pediatric-inspired regimens typically include lumbar puncture at the time of diagnostic workup; however, the NCCN Guidelines panel recommends that lumbar puncture, if performed, be done concomitantly with initial intrathecal therapy (see Guidelines and discussion sections on "NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement").

Prognostic Factors and Risk Stratification

Various disease-related and patient-specific factors may have prognostic significance in patients with ALL. In particular, patient age, white blood cell (WBC) count, immunophenotypic/cytogenetic subtype, and response to induction therapy have been identified as important factors in defining risks and assessing prognosis for both adult and childhood ALL.

Prognostic Factors in AYA with ALL

For childhood ALL, the initial risk assessment criteria established by the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) (the POG and CCG have since merged to form the Children's Oncology Group [COG]) was based on age and initial WBC count for precursor B-cell ALL; T-cell ALL was considered high risk, or risk could be assessed based on age and WBC count for these patients.[32] Subsequent risk assessment strategy assigned precursor B-cell ALL cases in patients 1 to <10 years of age and WBC count <50 × 10^9/L as "standard risk" while all others, including T-cell ALL (regardless of age or WBC count), were considered "high risk".[31] "Very high risk" was defined for patients with any of the following characteristics: t(9;22) chromosomal translocation (i.e., Ph-positive ALL) and/or presence of BCR-ABL fusion protein, hypodiploidy (<44 chromosomes) or failure to achieve remission with induction therapy.[17, 31] Lastly, "lower risk" was defined for patients with either the t(12;21) chromosomal translocation leading to the *TEL-AML1* subtype or simultaneous trisomies of chromosomes 4, 10 and 17.[31]

Variability exists across studies with regards to the age ranges defined for AYA patients. The National Cancer Institute (NCI) defines the age range for AYA as 15 to 39 years. This definition has been adopted for the AYA sections of the NCCN Guidelines for ALL. Historically, the AYA population has been treated either on a pediatric or adult ALL regimen depending upon referral patterns and institution. However, studies in the past have shown poorer outcomes among patients in the AYA group compared with children aged <10 years.[33] The AYA patient population generally presents with lower frequency of favorable chromosomal/cytogenetic abnormalities such as hyperdiploidy or *TEL-AML1*, increased frequency of T-cell immunophenotype, and slightly higher incidence of Ph-positive ALL, compared with younger children.[26, 33] In recent years, a number of retrospective studies from both the US and Europe have demonstrated that AYA patients (age 15 to 21 years) treated on a pediatric protocol have substantially improved event-free survival (EFS) outcomes compared with same-aged patients treated on adult ALL regimens.[17, 26] Thus, the choice of initial treatment regimen can have a profound impact on overall clinical outcomes in AYA patients.

Prognostic Factors in Adults with ALL

Both age and initial WBC count have historically been considered clinically significant prognostic factors in the management of adult patients with ALL.[9, 21] Early prospective multicenter studies

demonstrated that older age (>35 years) and higher initial WBC count (>30 × 10^9/L) were significantly predictive of decreased remission duration.[34, 35] Subsequent studies have confirmed the prognostic importance of these clinical parameters, although the cut-off values differed between studies.[9, 21]

In one of the largest studies to date (N=1521) conducted by the Medical Research Council (MRC) UK ALL/US Eastern Cooperative Oncology Group (ECOG), both age (>35 years) and WBC count (>30 × 10^9/L for B-cell lineage; >100 × 10^9/L for T-cell lineage) were found to be significant independent prognostic factors for decreased disease-free survival (DFS) and overall survival (OS) among patients with Ph-negative ALL; the independent prognostic value remained significant when these factors were evaluated as continuous variables in multivariate analysis.[13] All patients, regardless of Ph status, had received induction therapy followed by intensification (for patients with a complete remission [CR] post-induction) with contemporary chemotherapy combination regimens. Patients with a CR after induction received allogeneic HSCT (for patients <50 years old and with HLA-compatible siblings), autologous HSCT, or consolidation/maintenance treatment. Because Ph-positive ALL is associated with very poor prognosis, patients with this subtype were assigned to undergo allogeneic HSCT (including matched unrelated donor HSCT), where possible. The 5-year OS rate among patients with Ph-positive and Ph-negative disease was 25% and 41%, respectively.[13] Among the patients with Ph-negative ALL, those aged >35 years or with elevated WBC count (>30 × 10^9/L for B-cell lineage; >100 × 10^9/L for T-cell lineage) at diagnosis were initially identified as high risk, whereas all others were classified as having standard risk. The 5-year OS rate for the Ph-negative high-risk and standard-risk subgroups was 29% and 54%, respectively.[13] Further analysis of the Ph-negative population by risk factors showed that patients could be categorized as low risk (no risk factors based on age or WBC count), intermediate risk (either age >35 years or elevated WBC count) or high risk (both age >35 years and elevated WBC count). The 5-year OS rate based on these risk categories was 55%, 34%, and 5%, respectively, which suggested that Ph-negative patients in the high-risk subgroup had even poorer survival outcomes than the overall Ph-positive subgroup.[13]

In a subsequent analysis from this MRC UK ALL XII/ECOG 2993 study, cytogenetic data were evaluated in approximately 1000 patients.[36] The analysis confirmed the negative prognostic impact of Ph-positive ALL compared with Ph-negative disease, with significantly decreased 5-year EFS rate (16% vs 36%; P<0.001, adjusted for age, gender, and WBC count) and OS rate (22% vs 41%; P<0.001, adjusted for age, gender, and WBC count). Among patients with Ph-negative disease, the following cytogenetic subgroups had significantly decreased 5-year EFS (13% to 24%) and OS rates (13% to 28%) based on univariate analysis: t(4;11) *MLL* translocation; t(8;14); complex karyotype (≥5 chromosomal abnormalities); and low hypodiploidy (30-39 chromosomes)/near triploidy (60-78 chromosomes). In contrast, del(9p) or high hyperdiploidy (51-65 chromosomes) was associated with more favorable 5-year EFS (49% to 50%) and OS rates (53% to 58%).[36] Cases with 60 to 65 chromosomes were examined individually in order to determine the pattern of chromosomal gain that most closely resembled either hypodiploidy/triploidy or high hyperdiploidy. Based on multivariate Cox regression analysis, t(8;14), low hypodiploidy/near triploidy, and complex karyotype remained significant independent predictors for risk of relapse or death; the prognostic impact of these cytogenetic markers was independent of factors such as age, WBC count, or T-cell immunophenotype, and their significance was retained even after excluding patients who had undergone post-induction

HSCT.[36] The importance of cytogenetics as a prognostic factor for survival outcomes was demonstrated in other studies, including the Southwest Oncology Group (SWOG) study conducted in 200 adult patients with ALL.[37] In this study, the prognostic impact of the different cytogenetic categories outweighed that of the more traditional factors, such as age and WBC count; in multivariate analysis for both relapse-free survival and OS, cytogenetics remained a significant independent predictor of outcomes, whereas factors such as age and WBC count lost its prognostic significance.[37] Moreover, the subgroup (n=19) of patients with "very high risk" cytogenetic features (identified based on outcomes from the MRC/ECOG study mentioned above: presence of t(4;11) *MLL* translocation; t(8;14); complex karyotype; or low hypodiploidy/near triploidy) had substantially decreased 5-year relapse-free and OS rates (22%, for both endpoints); the 5-year relapse-free and OS rates among the patients with Ph-positive ALL (n=36) was 0% and 8%, respectively.[37]

NCCN Recommendations for Risk Assessment in ALL

Although some debate remains in the risk stratification approach in ALL, the NCCN Guidelines panel suggests the following approaches for defining risk in these patients.

Because AYA patients (defined as age 15 to 39 years) may benefit from pediatric-inspired ALL treatment protocols, this patient population is considered separately from the adult population (defined as age ≥40 years). Given the poor prognosis associated with Ph-positive ALL, and the wide availability of agents that specifically target the BCR-ABL kinase, initial risk stratification for all patients (AYA or adult) is based on the presence or absence of the t(9;22) chromosomal translocation and/or BCR-ABL fusion protein.

AYA patients with Ph-negative ALL can be further categorized as having 'high risk' disease, which may be particularly helpful when consolidation therapy with allogeneic HSCT is being considered. High risk is defined as having any of the following poor-risk factors: elevated WBC count (≥30 × 10^9/L for B-cell lineage; ≥100 × 10^9/L for T-cell lineage); hypodiploidy; *MLL* rearrangements. The absence of all of the above poor-risk factors is considered standard risk.

For adult patients with ALL (Ph-positive or Ph-negative), the Guidelines further stratify patients by age, using 65 years as the cut off, to guide treatment decisions. It should be noted, however, that chronological age alone is a poor surrogate for determining patient fitness for therapy. Patients should therefore be evaluated on an individual basis.

For adult patients with Ph-negative ALL aged <65 years (or for those with no substantial comorbidities), further risk stratification can be used to categorize patients as having 'high risk' disease. As with AYA patients, high risk is defined as having any of the following poor-risk factors: elevated WBC count (≥30 × 10^9/L for B-cell lineage; ≥100 × 10^9/L for T-cell lineage); hypodiploidy; *MLL* rearrangements. It should be noted, however, that data demonstrating the effect of WBC counts on prognosis in adult patients with ALL are less firmly established than for the pediatric population. The absence of all of the above poor-risk factors is considered standard risk. These additional risk stratification parameters are generally not employed for patients ≥65 years of age (or for patients with substantial comorbid conditions) with Ph-negative ALL.

Overview of Treatment Phases in ALL Management

The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. Although the specific treatment regimens and selection of drugs, dose schedules, and

treatment duration differ between AYA patients and adults, as well as between different subtypes of ALL, the basic treatment principles are similar. The most common treatment regimens employed in patients with ALL include modifications or variations of multiagent chemotherapy regimens originally developed by the Berlin-Frankfurt-Munster Group (BFM) for pediatric patients (e.g., regimens used by COG for children and AYA patients, CALGB regimen for adult patients), and the hyper-CVAD regimen developed at the M.D. Anderson Cancer Center. In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance. All treatment regimens for ALL include CNS prophylaxis and/or treatment.

Induction

The intent of initial induction therapy is to reduce tumor burden by clearing as many leukemic cells as possible from the bone marrow. Induction regimens are typically based on a backbone that includes a combination of vincristine, anthracyclines (e.g., daunorubicin, doxorubicin), and corticosteroids (e.g., prednisone, dexamethasone) with or without L-asparaginase and/or cyclophosphamide.[1, 9, 17, 21, 26] In addition, antimetabolites such as methotrexate, cytarabine, and/or mercaptopurine are often included at the time of induction therapy, primarily for CNS prophylaxis (see Discussion section below). The BFM/COG regimens are mainly based on a 4-drug induction regimen that includes a combination of vincristine, an anthracycline, a corticosteroid, and L-asparaginase.[38-42] The CALGB regimens are typically based on a 5-drug regimen, which adds cyclophosphamide to the above 4-drug combination.[11] Randomized studies comparing the use of dexamethasone with prednisone as part of induction therapy in children with ALL showed that dexamethasone significantly decreased the risk of isolated CNS relapse and improved EFS outcomes compared with prednisone.[43, 44] The observed advantage in outcomes with dexamethasone may, at least in part, be attributed to improved penetration of dexamethasone in the CNS.[45] In a recently published meta-analysis comparing outcomes with dexamethasone versus prednisone in induction regimens for childhood ALL, dexamethasone was associated with significantly reduced risk for events (i.e, death from any cause, refractory or relapsed leukemia, or second malignancy; risk ratio [RR] 0.80; 95% CI,, 0.68-0.94) and CNS relapse (RR 0.53; 95% CI, 0.44-0.65).[46] However, no advantage was seen with dexamethasone with regards to risks for bone marrow relapse (RR 0.90; 95% CI, 0.69-1.18) or overall mortality (RR 0.91; 95% CI, 0.76-1.09), and dexamethasone was associated with a significantly higher risk of mortality during induction therapy (RR 2.31; 95% CI, 1.46-3.66), neuro-psychiatric adverse events (RR 4.55; 95% CI, 2.45-8.46) and myopathy (RR 7.05; 95% CI, 3.00-16.58) compared with prednisone.[46] Thus, while dexamethasone appears beneficial in terms of reduced risks for CNS relapse and improved EFS, toxicities may be of concern and an advantage for OS has yet to be conclusively demonstrated.

The hyper-CVAD regimen may be considered a less complex treatment regimen compared with CALGB regimens, and comprises eight cycles of alternating treatment cycles with the “A” regimen (hyper-CVAD: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and “B” regimen (high-dose methotrexate and cytarabine).[10, 47, 48] CNS prophylaxis and/or CNS-directed treatment (which may include cranial irradiation for patients with CNS leukemia at diagnosis), and maintenance treatment (as discussed below) are also employed along with the hyper-CVAD regimen.

CNS Prophylaxis and Treatment

The aim of CNS prophylaxis and/or treatment is to clear leukemic cells within sites that cannot be readily accessed by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS

disease or relapse. CNS-directed therapy may include cranial irradiation, intrathecal chemotherapy (e.g., methotrexate, cytarabine, corticosteroids) and/or high-dose systemic chemotherapy (e.g., methotrexate, cytarabine, mercaptopurine, L-asparaginase).[1, 26, 45] CNS prophylaxis is typically given throughout the course of ALL therapy starting from induction, consolidation, to the maintenance phases of treatment.

Consolidation

The intent of post-induction consolidation is to eliminate potential leukemic cells that remain after induction therapy, including further eradication of residual disease. The post-remission induction phase of treatment (but prior to long-term maintenance therapy) may also be described as intensification therapy. The combination of drugs and duration of therapy for consolidation regimens largely vary between studies and between patient populations, but can comprise combinations of drugs similar to those used during the induction phase. High-dose methotrexate, cytarabine, mercaptopurine and L-asparaginase are frequently incorporated as part of consolidation/intensification regimens, particularly for regimens geared toward children with ALL.[9, 18, 21, 26, 41, 42]

Maintenance

The goal of extended maintenance therapy is to prevent disease relapse following post-remission induction and consolidation therapy. Most maintenance regimens are based on a backbone of daily mercaptopurine and weekly methotrexate (typically with the addition of periodic vincristine and corticosteroids) for 2 years in adults and 2 to 3 years in children.[9, 17, 21, 26] Maintenance therapy is omitted for patients with mature B-cell ALL (see the NCCN Guidelines for NHL: Burkitt's lymphoma), given that long-term remissions are seen early with short courses of intensive therapy in these patients, with relapses rarely occurring beyond 12 months.[9, 49]

Targeted Agents

During the last decade, the advent of novel agents targeted to specific genetic abnormalities, such as those associated with Ph-positive ALL, or to specific cell surface antigens, has contributed to improvements in outcomes in some subtypes of ALL. These agents include BCR-ABL selective tyrosine kinase inhibitors (TKIs) for Ph-positive ALL,[50-57] and anti-CD20 monoclonal antibody (e.g., rituximab) for CD20-expressing B-cell lineage ALL (especially for mature B-cell ALL).[58, 59] In addition, nelarabine has been approved for the treatment of relapsed/refractory T-cell lineage ALL.[60-62] These agents may be incorporated as part of frontline induction, consolidation, and/or maintenance regimens during the course of initial ALL therapy, as well as for relapsed/refractory disease settings.

Management of Ph-Positive ALL

Initial Treatment in AYA with Ph-positive ALL

Ph-positive ALL is relatively rare in children with ALL, occurring in only about 3% of pediatric cases compared with 25% of adult cases.[16] The frequency of Ph-positive ALL is slightly higher (5% to 7% of cases) among AYA patients,[42] although this subtype is still uncommon compared with older adults. Nevertheless, for children and adolescents with Ph-positive disease, the prognosis is generally much poorer compared with patients with Ph-negative B-cell ALL. In a retrospective analysis of children with Ph-positive ALL treated between 1986 and 1996 (N=326) with intensive chemotherapy regimens with or without allogeneic HSCT, the 5-year EFS (calculated from time of diagnosis) and OS rates were 28% and 40%, respectively, for the entire patient cohort.[30] The 7-year EFS and OS rates were 25% and 36%,

respectively. Even among the subgroup of patients considered to have a better prognosis (i.e., WBC count <50 × 10^9/L and age <10 years), the 5-year DFS rate (calculated from time of first CR) was only 49%.[30] In the subgroup of patients who underwent allogeneic HSCT with an HLA-matched related donor (n=38), significantly higher 5-year DFS rate (65% vs. 25%; *P*<0.001) and OS rate (72% vs. 42%; *P*=0.002) was observed compared with patients who received only chemotherapy; this benefit with HSCT versus chemotherapy alone was not observed with autologous HSCT or with HSCT from matched unrelated donors. This study showed that allogeneic HSCT from a matched related donor offered improvements in outcomes over chemotherapy alone. In a subsequent analysis of outcomes in children with Ph-positive ALL treated more recently (1995 to 2005) but also without targeted TKIs, the 7-year EFS and OS rates were 32% and 45%, respectively.[63] Outcomes with allogeneic HSCT from either matched related or unrelated donors appeared similar, and HSCT was shown to provide improved disease control over intensive chemotherapy alone.[63] Although this recent analysis showed improvements in 7-year EFS rates, outcomes remain suboptimal in patients with Ph-positive ALL.

The emergence of targeted therapies for hematologic malignancies, including the treatment of Ph-positive disorders with TKIs, represents an important advancement in ALL therapy. Imatinib mesylate is an inhibitor of BCR-ABL tyrosine kinase and is approved by the US FDA for the treatment of adult patients with relapsed or refractory Ph-positive ALL. In phase II studies in adults with ALL, imatinib has demonstrated efficacy as single-agent therapy in the relapsed/refractory setting[64] and frontline setting,[52, 65] and in combination with chemotherapy regimens during initial induction, consolidation and/or maintenance.[50, 55-57, 66-68]

Although allogeneic HSCT has been considered the standard of care for AYA patients with Ph-positive ALL, its role has become less clear with the advent of BCR-ABL-targeted TKIs such as imatinib. Several studies evaluated the role of allogeneic HSCT in the era of imatinib and whether imatinib-based therapies provided an additional benefit to HSCT.

In a single-center retrospective study in children and adolescents with Ph-positive ALL who underwent allogeneic HSCT (N=37; age 1 to 16 years), outcomes were compared between patients who received pre- and/or post-HSCT imatinib (n=13) and those who did not receive imatinib (n=24).[69] The 3-year DFS rate (62% vs. 53%, respectively) and 3-year relapse rate (15% vs. 26%, respectively) was not significantly improved with the use of imatinib. Patients who received HSCT in first CR had significantly improved DFS rates (71% vs. 29%; *P*=0.01) and lower relapse rates (16% vs. 36%; *P*=0.05) compared with those who underwent HSCT in second CR or later.[69]

In a recent study from the Spanish Cooperative Group, outcomes of children and adolescents (age 1 to 15 years) treated with intermediate-dose imatinib combined with intensive chemotherapy followed by allogeneic HSCT (n=16; 94% proceeded to HSCT) were compared with outcomes from historical control patients who did not receive imatinib prior to allogeneic HSCT (n=27; 63% proceeded to HSCT).[70] The 3-year EFS rate was significantly higher in the imatinib group compared with the historical controls (79% vs. 30%; *P*=0.01).

Imatinib combined with the hyper-CVAD regimen was evaluated in a phase II study at the M.D. Anderson Cancer Center in patients with previously untreated or minimally treated ALL (N=54; median age 51 years, range 17-84 years); 14 patients underwent subsequent allogeneic HSCT.[68] The 3-year OS rate with this regimen was 54%. Among the patients ≤40 years of age (n=16), a strong trend was

observed for OS benefit with allogeneic HSCT (3-year OS rate 90% vs. 33%; *P*=0.05).[68]

In a multicenter COG study (AALL-0031) of children and adolescents with high-risk ALL, the group of patients with Ph-positive ALL (N=92; age 1 to 21 years) were treated with an intensive chemotherapy regimen combined with imatinib (340 mg/m^2/day; given during post-remission induction therapy and maintenance).[54] Among the cohort of patients (n=44) who received continuous imatinib exposure (280 consecutive days prior to maintenance initiation), the 3-year EFS rate was 80.5% (95% CI, 64.5%-89.8%); this outcome compared favorably to a historical population of patients with Ph-positive ALL (N=120) treated on a POG protocol, which showed a 3-year EFS rate of only 35% (*P*<0.0001).[54] Moreover, the 3-year EFS rates were similar between the groups of patients who received chemotherapy combined with continuous imatinib (88%; n=25) or allogeneic HSCT from a related donor (57%; n=21) or unrelated donor (72%; n=11). No major toxicities were found to be associated with the addition of imatinib to the intensive chemotherapy regimen.[54]

Initial Treatment in Adults with Ph-positive ALL

Historically, treatment outcomes for adult patients with Ph-positive ALL have been extremely poor. Prior to the era of targeted TKIs, the 3-year OS rate with chemotherapy regimens was generally <20%.[55] Allogeneic HSCT, in the pre-imatinib era, resulted in some improvements over chemotherapy alone, with 2-year OS rates of 40-50%,[71, 72] and 3-year OS rates of 36-44%.[15, 73] In the large international collaborative MRC UK ALL XII/ECOG 2993 trial conducted in patients with previously untreated ALL, the subgroup of patients with Ph-positive disease (n=267; median age 40 years, range 15-60 years) was eligible for allogeneic HSCT if they were younger than 50-55 years of age and had a matched sibling or matched unrelated donor.[74] Among the Ph-positive patient cohort, post-remission induction treatment included matched sibling allogeneic HSCT (n=45), matched unrelated donor allogeneic HSCT (n=31) and chemotherapy alone (n=86). The 5-year OS rate according to post-remission therapy was 44%, 36%, and 19%, respectively; the 5-year EFS rate was 41%, 36%, and 9%, respectively.[74] Both the OS and EFS outcomes for patients who underwent allogeneic HSCT (related or unrelated) were significantly improved compared with those who received only chemotherapy. The incidence of transplant-related mortality was 27% with matched sibling allogeneic HSCT and 39% with matched unrelated donor HSCT. Based on an intent-to-treat analysis of patients with a matched sibling donor versus patients without a matched sibling donor, no statistically significant difference was observed in the 5-year OS rate (34% vs. 25%, respectively).[74]

The incorporation of imatinib in the treatment regimen for Ph-positive ALL has led to substantial improvements in outcomes compared with chemotherapy alone.[55, 57, 68] Numerous phase II studies have evaluated the efficacy of imatinib combined with chemotherapy regimens in previously untreated patients; these studies showed positive results with the combined regimen, particularly when treatment was followed by allogeneic HSCT.[50, 55-57, 66-68, 75]

In the phase II study from GRAALL (GRAAPH-2003), patients with previously untreated Ph-positive ALL (N=45; median age 45 years, range 16-59 years) received imatinib in combination with chemotherapy during either induction or consolidation therapy.[50, 67] Patients in CR with a donor received allogeneic HSCT (n=22) while those with CR and good molecular response but without a donor were eligible for autologous HSCT (n=10). After a median follow up of 46 months, the 4-year OS rate was not significantly different for patients with a donor compared with those without a donor (55% vs. 54%). This lack of a

benefit in the donor group likely reflected the favorable survival outcomes seen in patients without a donor but who underwent autologous HSCT. Among the patients who underwent allogeneic HSCT, the 4-year OS rate (55% vs. 25%; *P*=0.05) and DFS rate (47% vs. 25%; *P*=NS) were improved compared with the subgroup without HSCT; no significant differences in outcomes were observed between allogeneic and autologous HSCT.[67] The 4-year relapse rate was 24% and the incidence of treatment-related mortality was 32%.

In the subgroup of patients with Ph-positive ALL (N=94; median age 47 years, range 19-66 years) from the Northern Italy Leukemia Group study (NILG-09/00), outcomes were compared between patients who received chemotherapy with imatinib (n=59) or without imatinib (n=35), with or without subsequent HSCT (allogeneic or autologous).[75] The patients who received imatinib (63% of eligible patients underwent allogeneic HSCT) had significantly higher 5-year OS rate (38% vs. 23%; *P*=0.009) and DFS rate (39% vs. 25%; *P*=0.005) compared with patients who did not receive imatinib (39% of eligible patients underwent allogeneic HSCT). [75] The 5-year OS rates by treatment type were 47% for allogeneic HSCT (n=45), 67% for autologous HSCT (n=9), 30% for imatinib without HSCT (n=15), and 8% for no imatinib and no HSCT (n=13); the corresponding treatment-related mortality rates were 17%, 0%, 36%, and 23%, respectively. The 5-year relapse rates were 43%, 33%, 87%, and 100%, respectively.[75]

In a phase II study from the Spanish Cooperative Group, patients with Ph-positive ALL (N=30; median age 42 years, range 8-62 years; only 1 patient was under 15 years of age) were treated with intensive chemotherapy combined with imatinib, followed by HSCT and imatinib maintenance.[76] Overall, 53% of patients proceeded to allogeneic HSCT and 17% received autologous HSCT. At a median follow up of 4.1 years, both the OS rate and DFS rate were 30%. The incidence of transplant-related mortality was 27%.[76] Post-transplant maintenance with imatinib was not feasible in most patients, primarily due to transplant-related complications.

As previously discussed, imatinib combined with the hyper-CVAD regimen was evaluated in a phase II study in patients with previously untreated or minimally treated ALL (N=54; median age 51 years, range 17-84 years), with 14 patients undergoing subsequent allogeneic HSCT.[68] The 3-year OS rate with this regimen was 54%, overall. Among patients ≤60 years of age, no statistically significant difference was observed in the 3-year OS rate between patients who received HSCT and those who did not (77% vs. 57%). This finding is in contrast to results for younger patients (age ≤40 years) who received HSCT, as discussed above.

In another phase II study from GRAALL (GRAAPH-2005), induction therapy with imatinib combined with vincristine and dexamethasone was compared with imatinib combined with hyper-CVAD in patients <60 years of age with previously untreated Ph-positive ALL (N=118; n=83 evaluable; median age 42 years).[77] Eligible patients proceeded to HSCT (allogeneic or autologous) following induction/consolidation phases. In an early report from this study, 52 patients proceeded to HSCT (allogeneic, n=41; autologous, n=11). The estimated 2-year OS rate was 62%; no significant difference was observed between patients who received imatinib with vincristine and dexamethasone and those who received imatinib with hyper-CVAD (68% vs. 54%, respectively).[77] The 2-year DFS rate was 43%, with no difference between induction arms (54% vs. 32%, respectively).

In a phase II study from the Japan Adult Leukemia Study Group (ALL-202), patients with Ph-positive ALL (N=100) were treated with chemotherapy combined with imatinib administered during induction,

consolidation and maintenance phases.[57, 73] An early analysis (N=80; median age 48 years, range 15-63 years) reported a 1-year OS rate of 73% among patients who underwent allogeneic HSCT, compared with 85% for those who did not.[57] In a subsequent analysis, outcomes for the subgroup of patients who received allogeneic HSCT at first CR in this study (n=51; median age 38 years, range 15-64 years) were compared with outcomes for a historical cohort of patients who received allogeneic HSCT without prior imatinib (n=122).[73] Both the 3-year OS rate (65% vs. 44%; *P*=0.015) and DFS rate (58% vs. 37%; *P*=0.039) were significantly higher among patients who were treated with imatinib compared with the historical cohort; the 3-year non-relapse mortality rate was similar between cohorts (21% vs. 28%, respectively).[73]

Collectively, the above studies suggest that the incorporation of imatinib in the therapeutic regimen improves outcomes for adult patients with Ph-positive ALL, particularly when administered prior to allogeneic HSCT. It should be noted, however, that no randomized controlled studies have been conducted, to date, to establish the role of imatinib in the frontline or HSCT settings. In addition, a proportion of patients with Ph-positive ALL are resistant to initial therapy with imatinib-containing regimens or may relapse following imatinib therapy; resistance to imatinib is attributed, at least in part, to the presence of point mutations within the *ABL* kinase domain.[78-81] Moreover, CNS relapse has been reported in both patients responsive to imatinib therapy (isolated CNS relapse with CR in marrow) and those resistant to imatinib.[82-85] The concentration of imatinib in the cerebrospinal fluid has been shown to be about two logs lower than that achieved in the blood, suggesting that this agent does not adequately penetrate the blood-brain barrier to ensure CNS coverage.[83, 85] A study showed that among patients with ALL treated with imatinib and who did not receive routine prophylactic intrathecal therapy or cranial irradiation, 12% developed CNS leukemia.[84] Patients who were imatinib resistant and developed CNS disease rapidly died due to progressive disease; conversely, imatinib-sensitive patients who developed isolated CNS relapse could be successfully treated with intrathecal therapy with or without cranial irradiation.[82, 84]

Dasatinib is a second-generation TKI that inhibits both the BCR-ABL kinase and SRC family kinase, the latter of which is thought to be involved in an alternative signaling pathway in imatinib-resistant ALL; moreover, dasatinib displayed a 325-fold increase in potency in inhibiting *in vitro* growth of cells with wild type *BCR-ABL* compared with imatinib,[86] and maintained activity against cells harboring imatinib-resistant *ABL* kinase domain mutations with the exception of the T315I, V299L, and F317L mutations.[86-88] In phase II and phase III dose comparison studies, dasatinib demonstrated activity in patients with relapsed or refractory ALL who could not tolerate imatinib or who were resistant to imatinib therapy.[51, 88, 89] Additionally, dasatinib showed activity against CNS leukemia in preclinical *in vivo* models and in a small group of patients with Ph-positive ALL with CNS involvement.[90] Thus, it appears that dasatinib may provide some benefit over imatinib in terms of increased potency in inhibiting signaling pathways, activity against various *ABL* kinase mutations, and greater penetration of the blood-brain barrier. Recent studies have demonstrated the promising activity of dasatinib when incorporated as part of frontline regimens for patients with ALL. In a phase II study from the M.D. Anderson Cancer Center, dasatinib was combined with hyper-CVAD and subsequent maintenance therapy in patients with previously untreated Ph-positive ALL (N=35; median age 53 years, range 21-79 years; 31% were age >60 years); 4 of the patients received allogeneic HSCT at first CR.[53] The 2-year OS rate and EFS rate was 64% and 57%, respectively. In a study from GIMEMA (LAL-1205), patients with Ph-positive ALL (N=53 evaluable; median age 54 years, range 24-76.5 years) received induction therapy with dasatinib and prednisone.[91, 92] Post-induction therapy included no further therapy (n=2), TKI only (n=19), TKI

combined with chemotherapy (n=10) with or without autologous HSCT (n=4), or allogeneic HSCT (n=18). All patients achieved a CR after induction therapy. The median OS was 31 months and the median DFS (calculated from day +85) was 21.5 months. At 20 months, the OS rate and DFS rate was 69% and 51%, respectively.[92] Among 17 patients who relapsed, T315I mutation was detected in 12 cases (71%).

The treatment of older patients with Ph-positive ALL may pose a challenge, as elderly patients or those with comorbidities may not tolerate aggressive regimens with multiagent chemotherapy combined with TKIs. Several studies have evaluated outcomes with imatinib induction, with or without concurrent corticosteroids, in the older adult population with Ph-positive ALL. In a study that randomly assigned older patients with Ph-positive ALL (N=55; median age 68 years, range 54-79 years; 94.5% were age ≥60 years) to induction therapy with imatinib versus chemotherapy alone, followed by imatinib-containing consolidation therapy, the estimated 2-year OS rate was 42%; no significant difference was observed between induction treatment arms.[52] The median OS was numerically higher (but not statistically significantly different) among patients who received imatinib induction compared with those randomized to chemotherapy induction (23.5 months vs. 12 months). However, the incidence of severe adverse events was significantly lower with imatinib induction (39% vs. 90%; *P*=0.005), which suggested that induction therapy with imatinib may be better tolerated compared with chemotherapy in older patients with Ph-positive ALL.[52] In a small phase II study from GRAALL (AFR-09 study), older patients (age ≥55 years) with Ph-positive ALL (N=29 evaluable; median age 63 years) were treated with chemotherapy induction followed by a consolidation regimen with imatinib and methylprednisolone.[93] The 1-year OS rate in this study was significantly higher compared with historical control patients who received the same induction therapy but did not receive imatinib as part of consolidation (66% vs. 43%; *P*=0.005); the median OS in this study population was longer than that of control patients (23 months vs. 11 months, respectively). In addition, the 1-year relapse-free survival rate was significantly increased with the addition of imatinib (58% vs. 11%; *P*<0.001).[93] A phase II study by GIMEMA (LAL0201-B study) also evaluated imatinib combined with corticosteroids in older patients (age >60 years) with Ph-positive ALL (N=29 evaluable; median age 69 years).[94] Patients received imatinib in combination with prednisone for induction. The estimated 1-year OS rate and DFS rate was 74% and 48%, respectively; the median OS was 20 months.[94]

Treatment of Relapsed Ph-positive ALL

The treatment of patients who relapse after initial therapy for ALL remains a challenge, as these patients have very poor prognosis. Several large studies have reported a median OS of only 4.5 months to 6 months, and a 5-year OS rate of 3% to 10% among patients who relapse following initial treatment.[95-98] One of the major factors associated with poorer survival outcomes following salvage therapy for relapsed ALL is the duration of response to frontline treatment. In an analysis of data from patients who relapsed in the PATHEMA trials, the group of patients who relapsed more than 2 years after frontline therapy had significantly higher 5-year OS rate compared with the groups of patients who relapsed within 1 to 2 years or within 1 year of frontline therapy (31% vs. 15% vs. 2%; *P*<0.001).[96] Similarly, in the analysis of the group of patients who relapsed after frontline therapy in the MRC UK XII/ECOG 2993 trial, the patients who relapsed more than 2 years from initial diagnosis had a significantly higher 5-year OS rate compared with those who relapsed within 2 years (11% vs. 5%; *P*<0.001).[95] In the pre-imatinib era, patients with Ph-positive ALL who relapsed after frontline therapy also had dismal outcomes; subgroup data from the large, prospective trials LALA-94 and MRC UK XII/ECOG 2993 showed a median OS of 5 months and a 5-year OS rate of 3% to

6% among patients subsequently treated for relapsed Ph-positive ALL.[95, 97]

As discussed in the sections above, the incorporation of TKIs such as imatinib in the frontline treatment regimen for Ph-positive ALL has become the established standard of care. However, the emergence of resistance to TKI therapy poses a challenge for patients who are primary refractory to or who relapse after initial treatment with TKI-containing regimens. Point mutations within the *ABL* kinase domain and alternative signaling pathways mediated by the SRC family kinase have been implicated in the mechanisms of resistance to imatinib.[78-81, 87, 99] Mutations within the *ABL* kinase domain have been identified in a large proportion of patients with disease recurrence following imatinib-containing therapy.[79, 80] Moreover, *ABL* kinase domain mutations may be present in a small group of imatinib-naïve patients even before initiation of any TKI therapy.[100, 101] Dasatinib and nilotinib are second-generation TKIs that have demonstrated greater potency in inhibiting *BCR-ABL* compared with imatinib, as well as retention of anti-leukemic activity in cells with certain imatinib-resistant *ABL* mutations.[86-88, 102, 103] Both TKIs have been evaluated as single-agent therapy in patients with Ph-positive ALL resistant to or intolerant of imatinib treatment.[51, 89, 104, 105] A randomized phase III study examined the activity of dasatinib administered as once daily dosing (140 mg daily) versus twice daily (70 mg BID) in patients with Ph-positive leukemia resistant to imatinib.[89] In the group of patients with Ph-positive ALL (n=84), the once daily dosing resulted in higher response rates (major hematologic responses) compared with the twice daily dosing (70% vs. 52%); the median OS was also improved with the twice daily dosing (9 months vs. 6.5 months), but median PFS was decreased (3 months vs. 4 months) compared with twice daily dosing.[89] These differences in outcomes between the dosing arms were not statistically significant. Dasatinib is currently approved in the US for the treatment of patients with Ph-positive ALL who are intolerant or resistant to prior therapy.

Not all imatinib-resistant *ABL* mutations are susceptible to the newer TKIs, however. For instance, dasatinib is not as active against cells harboring the *ABL* mutations T315I, V299L, and F317L.[81, 86-88, 106-108] Thus, for patients who show resistance to TKI therapy, it becomes important to identify potential *ABL* mutations that may underlie the observed resistance to treatment. A panel of experts from the European LeukemiaNet recently published recommendations for the analysis of *ABL* kinase domain mutations in patients with CML, and treatment options according to the presence of different *ABL* mutations.[109] Investigational TKIs such as ponatinib and bosutinib have shown promising activity in recent studies of patients with Ph-positive leukemias (including patients with ALL) resistant or intolerant to prior TKIs.[110, 111] For example, in an early analysis from the multicenter open-label phase II study (PACE trial; N=403 enrolled), ponatinib demonstrated substantial activity in patients with Ph-positive leukemias resistant or intolerant to second-generation TKIs, including in heavily pretreated patients with the *ABL* T315I gene mutation.[110] Both ponatinib and bosutinib are investigational at this time, and are not FDA approved for any indication.

Treatment options are extremely limited for patients with Ph-positive ALL who relapse after receiving allogeneic HSCT. Several published cases have reported on the feasibility of inducing a molecular CR with dasatinib in patients with Ph-positive ALL who have experienced early relapse following first allogeneic HSCT.[112, 113] The patients subsequently received a second allogeneic HSCT. The use of donor lymphocyte infusion (DLI) to induce further graft-versus-leukemia effect in patients relapsing after allogeneic HSCT has been evaluated in a number of case reports and small studies. Several studies have

reported little to no benefit of using DLI in Ph-positive ALL patients with disease relapse following HSCT.[114, 115] These studies appeared to have administered DLI at the time of hematologic relapse, where the leukemic tumor burden may have been too high to control effectively with DLI. Indeed, recent case reports have suggested that the use of DLI for residual disease or molecular relapse (as noted by levels of *BCR-ABL* fusion mRNA measured by PCR) after allogeneic HSCT may eliminate residual leukemic clones and thereby prevent overt hematological relapse.[116-118] Moreover, case reports have also suggested the use of newer TKIs such as dasatinib and nilotinib along with DLI in managing relapse following allogeneic HSCT.[119, 120] Although these approaches are promising, data from prospective studies are needed to establish the role of DLI, with or without TKIs, in the treatment of relapse.

NCCN Recommendations for Ph-positive ALL

AYA patients (age 15-39 years) with Ph-positive ALL

The NCCN Guidelines panel recommends that AYA patients with Ph-positive ALL be treated on a clinical trial, where possible. In the absence of an appropriate clinical trial, the recommended induction therapy would comprise multiagent chemotherapy combined with a TKI. Treatment regimens should include adequate CNS prophylaxis for all patients. It is also important to adhere to the treatment regimens for a given protocol in its entirety, from induction therapy to consolidation/delayed intensification to maintenance therapy. For patients achieving a CR following initial induction therapy, consolidation with allogeneic HSCT should be considered if a matched donor is available. It should be noted, however, that in younger AYA patients (age ≤21 years), emerging data suggest that allogeneic HSCT may not confer an advantage over chemotherapy combined with TKIs.[54] Following HSCT, maintenance therapy (typically, weekly methotrexate, daily 6-mercaptopurine, and monthly pulses of vincristine/prednisone for 2-3 years) with the addition of a TKI is recommended. For patients without a donor, consolidation therapy following a CR should comprise a continuation of multiagent chemotherapy combined with a TKI. These patients should continue to receive post-consolidation maintenance therapy with a regimen that includes a TKI. Individuals who inherit a non-functional variant allele of the gene encoding the enzyme thiopurine S-methyltransferase (TPMT) are known to be at high risk for developing hematopoietic toxicity (in particular, severe neutropenia) after treatment with mercaptopurine.[121] Testing for *TPMT* gene polymorphism should be considered for patients receiving 6-mercaptopurine as part of maintenance therapy, particularly in patients who experience severe bone marrow toxicities.

For patients achieving less than a CR following initial induction therapy (i.e., having primary refractory disease), the treatment approach would be similar to patients with relapsed/refractory ALL. Mutation testing for the *ABL* gene should be considered, as certain mutations may account for the observed resistance to induction therapy. For these patients with less than a CR to induction, a clinical trial with new investigational agents/regimens would be preferred. In the absence of a suitable clinical trial, the patients may be treated with multiagent chemotherapy combined with an alternative TKI (i.e., different from the TKI used as part of induction therapy). The choice of TKI would depend on the presence of specific *ABL* kinase domain mutations, as different mutations may confer greater resistance or susceptibility to particular TKIs. The NCCN Guidelines panel has adopted the recommendations for treatment options based on *ABL* mutations status for CML, as recently published by the European LeukemiaNet.[109] Based upon these published recommendations, dasatinib (if not administered during initial induction) should be considered for patients with relapsed/refractory

Ph-positive disease found to have the mutations Y253H, E255K/V, or F359V/C/I. For patients with relapsed/refractory disease found to have the mutations V299L, T315A, or F317L/V/I/C, nilotinib should be considered. Patients with the T315I mutation should be considered for allogeneic HSCT or participation in a clinical trial, if available, as this mutation is known to be resistant to currently available TKIs.[109] For any other mutations of the *ABL* gene, either high-dose imatinib, dasatinib, or nilotinib may be considered. If a second CR is achieved with second-line treatment, the patient may be considered for allogeneic HSCT. Treatment with DLI is also an option if the patient has relapsed following allogeneic HSCT.

For patients with relapsed/refractory disease, participation in a clinical trial is preferred. In the absence of an appropriate trial, the patient may be considered for second-line therapy with multiagent chemotherapy combined with an alternative TKI (i.e., different from the TKI used as part of induction therapy), allogeneic HSCT (if a second CR is achieved), or DLI (if the patient relapsed after allogeneic HSCT).

Adult patients (age ≥40 years) with Ph-positive ALL

For adult patients with Ph-positive ALL, the NCCN Guidelines panel recommends treatment on a clinical trial, where possible. In the absence of an appropriate clinical trial, the recommended induction therapy would initially depend on the patient's age and/or presence of comorbid conditions. As previously mentioned, treatment regimens should include adequate CNS prophylaxis for all patients, and a given treatment protocol should be followed in its entirety, from induction therapy to consolidation/delayed intensification to maintenance therapy. Although the age cut-off indicated in the Guidelines has been set at 65 years, it should be noted that chronological age alone is not a sufficient surrogate for defining fitness; patients should be evaluated on an individual basis to determine fitness for therapy based on factors such as performance status, end organ function and end organ reserve.

For relatively fit patients (age <65 years or with no substantial comorbidities), the recommended treatment approach is similar to that of AYA patients. Induction therapy would comprise multiagent chemotherapy combined with a TKI. For patients achieving a CR following induction, consolidation with allogeneic HSCT should be considered if a matched donor is available. Following HSCT, maintenance therapy (typically, weekly methotrexate, daily 6-mercaptopurine, and monthly pulses of vincristine/prednisone for 2-3 years) with the addition of a TKI is recommended. For patients without a donor, consolidation therapy following a CR should comprise a continuation of multiagent chemotherapy combined with a TKI. These patients should continue to receive post-consolidation maintenance therapy with a regimen that includes a TKI. Again, testing for *TPMT* gene polymorphism should be considered for patients receiving 6-mercaptopurine as part of maintenance therapy, especially for patients who develop severe bone marrow toxicities after initiating 6-mercaptopurine. For patients with less than a CR after induction, the treatment approach would be similar to patients with relapsed/refractory disease (as discussed below).

For patients who are less fit (age ≥65 years or with substantial comorbidities), the recommended induction therapy includes a TKI with corticosteroids or TKI with chemotherapy regimens. Dose modifications may be required for chemotherapy agents, as needed. Patients with a CR to induction should continue consolidation therapy with a TKI with or without corticosteroids or TKI with or without chemotherapy; maintenance therapy (typically, weekly methotrexate, daily 6-mercaptopurine, and monthly pulses of vincristine/prednisone for 2-3 years) with the addition of a TKI is recommended. Patients with less

than a CR after induction should be managed similar to patients with relapsed/refractory disease.

For adult patients with relapsed/refractory disease, mutation testing for the *ABL* gene should be considered, and participation in a clinical trial with new investigational agents/regimens is suggested. In the absence of a suitable clinical trial, patients may be treated with an alternative TKI with or without corticosteroids or TKI with or without chemotherapy, or may be considered for allogeneic HSCT (if a CR is achieved, and if the patient is sufficiently physically fit to undergo the procedure).

Management of Ph-negative ALL

Initial Treatment in AYA with Ph-negative ALL

As previously mentioned, the AYA population with ALL can pose a unique challenge given that these patients may be treated under a pediatric or adult protocol depending upon local referral patterns and institutional practices. Retrospective analyses based on cooperative group studies from both the US and Europe have consistently demonstrated the superior outcomes for AYA patients (ranging between 15 to 21 years of age) treated on pediatric versus adult ALL regimens. In the AYA population, 5-year EFS rates ranged from 63%-74% for those treated on a pediatric study protocol versus 34%-49% for patients receiving the adult protocol.[42, 122-125] In a recent retrospective comparative study that analyzed outcomes of AYA patients (age 16 to 20 years) treated on a pediatric CCG study protocol (n=197; median age, 16 years) versus an adult CALGB study protocol (n=124; median age, 19 years), the 7-year EFS rate was significantly improved for patients treated on the pediatric regimen compared with those on the adult regimen (63% vs 34%; *P*<0.001); the 7-year OS rate was 67% versus 46%, respectively (*P*<0.001).[42] Moreover, AYA patients treated on the adult protocol experienced a significantly higher rate of isolated CNS relapse at 7 years (11% vs 1%; *P*=0.006). The substantial improvements in outcomes observed with the pediatric regimen in this study, as well as in the earlier retrospective analyses from other cooperative groups, may largely be attributed to its greater cumulative doses of drugs such as corticosteroids (prednisone and/or dexamethasone), vincristine, and L-asparaginase, as well as earlier, more frequent, and/or more intensive CNS-directed therapy, compared with adult regimens.[42]

Favorable outcomes with the use of pediatric-based treatment protocols in the AYA population have also been reported in other recent studies. In an analysis of outcomes in children and AYA patients treated in the Dana Farber Cancer Institute (DFCI) ALL Consortium study protocols (1991 to 2000), the 5-year EFS rate among younger AYA patients (age 15 to 18 years; n=51) was 78%, which was not significantly different from the EFS rates observed for children aged 10 to 15 years (77%; n=108) or those aged 1 to 10 years (85%; n=685).[126] The CCG 1961 study was designed to evaluate the benefit of augmented post-induction intensification therapy versus standard post-induction intensification in children aged 1 to 9 years with high WBC counts (≥50 × 10^9/L) or in older children and adolescents aged 10 to 21 years.[41] Patients were stratified by their initial response to induction therapy; slow early responders (patients with >25% bone marrow blasts on Day 7 of induction) and rapid early responders. Among the patients who were rapid early responders to induction (N=1299), the augmented post-induction intensity arm was associated with significantly increased 5-year EFS rate (81% vs. 72%; *P*<0.0001) and OS rate (89% vs. 83%; *P*=0.003) compared with the standard intensity arm.[41] In the subgroup of AYA patients (age 16 to 21 years; N=262) from the CCG 1961 study treated with either augmented or standard intensity regimens, the 5-year EFS rate and OS rate was 71.5% and 77.5%, respectively.[127]

Among the AYA patients who were considered rapid early responders, no statistically significant differences were observed between the augmented intensity (n=88) and standard intensity (76) arms for 5-year EFS rate (82% vs. 67%, respectively) or OS rate (83% vs. 76%, respectively). For the AYA patients who were considered slow early responders (all of whom received the augmented intensity regimen), the 5-year EFS rate was 71%.[127]

Data from the most recent Total Therapy (XV) study by the St Jude Children's Research Hospital also showed dramatic improvements in survival outcomes for the AYA population. In this study, patients were primarily risk stratified based on treatment response; patients were treated according to risk-adjusted intensive chemotherapy, with the incorporation of MRD evaluation during induction (day 19) to determine the need for additional doses of asparaginase.[128, 129] The 5-year EFS rate for the AYA population (age 15 to 18 years; n=45) was 86% (95% CI, 72%-94%), which was not significantly different from the 87% EFS rate (95% CI, 84%-90%; *P*=0.61) observed for the younger patients (n=448). The 5-year OS rate for the AYA patients and younger patients was 88% and 94%, respectively (*P*=0.13).[128, 129] The favorable EFS and OS outcomes in AYA patients in this study was attributed, in part, to the use of intensive dexamethasone, vincristine, and asparaginase, in addition to early intrathecal therapy (i.e., triple intrathecal chemotherapy with cytarabine, hydrocortisone and methotrexate) for CNS-directed therapy. In addition, the use of prophylactic cranial irradiation was safely omitted in this study; the 5-year cumulative incidence of isolated CNS relapse and any CNS relapse was 3% and 4%, respectively, for the entire study population (N=498).[128] Moreover, all 11 patients with isolated CNS relapse were among children <12 years of age. This study demonstrated that with intensive risk-adjusted therapy and effective CNS-directed intrathecal regimens, AYA patients can obtain long-term EFS without the need for cranial irradiation or routine allogeneic HSCT.[128, 129]

Given the success seen with multiagent, intensive chemotherapy regimens for pediatric patients with ALL, several clinical trials have evaluated pediatric-inspired regimens for the AYA patient population. In one of these trials (PATHEMA ALL-96), adolescent (n=35; age 15 to 18 years) and young adult (n=46; age 19 to 30 years) patients with standard-risk Ph-negative ALL (defined as WBC count <30 × 10^9/L; absence of t(9;22), t(1;19), t(4;11) or any other 11q23 rearrangements) received frontline therapy with a 5-drug induction regimen (vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide), consolidation/re-induction, and maintenance, along with triple intrathecal therapy throughout the treatment period.[130] The 6-year EFS rate and OS rate for the entire patient cohort was 61% and 69%, respectively. No difference in EFS rate was observed between adolescents (60%; 95% CI, 43-77%) and adults (63%; 95% CI, 48-78%); similarly, no significant difference was observed in OS rate for adolescents (77%; 95% CI, 63-91%) versus adults (63%; 95% CI, 46-80%).[130] Based on multivariate regression analysis, slow response to induction therapy (defined as having >10% blast cells in the bone marrow aspirate performed on day 14 of treatment) was the only factor associated with a poor EFS (odds ratio [OR]=2.99; 95% CI, 1.25-7.17) and OS (OR=3.26; 95% CI, 1.22-8.70).[130]

A multicenter phase II trial evaluated a pediatric-inspired regimen (based on the DFCI Childhood Consortium ALL Protocol 00-01) in AYA and adult patients (age 16 to 50 years) with previously untreated ALL; 20% of the patients on this study were Ph-positive.[131] The treatment regimen comprised induction (vincristine, doxorubicin, prednisone, L-asparaginase, and high-dose methotrexate), triple intrathecal therapy, intensification and maintenance. Among the 75 patients with evaluable

data, the estimated 2-year EFS rate and OS rate was 72.5% and 77.1%, respectively.[131] Adverse events included 1 death due to sepsis (during induction), pancreatitis in 9 patients (12%; including 1 death), osteonecrosis in 2 patients (3%), thrombosis/embolism in 14 patients (19%), and neutropenic infection in 23 patients (31%).[131] Although this intensive regimen was feasible in adult patients, further follow-up data are needed to evaluate long-term survival outcomes.

The prospective phase II GRAALL-2003 study evaluated a pediatric-inspired regimen (using intensified doses of vincristine, prednisone and asparaginase) for adolescents and adults with Ph-negative ALL (N=225; median age 31 years, range 15-60 years).[132] The induction regimen comprised vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide. Patients with high-risk disease and donor availability were allowed to proceed to allogeneic HSCT. The EFS and OS rate at 42 months was 55% and 60%, respectively. When data from patients who underwent transplantation at first CR were censored, the DFS rate at 42 months was 52% for high-risk patients and 68% for standard-risk patients (risk assignment based on GRAALL protocol); these DFS outcomes by risk groups were similar to outcomes using the MRC UK/ECOG definition for risk classification.[132] Advanced age predicted for poorer survival outcomes on this study; the OS rate at 42 months was 41% for patients age >45 years compared with 66% for those age ≤45 years. Moreover, advanced age (using 45 years as the cutoff) was associated with a higher cumulative incidence of therapy-related deaths (23% vs. 5%) and deaths in first CR (22% vs. 5%).[132] Thus, it appears that the benefit of this pediatric-inspired regimen outweighed the risks for therapy-related deaths only for those patients up to 45 years of age with Ph-negative ALL.

A multicenter phase II Intergroup study (CALGB 10403) is currently ongoing to evaluate a pediatric-inspired regimen in the treatment of AYA patients with Ph-negative ALL up to 40 years of age (i.e., eligible patients are age 16 to 39 years). One of the objectives of this study is to compare the outcomes of patients treated on this trial with a similar group of patients (with regards to age and disease characteristics) treated by pediatric oncologists on the COG trial (AALL-0232). The treatment protocol includes a 4-drug induction regimen with IT cytarabine and IT methotrexate, consolidation, interim maintenance, delayed intensification, maintenance (for 2-3 years), and radiotherapy (for patients with testicular or CNS disease or for patients with T-cell ALL).

For patients with T-cell ALL, the addition of nelarabine may be a promising approach. Nelarabine is a nucleoside metabolic inhibitor and a pro-drug of ara-G, approved for the treatment of patients with T-cell ALL who have not responded to or have relapsed after at least two chemotherapy regimens.[133] This drug is currently under evaluation as part of frontline chemotherapy regimens in AYA patients with T-cell ALL. The initial safety results from the randomized phase III COG study (AALL-0434) of the augmented BFM chemotherapy regimen, with or without nelarabine, showed that the toxicity profiles were similar between patients with high-risk T-cell ALL who received nelarabine (n=28) and those who did not (n=29).[134] No significant differences were observed in the occurrence of neurologic adverse events between these groups, including peripheral motor neuropathy, peripheral neuropathy, or CNS neurotoxicity. The incidence of adverse events such as febrile neutropenia and elevation of liver enzymes was also similar between treatment groups. These initial safety data suggest that nelarabine may be better tolerated in frontline regimens than in the relapsed/refractory setting.[134] Results from the efficacy phase of this study are awaited.

For AYA patients in first CR, allogeneic HSCT may be considered for high-risk cases such as elevated WBC counts and poor-risk cytogenetics (e.g., hypodiploidy, *MLL* rearrangement) at diagnosis. A large multicenter trial (LALA-94 study) evaluated the role of post-induction HSCT as one of the study objectives in adolescent and adult ALL patients receiving initial therapy for previously untreated ALL (N=922; median age 33 years, range 15-55 years).[15] Patients were stratified by risk groups, which included the following 4 groups: Ph-negative standard risk disease (defined as achievement of CR after 1 course of chemotherapy; absence of CNS disease; absence of t(4;11), t(1;19), or other 11q23 rearrangements; WBC count <30 × 10^9/L), Ph-negative high-risk ALL (defined as patients with non-standard risk disease and without CNS involvement), Ph-positive ALL, and patients with evidence of CNS disease. Following induction therapy, patients with Ph-negative high-risk ALL were eligible to undergo allogeneic HSCT if a matched sibling donor was available; those without a sibling donor were randomized to undergo autologous HSCT or chemotherapy alone.[15] Among the subgroup of patients with Ph-negative high-risk ALL (n=211), the median DFS and OS was 16 months and 29 months, respectively. The 5-year DFS rate and OS rate was 30% and 38%, respectively. Based on intent-to-treat analysis, outcomes in patients with Ph-negative high-risk ALL were similar for autologous HSCT (n=70) and chemotherapy alone (n=59) with regards to median DFS (15 months vs. 11 months), median OS (28 months vs. 26 months), and 5-year OS rate (32% vs. 21%).[15] Outcomes were improved in patients with Ph-negative high-risk ALL and those with CNS involvement allocated to allogeneic HSCT. The median DFS was 21 months for these patients, and the median OS has not yet been reached; the 5-year OS rate was 51%.[15] Thus, it appeared that in patients with Ph-negative high-risk disease, allogeneic HSCT in first CR improved DFS outcomes while autologous HSCT did not result in significant benefit compared with chemotherapy alone.

In the PETHEMA ALL-93 trial, adult patients with high-risk ALL (defined as 30 to 50 years of age; WBC count ≥25 × 10^9/L; or t(9;22), t(4;11) or other 11q rearrangements, or t(1;19)) received post-remission induction therapy (N=222 eligible; median age 27 years, range 15-50 years) with allogeneic HSCT (n=84; if matched related donor available), autologous HSCT (n=50) or chemotherapy alone (n=48).[135] Based on intent-to-treat analysis of data from Ph-negative high-risk patients, no significant advantage was observed in a donor versus no donor comparison with regards to median DFS (21 months vs. 38 months), median OS (32 months vs. 67 months), 5-year DFS rate (37% vs. 46%), or 5-year OS rate (40% vs. 49%). In addition, when the analysis was conducted on the basis of the actual post-remission treatment received, no significant differences were noted between treatment arms for 5-year DFS rates (50% for allogeneic HSCT; 55% for autologous HSCT; 54% for chemotherapy alone).[135]

The role of allogeneic HSCT in adults with ALL was also evaluated in the large multicenter MRC UK ALL XII/ECOG 2993 study (N=1913; age 15-59 years).[136] In this study, high risk was defined as age ≥35 years, time to CR >4 weeks from induction, elevated WBC counts (>30 × 10^9/L for B-cell ALL; >100 × 10^9/L for T-cell ALL), or the presence of Ph chromosome; all others were considered to be standard risk. Patients achieving a remission with induction therapy were eligible to undergo allogeneic HSCT if a matched sibling donor was available, or in the absence of a sibling donor, were randomized to undergo autologous HSCT or chemotherapy. The 5-year OS rate was higher for patients randomized to chemotherapy alone compared with autologous HSCT (46% vs. 37%; *P*=0.03). In a donor versus no donor comparison for all patients with Ph-negative ALL, the 5-year OS rate was significantly

higher in the donor group compared with the no donor group (53% vs. 45%; *P*=0.01). This advantage in OS outcomes for the donor group was observed for patients with standard risk (62% vs. 52%; *P*=0.02) but not for those with Ph-negative high-risk disease (41% vs. 35%).[136] This was in part due to the high rate of non-relapse mortality observed with the donor group compared with the no donor group in patients with high-risk disease (36% vs. 14% at 2 years). Among patients with standard risk, the non-relapse mortality rate at 2 years was 19.5% for the donor group and 7% for the no donor group. Relapse rate was significantly lower in the donor group compared with no donor for both the subgroup of patients with standard risk (24% vs. 49%; *P*<0.001) and high risk (37% vs. 63%; *P*<0.001).[136] Nevertheless, the high non-relapse mortality rate in the donor group among high-risk patients appeared to diminish the advantage of reduced risks for relapse in this group. This study suggested that allogeneic HSCT in first CR was beneficial in patients with standard risk ALL.

The benefit of matched sibling allogeneic HSCT in adult patients with standard risk ALL was also reported by the HOVON cooperative group. In a donor versus no donor analysis of patients with standard risk ALL undergoing post-remission therapy with matched sibling allogeneic HSCT or autologous HSCT, the donor arm was associated with a significantly reduced 5-year relapse rate (24% vs. 55%; *P*<0.001) and higher 5-year DFS rate (60% vs. 42%; *P*=0.01) compared with the no donor arm.[137] In the donor group, the non-relapse mortality rate at 5 years was 16% and the 5-year OS rate was 69%.[137]

A recent systemic review and meta-analysis of published randomized trials on post-remission induction therapy in adults with ALL reported a significant reduction in all-cause mortality with allogeneic HSCT in first CR (RR=0.88; 95% CI, 0.80-0.97) compared with autologous HSCT or chemotherapy.[138] A subgroup analysis showed that significant survival advantage with allogeneic HSCT was observed in standard-risk ALL while a non-significant advantage was seen in high-risk ALL.[138] Autologous HSCT in first remission was not shown to be beneficial relative to chemotherapy, as demonstrated by several large studies and meta-analyses.[15, 136, 138, 139]

Initial Treatment in Adults with Ph-negative ALL

Typically, induction regimens for adult ALL are also based on a backbone of vincristine, corticosteroids, and anthracyclines. The CALGB 8811 trial evaluated a 5-drug induction regimen (comprising vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide) as part of an intensive chemotherapy regimen for patients with previously untreated ALL (N=197; Ph-positive in 29%; median age 32 years, range 16-80 years).[11] The median OS for all patients was 36 months, after a median follow up of 43 months. Among patients who achieved a CR (85% of all patients), the median remission duration was 29 months. The estimated 3-year OS rate was higher for the subgroup of patients age <30 years compared with those age 30 to 59 years (69% vs. 39%). Among the subgroup of patients who were both Ph-negative and BCR-ABL-negative (n=57), median OS was 39 months and the 3-year OS rate was 62%.[11] Linker et al evaluated an intensified chemotherapy regimen that incorporated a 4-drug induction regimen (comprising vincristine, daunorubicin, prednisone, and asparaginase) in adolescent and adult patients with ALL (N=84; Ph-positive in 16%; median age 27 years, range 16-59 years).[12] The 5-year EFS and OS rate for all patients was 48% and 47%, respectively. Among the patients who achieved a CR (93% of all patients), the 5-year EFS rate was 52%. Among the subgroup of patients without high-risk features (n=53), the 5-year EFS rate was 60%.[12]

In one of the largest multicenter prospective trials conducted to date (MRC UK ALL XII/ECOG 2993 study), previously untreated adolescent

and adult patients (N=1521; age 15 to 59 years) received induction therapy comprising vincristine, daunorubicin, prednisone, and L-asparaginase for 4 weeks (phase 1) followed by cyclophosphamide, cytarabine, oral 6-mercaptopurine, and intrathecal methotrexate for 4 weeks (phase 2).[13] Following completion of induction therapy, patients who achieved a CR received intensification therapy with 3 cycles of high-dose methotrexate (with standard leucovorin rescue) and L-asparaginase. After intensification, patients received the following consolidation therapy: patients aged <50 years who had an HLA-compatible sibling underwent allogeneic HSCT; all others were randomized to receive autologous HSCT or consolidation/maintenance treatment.[13] For Ph-negative disease, high risk was defined as having any of the following factors: age ≥35 years; time to CR >4 weeks; or elevated WBC count (>30 × 10^9/L for B-cell lineage; >100 × 10^9/L for T-cell lineage). All other Ph-negative patients were considered to have standard risk disease. The 5-year OS rate for all Ph-negative patients was 41%; the OS rate for the subgroups with standard risk (n=533) and high risk (n=590) was 54% and 29%, respectively.[13] In the subgroup of patients with T-cell ALL (n=356), the 5-year OS rate was 48%; the OS rate was improved to 61% for those with a matched sibling donor, primarily due to lower incidence of cumulative relapse.[140] Among the patients with T-cell ALL, those with complex cytogenetic abnormalities had poor 5-year OS outcomes (19%).

As previously mentioned, the hyper-CVAD regimen (cycles of fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; alternating with cycles of high-dose methotrexate and cytarabine) constitutes another commonly employed ALL treatment regimen for adult patients. A phase II study from the M.D. Anderson Cancer Center evaluated hyper-CVAD in adolescents and adults with previously untreated ALL (N=288; median age 40 years, range, 15-92 years; Ph-positive in 17%).[10] The median OS for all patients was 32 months and the 5-year OS rate was 38% with a median follow up of 63 months. Among patients who achieved a CR (92% of all patients), the 5-year CR duration rate was 38%.[10] Death during induction therapy occurred in 5% of patients, and was more frequent among patients age ≥60 years. Among the patients with Ph-negative ALL (n=234), the 5-year OS rate was 42%.[10]

Based on retrospective analyses of data from adults with B-cell ALL treated in clinical trials, CD20 positivity (generally defined as CD20 expression on >20% of blasts) was found to be associated with adverse outcomes with regards to a higher cumulative incidence of relapse, decreased CR duration, or decreased survival.[22, 141] Given the prognostic significance of CD20 expression in these patients, treatment regimens incorporating the CD20 monoclonal antibody rituximab have been evaluated. In a phase II study from the M.D. Anderson Cancer Center, hyper-CVAD with or without rituximab was evaluated in previously untreated patients with Ph-negative B-lineage ALL (N=282; median age 41 years, range 13-83 years).[59] Among the subgroup of patients with CD20-positive ALL who were treated with hyper-CVAD combined with rituximab, the 3-year CR duration rate and OS rate was 67% and 61%, respectively. In addition, among the younger patients (age <60 years) with CD20-positive disease, modified hyper-CVAD plus rituximab resulted in significantly improved CR duration rate (70% vs. 38%; P<0.001) and OS rate (75% vs. 47%; P=0.003) compared with the standard hyper-CVAD regimen without rituximab.[59] No significant differences in outcomes with the addition of rituximab were noted for the subgroup of patients who were CD20 negative. Notably, older patients (age ≥60 years) with CD20-positive disease did not appear to benefit from the addition of rituximab, due in part to a high incidence of death in CR among older patients.

For discussion of HSCT in first CR in adult patients with Ph-negative ALL, refer to the discussion section above, under "Initial Treatment in AYA with Ph-negative ALL".

Treatment of Relapsed Ph-negative ALL

Despite major advances in the treatment of childhood ALL, approximately 20% of pediatric patients relapse following initial CR to frontline treatment regimens.[6, 7, 142] Among these patients who experience relapse, only about 30% achieve long-term remission with subsequent therapies.[60, 143, 144] Based upon a retrospective analysis of historical data from COG studies (for patients enrolled between 1998 and 2002; N=9585), early relapse (<18 months from diagnosis) was associated with very poor outcomes with an estimated 5-year survival (from time of relapse) of 21%.[142] For cases of isolated bone marrow relapse, the 5-year survival estimates among early (n=412), intermediate (n=324), and late (n=387) relapsing patients were 11.5%, 18%, and 43.5%, respectively (P<0.0001). Intermediate relapse was defined as relapses occurring between 18 to 36 months from time of diagnosis; late cases were defined as relapses occurring ≥36 months from diagnosis. For cases of isolated CNS relapse, the 5-year survival estimates among early (n=175), intermediate (n=180) and late (n=54) relapsing patients were 43.5%, 68% and 78%, respectively (P<0.0001).[142] Based on multivariate analysis (adjusted for both timing and site of relapse), age (>10 years), presence of CNS disease at diagnosis, male gender, and T-cell lineage disease were found to be significant independent predictors of decreased survival following relapse.[142] In a separate analysis of data from one of the above COG studies (CCG-1952), the timing and site of first relapse was significantly predictive of EFS and OS outcomes, even among the patients with standard-risk ALL (N=347; based on NCI criteria: age 1 to <10 years of age and WBC count <50 × 10^9/L).[145] Early bone marrow relapse (duration of first CR <36 months) was associated with significantly shorter estimated 3-year EFS (30% vs 44.5%; P=0.002) and OS (35% vs 58%; P=0.001) compared with late bone marrow relapse.[145] Similarly, early isolated extramedullary relapse (duration of first CR <18 months) was associated with significantly shorter estimated 3-year EFS (37% vs 71%; P=0.01) and OS (55% vs 81.5%; P=0.039) compared with late extramedullary relapse. In a multivariate regression analysis, early bone marrow and extramedullary relapse were independent predictors of poorer EFS outcomes.[145]

AYA and adult patients with ALL who relapse after initial therapy have extremely poor long-term outcomes. Based on data from patients with disease relapse following frontline therapy in the MRC UK XII/ECOG 2993 study and PETHEMA studies, the median OS after relapse was only 4.5 to 6 months; the 5-year OS rate was 7% to 10%.[95, 96] About 20% to 30% of patients achieve a second CR with salvage therapies.[96, 98] Factors predictive of more favorable outcomes after salvage therapies included younger age and a first CR duration of more than 2 years.[74, 96] Among younger patients (age <30 years) who relapsed after experiencing a first CR duration longer than 2 years with frontline treatment on PATHEMA trials, the 5-year OS rate from the time of first relapse was 38%.[96]

The treatment of AYA and adult patients with relapsed and/or refractory ALL remains a challenge. Clofarabine is a nucleoside analog approved for the treatment of pediatric patients (age 1 to 21 years) with ALL relapsed or refractory after at least 2 prior regimens.[146] In a phase II study of single-agent clofarabine in heavily pretreated pediatric patients with relapsed or refractory ALL (N=61; median age 12 years, range 1-20 years; median 3 prior regimens), the response rate (CR + CRp) was 20%.[147] Among the responding patients, the median duration of remission was 29 weeks. The median OS for all patients was 13 weeks,

and has not yet been reached among the patients with a CR; median OS was 54 weeks for patients with a CRp, and 30 weeks for patients with a partial remission.[147] In a small phase II study that evaluated the combination of clofarabine with cyclophosphamide and etoposide in pediatric patients with refractory or multiple relapsed ALL (N=25; median age 12.5 years), the regimen resulted in a CR rate of 52% (plus an additional 4% CRp) with an 18-month OS probability of 39% among responders.[148] Clofarabine has been shown to be active in combination with other chemotherapy in adults with relapsed/refractory disease. In a recent study from GRAALL, clofarabine in combination with conventional chemotherapy regimens yielded a CR rate of 44% in patients with relapsed/refractory ALL (N=55); the median OS was 6.5 months after a short median follow up of 6 months.[149] Another alkylator-containing salvage regimen, comprising ifosfamide, etoposide and mitoxantrone, was evaluated in a small phase II study in adult patients with relapsed or refractory all (N=11); 8 patients (73%) achieved a CR, and median DFS and OS from time of remission was 3.1 months and 7.7 months, respectively.[150] The combination of high-dose cytarabine and idarubicin was evaluated as a salvage regimen in adult patients with relapsed/refractory ALL (N=29).[151] In this study, 11 patients (38%) achieved a CR and the median OS for responding patients was 8 months. Four patients who achieved a CR with salvage therapy proceeded to allogeneic HSCT. The median OS for all patients on the study was 6 months.[151]

A recent phase II study from the M.D. Anderson Cancer Center evaluated an augmented hyper-CVAD regimen (that incorporated asparaginase, intensified vincristine, and intensified dexamethasone) as salvage therapy in adults with relapsed/refractory ALL (N=90; median age 34 years, range 14-70 years; median 1 prior regimen).[152] Among evaluable patients (n=88), the CR rate was 47%; an additional 13% achieved a CRp and 5% achieved a partial remission. The 30-day mortality rate was 9%, and was lower among the subgroup who received pegasparaginase compared with those who received L-asparaginase (1% vs. 12%). Median remission duration was 5 months. The median OS for all evaluable patients was 6.3 months; median OS was 10.2 months for patients who achieved a CR. In this study, 32% of patients were able to proceed to HSCT.[152]

As previously discussed, nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-cell ALL who have not responded to or have relapsed after at least two chemotherapy regimens.[133] A phase II study of nelarabine monotherapy in children and adolescents with relapsed/refractory T-cell ALL or T-cell NHL (N=121) showed a 55% response rate among the subgroup with T-cell ALL with first bone marrow relapse (n=34) and a 27% response rate in the subgroup with ≥ second bone marrow relapse (n=36).[60] Major toxicities with this agent included ≥grade 3 neurologic (both peripheral and CNS) adverse events in 18% of patients. Nelarabine as single agent was also evaluated in adults with relapsed/refractory T-cell ALL or T-cell lymphoblastic leukemia in a phase II study (N=39; median age 34 years, range, 16-66 years; median 2 prior regimens; T-cell ALL, n=26).[62] The CR rate (include CRi) was 31%; an additional 10% of patients achieved a partial remission. The median DFS and OS were both 20 weeks. The 1-year OS rate was 28%. Grade 3 or 4 myelosuppression was common, but only 1 case of grade 4 CNS toxicity (reversible) was observed.[62]

Novel monoclonal antibodies are currently under clinical investigation. Inotuzumab ozogamicin is an anti-CD22 antibody-drug conjugate that has demonstrated high CR rates (57%) in patients with relapsed/refractory ALL (N=49).[153] Blinatumomab is a bispecific anti-CD3/CD19 monoclonal antibody that showed high CR rates (67%;

including rapid MRD-negative responses) in patients with relapsed/refractory B-precursor ALL (N=18).[154] In an earlier study, blinatumomab was shown to eliminate residual disease in patients with relapsed or MRD-positive B-precursor ALL following intensive chemotherapy (N=21).[155] These antibodies are investigational, and are not FDA approved for any indication.

Based on findings from evidence-based review of the published literature, the ASBMT guidelines recommend HSCT over chemotherapy alone for adult patients with ALL achieving a second CR.[156] Several studies have demonstrated that for AYA patients in second CR, allogeneic HSCT may improve outcomes, particularly for patients who have early bone marrow relapse or have other high-risk factors such as T-cell ALL.[143, 144, 157] In a retrospective analysis of children and adolescents (age 1 to 18 years) with precursor B-cell ALL achieving a second CR after bone marrow relapse, outcomes were compared between patients who underwent allogeneic HSCT (n=186) and patients who received chemotherapy regimens on the POG trials (n=188).[157] The study showed that among patients with early bone marrow relapse (<36 months from time of diagnosis), total body irradiation (TBI)-containing allogeneic HSCT was associated with significantly lower risks of a second relapse (relative risk [RR]: 0.49; 95% CI, 0.33-0.71; *P* <0.001) or overall mortality (RR: 0.58; 95% CI, 0.41-0.83; *P*=0.003) compared with chemotherapy regimens; this advantage with TBI-containing allogeneic HSCT was not observed among the subgroup with a late first relapse (≥ 36 months), and no advantages were seen with the use of non-TBI-containing HSCT regimens regardless of the timing of first relapse.[157] Thus, among patients with precursor B-cell ALL in second CR after early bone marrow relapse, TBI-containing allogeneic HSCT may improve outcomes compared with chemotherapy alone; however, for patients with late bone marrow relapse, there may be no advantage with HSCT over chemotherapy regimens.

A BFM study (BFM-87) evaluated long-term outcomes with intensive chemotherapy or HSCT (for poor prognosis disease) in patients with ALL relapsing after frontline treatment (N=207; age up to 18 years).[143] In this study, patients with poor prognosis included those having an early bone marrow relapse (defined as relapse occurring during therapy or up to 6 months after completion of frontline treatment) or T-cell ALL. The 15-year EFS rate and OS rate for the entire patient cohort was 30% and 37%, respectively.[143] The 10-year EFS rate was significantly higher among the patients who received allogeneic HSCT after second CR (n=27) compared with those who received chemotherapy/radiotherapy only (n=145; 59% vs 30%; *P*=0.026). All recipients of allogeneic HSCT received TBI as part of the conditioning regimen. Based upon multivariate regression analysis, the timing and site of relapse (with early relapse, and isolated bone marrow relapse associated with poor outcomes), T-cell lineage disease, and performance of HSCT were significant independent predictors of EFS outcomes.[143] The more recent BFM study (BFM-90) in patients with ALL relapsing after frontline therapy (N=525; age 1 to 18 years) further confirmed the benefits of allogeneic HSCT in second CR.[144] In this study, the timing of first relapse was defined as very early (within 18 months from initial diagnosis), early (>18 months from initial diagnosis and <6 months after completion of frontline therapy), and late (>6 months after completion of frontline treatment). The overall 10-year EFS rate and OS rate in this study was 30% and 36%, respectively.[144] Among the patients with high-risk disease (i.e., having early isolated bone marrow relapse, early combined bone marrow and extramedullary relapse, very early bone marrow relapse or T-cell lineage ALL regardless of relapse timing), patients who received chemoradiotherapy

alone had significantly shorter 10-year EFS (n=76; 20%) compared with patients who received HSCT (n=84; 33% EFS rate; *P*<0.005) or with the subgroup of patients who received HLA-compatible allogeneic HSCT (n=53; 40% EFS rate; *P*<0.001). This EFS benefit with HSCT (or with allogeneic HSCT) was not observed among the subgroup of patients with intermediate risk disease (i.e., late bone marrow relapse or isolated extramedullary relapse regardless of relapse timing). The preferred conditioning regimen for HSCT in this study included TBI.[144]

Somewhat contrastingly, the aforementioned COG study (CCG-1952) showed that prognosis after early bone marrow relapse remained poor in patients with standard-risk ALL (age 1 to <10 years of age and WBC count <50 × 10^9/L); no apparent advantage with HSCT was observed, regardless of timing (e.g., early or late) of bone marrow relapse.[145] For these patients with bone marrow relapse, no significant differences were observed in the EFS or OS rates between treatment with HSCT (n=77) or chemotherapy (n=81); the 2-year estimated EFS with HSCT and chemotherapy was 49.5% and 49%, respectively (*P*=0.39). Moreover, no significant differences in EFS rates were observed in the subgroup of patients with early or late bone marrow relapses.[145] It should be noted, however, that data were not available on the conditioning regimen used for HSCT in this study.

NCCN Recommendations for Ph-negative ALL

AYA patients (age 15-39 years) with Ph-negative ALL

The NCCN Guidelines panel recommends that AYA patients with Ph-negative ALL (regardless of risk group) be treated on a clinical trial, where possible. In the absence of an appropriate clinical trial, the recommended induction therapy would comprise multiagent chemotherapy regimens based on pediatric-inspired protocols such as the CCG-1961, PETHEMA ALL-96, GRAALL-2003, COG AALL-0434 (for T-cell ALL) regimens or the ongoing CALGB 10403 protocol. Treatment regimens should include adequate CNS prophylaxis for all patients. It is also important to adhere to the treatment regimens for a given protocol in its entirety, from induction therapy to consolidation/delayed intensification to maintenance therapy. Testing for *TPMT* gene polymorphism should be considered for patients receiving 6-mercaptopurine as part of maintenance therapy, especially in patients who experience severe bone marrow toxicities.

For patients achieving a CR following initial induction therapy, monitoring for MRD may be considered (see discussion section below on “NCCN Recommendations for MRD Assessment”). In these patients, continuation of the multiagent chemotherapy protocol for consolidation and maintenance would be appropriate (particularly for patients with MRD-negative remission after induction, if MRD is assessed). If a matched donor is available, consolidation with allogeneic HSCT may also be considered, particularly for patients with residual disease as assessed by MRD assays, or for those with high-risk disease features (i.e., WBC count ≥30 × 10^9/L for B-cell lineage; ≥100 × 10^9/L for T-cell lineage, hypodiploidy, or *MLL* rearrangements). The benefit of allogeneic HSCT in the setting of MRD-positive remission is unclear at the present time. For AYA patients achieving less than a CR following initial induction therapy (i.e., having primary refractory disease), the treatment approach would be similar to patients with relapsed/refractory ALL.

For patients with relapsed/refractory disease following an initial CR, the approach to second-line treatment may depend on the duration of the initial response. For late relapses (i.e., relapse occurring ≥36 months from initial diagnosis), re-treatment with the same induction regimen may be reasonable. Participation in a clinical trial is preferred, where possible. In the absence of an appropriate trial, the patient may be considered for second-line therapy with induction regimens not

previously used, salvage chemotherapy (with regimens containing clofarabine, nelarabine [for T-cell ALL], cytarabine or alkylating agents) or allogeneic HSCT (if a second CR is achieved).

Adult patients (age ≥40 years) with Ph-negative ALL

For adult patients with Ph-negative ALL, the NCCN Guidelines panel also recommends treatment on a clinical trial, where possible. In the absence of an appropriate clinical trial, the recommended treatment approach would initially depend on the patient's age and/or presence of comorbid conditions. As previously mentioned, treatment regimens should include adequate CNS prophylaxis for all patients, and a given treatment protocol should be followed in its entirety, from induction therapy to consolidation/delayed intensification to maintenance therapy. Again, testing for *TPMT* gene polymorphism should be considered for patients receiving 6-mercaptopurine as part of maintenance therapy, especially in patients who develop severe bone marrow toxicities.

Although the age cut-off indicated in the Guidelines has been set at 65 years, it should be noted that chronological age alone is not a sufficient surrogate for defining fitness; patients should be evaluated on an individual basis to determine fitness for therapy based on factors such as performance status, end-organ function and end-organ reserve.

For relatively fit patients (age <65 years or with no substantial comorbidities), the recommended treatment approach is similar to that of AYA patients. Induction therapy would comprise multiagent chemotherapy such as those based on protocols from the CALGB 8811 study (Larson regimen), the Linker regimen, hyper-CVAD (with or without rituximab), or the MRC UK ALL XII/ECOG 2993 study. For patients achieving a CR following initial induction therapy, monitoring for MRD may be considered (see discussion section below on "NCCN Recommendations for MRD Assessment"). In these patients, continuation of the multiagent chemotherapy protocol for consolidation and maintenance would be appropriate (particularly for patients with MRD-negative remission after induction, if MRD is assessed). If a matched donor is available, consolidation with allogeneic HSCT may be considered for patients with residual disease as assessed by MRD assays, although the benefit of allogeneic HSCT in this setting is unclear at the present time. In addition, allogeneic HSCT may also be considered for relatively fit adult patients (age <65 years or with no substantial comorbidities) with high-risk disease features (i.e., WBC count ≥30 × 10^9/L for B-cell lineage; ≥100 × 10^9/L for T-cell lineage, hypodiploidy, or *MLL* rearrangements). It should be noted that the effect of WBC counts on prognosis in adult patients with ALL is less firmly established than in pediatric populations. For adult patients achieving less than a CR following initial induction therapy, the treatment approach would be similar to patients with relapsed/refractory ALL (as discussed below).

For patients who are less fit (age ≥65 years or with substantial comorbidities), the recommended induction therapy includes multiagent chemotherapy regimens or corticosteroids. Dose modifications may be required for chemotherapy agents, as needed. Patients with a CR to induction should continue consolidation with chemotherapy regimens; maintenance therapy (typically, weekly methotrexate, daily 6-mercaptopurine, and monthly pulses of vincristine/prednisone for 2-3 years) is recommended. For patients with less than a CR to induction, the treatment option would be similar to patients with relapsed/refractory ALL.

For patients with relapsed/refractory disease following an initial CR, participation in a clinical trial is preferred, where possible. In the absence of an appropriate trial, the patient may be considered for second-line therapy with induction regimens not previously used,

salvage chemotherapy (with regimens containing clofarabine, nelarabine [for T-cell ALL], cytarabine or alkylating agents) or allogeneic HSCT (if a second CR is achieved) for patients who are physically fit enough to undergo transplantation.

For recommendations on the treatment of adult patients with mature B-cell ALL, refer to the NCCN Guidelines for NHL, under Burkitt's lymphoma.

Evaluation and Treatment of Extramedullary Disease

CNS Involvement in ALL

Although the presence of CNS involvement at the time of diagnosis is uncommon (about 3% to 7%), a substantial proportion of patients (>50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.[1, 26] CNS leukemia is defined by the presence of WBC ≥5/mcL in the cerebrospinal fluid with presence of lymphoblasts.[1, 26] In children with ALL, CNS leukemia at diagnosis was associated with significantly decreased EFS rates.[40, 128, 158] Factors associated with increased risks for CNS leukemia in children include T-cell immunophenotype, high presenting WBC counts, Ph-positive disease, t(4;11) translocation, and presence of leukemic cells in the cerebrospinal fluid.[45] In adults with ALL, CNS leukemia at diagnosis has been associated with significantly higher risk for CNS relapse in large trials, although no differences were observed for 5-year EFS or DFS rates compared with subgroups without CNS leukemia at presentation.[159, 160] CNS leukemia at diagnosis was associated with significantly decreased 5-year OS rate in one trial (29% vs 38%; P=0.03)[159] but not in another trial (35% vs 31%).[160] Factors associated with increased risks for CNS leukemia in adults include mature B-cell immunophenotype, T-cell immunophenotype, high presenting WBC counts, and elevated serum lactate dehydrogenase (LDH) levels.[21, 159]

CNS-directed therapy may include cranial irradiation, intrathecal chemotherapy (e.g., methotrexate, cytarabine, corticosteroids) and/or high-dose systemic chemotherapy (e.g., methotrexate, cytarabine, mercaptopurine, L-asparaginase).[1, 26, 45]

Although cranial irradiation is an effective treatment modality for CNS leukemia, it can be associated with serious adverse events such as neuro-cognitive dysfunctions, secondary malignancies, and other long-term complications.[1, 45] With the increasing use of effective intrathecal chemotherapy and high-dose systemic chemotherapy regimens, studies have examined the feasibility of eliminating cranial irradiation as part of CNS prophylaxis. In studies of children with ALL who only received intrathecal and/or intensive systemic chemotherapy for CNS prophylaxis, the 5-year cumulative incidence of isolated CNS relapse or any CNS relapse was 3%-4% and 4%-5%, respectively.[38, 128] In adult patients with ALL who only received intrathecal chemotherapy and intensive systemic chemotherapy for CNS prophylaxis, the overall CNS relapse rate was 2%-6%.[8, 10, 47, 161] Therefore, with the incorporation of adequate systemic chemotherapy (e.g., high-dose methotrexate and cytarabine) and intrathecal chemotherapy regimens (e.g., methotrexate alone or with cytarabine and corticosteroid, which constitutes the triple intrathecal regimen), it is possible to avoid the use of upfront cranial irradiation except in cases of overt CNS leukemia at presentation, and to reserve the use of irradiation for salvage therapy settings. CNS prophylaxis is typically given throughout the course of ALL therapy starting from induction, consolidation, to the maintenance phases of treatment.

NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement

Given the risks of neurological adverse events associated with CNS-directed therapy, comprehensive neuropsychological testing may be

useful at baseline and during post-treatment follow up. CNS involvement should be evaluated by lumbar puncture at the appropriate timing in accordance with the specific treatment protocol used for each patient. Pediatric-inspired treatment regimens typically include lumbar puncture at the time of diagnostic workup. The NCCN Guidelines panel recommends that lumbar puncture, if performed, be performed concomitantly with initial intrathecal therapy. All patients being treated for ALL should receive adequate CNS prophylaxis with intrathecal therapy and/or systemic therapy that incorporates methotrexate.

The classification of CNS status includes the following: CNS-1 refers to no lymphoblasts in the CSF regardless of WBC count; CNS-2 is defined as WBC <5/mcL in CSF with presence of blasts; and CNS-3 is defined as WBC ≥5/mcL with presence of blasts. If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic (containing ≥5/mcL WBCs in CSF with blasts), then the Steinherz-Bleyer algorithm can be used to determine the CNS classification (if the WBC/RBC ratio in the CSF is at least two-fold greater than the WBC/RBC ratio in the blood, then the classification would be CNS-3; if not, the classification would be CNS-2).

In general, patients with CNS involvement at diagnosis (i.e., CNS-3) should receive 18 Gy of cranial irradiation. In younger AYA patients with high-risk ALL (i.e., evidence of t(9;22) or BCR-ABL; t(4;11) or MLL-AF4) or T-cell ALL, use of prophylactic cranial irradiation may be an option. It should be noted that areas of the brain targeted by the radiation field in the management of patients with ALL are different from those targeted for brain metastases of solid tumors. In addition, patients with CNS leukemia at diagnosis should receive adequate systemic therapy, as well as intrathecal therapy containing methotrexate throughout the treatment course. Adequate systemic therapy should also be given in the management of patients with isolated CNS or testicular relapse.

A testicular exam should be performed for all male patients at the time of diagnostic workup; testicular involvement is especially common among patients with T-cell ALL. Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of induction therapy should be considered for radiation to the testes. Radiation therapy is typically performed concurrently with the first cycle of maintenance chemotherapy.

Response Assessment and Surveillance

Response Criteria

Response in Bone Marrow and Peripheral Blood

A complete response (CR) requires the absence of circulating blasts and absence of extramedullary disease (i.e., no lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, or CNS involvement). A bone marrow assessment should show trilineage hematopoiesis and <5% blasts. For a CR, absolute neutrophile counts (ANC) should be >1.0 × 10^9/L and platelet counts should be >100 × 10^9/L. In addition, no recurrence should be observed for at least 4 weeks. A patient is considered to have a CR with incomplete recovery of counts (CRi) if criteria for CR are met except for ANC <1.0 × 10^9/L or platelets <100 × 10^9/L.

Refractory disease is defined as failure to achieve a CR at the end of induction therapy. Progressive disease is defined as an increase of at least 25% in the absolute number of circulating (in peripheral blood) or bone marrow blasts, or the development of extramedullary disease. Relapsed disease is defined as the reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after achievement of a CR.

Response in CNS Disease

Remission of CNS disease is defined as achievement of CNS-1 status (no lymphoblasts in CSF regardless of WBC count) in a patient with CNS-2 (WBC count <5 /mcL in CSF with presence of blasts) or CNS-3 (WBC count ≥5 /mcL in CSF with presence of blasts) at diagnosis. CNS relapse is defined as development of CNS-3 status or development of clinical signs of CNS leukemia (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome).

Response in Mediastinal Disease

A CR of mediastinal disease is defined as complete resolution of mediastinal enlargement by CT scan. An unconfirmed CR (CRu) is defined as residual mediastinal enlargement that has regressed by >75% in the sum of the products of the greatest perpendicular diameters (SPD). A partial response (PR) is defined as >50% decrease in the SPD of mediastinal enlargement. Progressive disease is defined as >25% increase in the SPD. No response indicates failure to meet the criteria for a PR and not having progressive disease (as defined above). Relapsed mediastinal disease is defined as recurrence of mediastinal enlargement after achievement of a CR or CRu.

Surveillance

Following completion of the ALL treatment regimen (including maintenance therapy), the NCCN Guidelines panel recommends surveillance at regular intervals to assess disease status. During the first year after completion of therapy, patients should undergo a complete physical exam and blood tests (CBC with differential) on a monthly basis. Liver function tests should be performed every 2 months until normal values are achieved. Assessment of bone marrow aspirate, CSF, and echocardiogram should be performed as clinically indicated; if a bone marrow aspirate is performed, comprehensive cytogenetics (including FISH), flow cytometry and molecular tests should be considered. During the second year after completion of therapy, a physical exam (including a testicular exam for all male patients) and blood tests (CBC with differential) should be performed every 3 months. During the third year (and beyond) after completion of therapy, physical exam (including a testicular exam for all male patients) and blood tests (CBC with differential) can be performed every 6 months or as clinically indicated.

The COG has recently published guidelines on long-term survivorship issues for survivors of childhood cancers.[162] These guidelines serve as a resource for clinicians and family members/caretakers, and aim to provide screening and management recommendations for late effects (e.g., those that may impact growth, cognitive function, emotional concerns, reproductive health, risks for secondary malignancies, and other important health issues) that may arise during the lifetime of an AYA cancer survivor as a result of the therapeutic agents used during the course of anti-tumor treatment.

Role of Minimal Residual Disease (MRD) Evaluation

MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow, up to 10^{10} malignant cells.[9, 163]

The most frequently employed methods for MRD assessment include multicolor flow cytometry to detect abnormal immunophenotypes and polymerase chain reaction (PCR) assays to detect clonal rearrangements in immunoglobulin heavy chain genes and/or T-cell receptor genes. Current flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ (<0.01%) bone marrow mononuclear cells. The concordance rate for detecting MRD

between these methods is high. In a study that analyzed MRD using both flow cytometry and PCR in 1375 samples from 227 patients with ALL, the concordance rate for MRD assessment (based on a detection threshold of $<1 \times 10^{-4}$ for both methods) was 97%.[164] The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.[164, 165] However, high-sensitivity PCR assays require the identification of patient-specific markers that involve direct sequencing, and may therefore be labor- and resource-intensive for routine application in the clinical practice setting. Numerous studies in both childhood and adult ALL have demonstrated the prognostic importance of post-induction (and/or post-consolidation) MRD measurements in predicting likelihood of disease relapse.

MRD Assessment in Childhood ALL

Among children with ALL who have a CR by morphologic evaluation following induction therapy, approximately 25% to 50% may still have detectable MRD based on sensitive assays (in which the threshold of MRD negativity is $<1 \times 10^{-4}$ bone marrow mononuclear cells).[166, 167] An early study in children with ALL (N=178) showed that patients with detectable MRD following initial induction therapy (42% of patients) had significantly shorter time to relapse than patients with MRD-negative status ($P<0.001$), where MRD negativity was defined based on a sensitivity level $<1.5 \times 10^{-4}$ by PCR methods.[168] Patients with MRD after induction also had a 10-fold increase in risk of death compared with those without detectable MRD. Moreover, the level of detectable MRD was found to be correlated with relapse; patients with MRD $\geq 1 \times 10^{-2}$ had a 16-fold higher risk of relapse compared with patients who had MRD levels $<1 \times 10^{-3}$.[168] In another study in children with ALL (N=158), patients with detectable MRD (measured by flow cytometry with sensitivity level $<1 \times 10^{-4}$) at the end of induction therapy had a significantly higher 3-year cumulative incidence of relapse compared with those who were MRD negative (33% vs 7.5%; $P<0.001$).[169] Subsequent studies have confirmed these findings. In a study of patients (N=165) with MRD assessment (measured by flow cytometry with sensitivity level $<1 \times 10^{-4}$) following induction therapy, the 5-year relapse rate was significantly higher among patients with MRD versus those without detectable disease (43% vs 10%; $P<0.001$).[167] In addition, the persistence of MRD during the course of therapy was associated with risks of relapse in this study; the cumulative rate of relapse was significantly higher among patients with MRD persisting through week 14 of continued treatment compared with patients who became MRD-negative by this time point (68% vs 7%; $P=0.035$).[167] MRD evaluation was shown to be a significant independent predictor of outcomes in this study. MRD assessments at an earlier time point in the course of treatment (e.g., during induction therapy) was also shown to be highly predictive of outcomes in children with ALL. In one study, nearly 50% of patients had MRD clearance (in which MRD negativity was defined as $<1 \times 10^{-4}$ by flow cytometry) by day 19 of induction therapy (about 2-3 weeks from initiation of induction); the 5-year cumulative incidence of relapse was shown to be significantly higher among patients with MRD at day 19 of treatment compared with those without detectable MRD (33% vs 6%; $P<0.001$).[166] More recently, the prognostic significance of MRD detection at lower levels (sensitivity threshold $\leq 1 \times 10^{-5}$, or ≤0.001%, by PCR) was evaluated in children with B-cell lineage ALL treated with contemporary regimens.[170] At the end of induction therapy, 58% of patients had undetectable disease by PCR. Among the remaining patients with detectable MRD, 17% had MRD ≥0.01%, 14% had <0.01% (but ≥0.001%) and 11% had <0.001%. The 5-year cumulative incidence of relapse was significantly higher among patients with MRD ≥0.01% versus those with <0.01% or undetectable disease (23% vs 6%; $P<0.001$).[170] Furthermore, the 5-

year cumulative incidence of relapse was significantly higher among the subgroup of patients with MRD <0.01% (but ≥0.001%) compared with those with MRD <0.001% or undetectable disease (13% vs 5%; *P*<0.05). MRD status at the end of induction therapy was strongly correlated with MRD levels (measured by flow cytometry with sensitivity level <0.01%) at day 19 during induction; all patients who had MRD ≥0.01% at end of induction had ≥0.01% at day 19 based on flow cytometry. Although this study showed a higher risk of relapse among the patients with MRD below the generally accepted threshold level (<0.01% but ≥0.001%) compared with those with very low MRD (<0.001%) or no detectable disease, it is unknown whether this lower threshold should be used to risk stratify patients or guide decisions surrounding treatment intensification.[170]

In one of the largest collaborative studies conducted in Europe (the AIEOP-BFM ALL 2000 Study), children with Ph-negative B-cell lineage ALL (N=3184 evaluable) were risk stratified according to MRD status (measured by PCR with sensitivity level ≤0.01%) at 2 time points, day 33 and day 78, which were then used to guide post-induction treatment.[171] Patients were considered standard risk if MRD negativity (≤0.01%) was achieved at both days 33 and 78, intermediate risk if MRD >0.01% (but <0.1%) on either day 33 or day 78 (the other time point being MRD negative) or on both days 33 and 78, and high risk if MRD ≥0.1% on day 78. Nearly all patients with favorable cytogenetic/molecular markers such as the *TEL-AML1* subtype or hyperdiploidy were either standard risk or intermediate risk based on MRD evaluation.[171] The 5-year EFS rate was 92% for patients categorized as standard risk (n=1348), 78% for intermediate risk (n=1647), and 50% for high risk patients (n=189; *P*<0.001); the 5-year OS rate was 98%, 93%, and 60%, respectively. MRD-based risk stratification was able to significantly differentiate risks for relapse (between standard versus intermediate risk subgroups) even among patient populations with *TEL-AML1* or hyperdiploidy. Importantly, MRD remained a significant and powerful independent prognostic factor for relapse in the overall population in this large-scale collaborative study.[171]

Several studies have suggested that an early assessment of MRD during induction treatment (e.g., day 15 from initiation of treatment) may be highly predictive of subsequent relapse in children with ALL.[172, 173] This raises the possibility of identifying high-risk patients who may potentially benefit from earlier intensification or tailoring of treatment regimens, or for potentially allowing less intensive treatments to be administered in patients at low risk for relapse based on early MRD measurements. Large trials are warranted to address these possibilities, although it is very likely that serial MRD measurements would still be needed to monitor leukemic cell kinetics during the long course of treatment in ALL.

Approximately 20% of children treated with intensive therapies for ALL will ultimately experience disease relapse.[174] MRD assessment may also play a prognostic role in the management of patients in the relapsed setting.[175, 176] In patients (N=35) who achieved second remission (morphologic CR) following re-induction treatment, MRD (measured by flow cytometry with sensitivity level <0.01%) after re-induction (day 36) was significantly associated with risks for relapse; the 2-year cumulative incidence of relapse was 70% among patients with MRD ≥0.01% versus 28% among those with MRD <0.01% (*P*=0.008).[175] In addition, among the subgroup of patients who experienced first relapse after cessation of treatment, the 2-year cumulative incidence of second relapse was 49% among patients with MRD ≥0.01% versus 0% for those with MRD <0.01% (*P*=0.014). Both the presence of MRD at day 36 of re-induction therapy and first relapse

occurring during therapy were significant independent predictors of second relapse based on multivariate analysis.[175] In another study, MRD (measured by PCR with sensitivity level <0.01%) was evaluated in high-risk children with ALL (N=60) who experienced first relapse within 30 months from the time of diagnosis.[176] Categories based on MRD evaluation after the first chemotherapy cycle (3 to 5 weeks after initiation of re-induction treatment) included MRD negativity (undetectable MRD), MRD positive but unquantifiable (levels <0.01%), and MRD ≥0.01%. The 3-year EFS rate based on these MRD categories was 73%, 45%, and 19%, respectively (P<0.05).[176] Thus, MRD assessment can identify patients with a high probability of second relapse, which may offer an opportunity for risk-adapted second-line treatment strategies in such patients.

MRD Assessment in Adult ALL

Studies in adults with ALL have also demonstrated the strong correlation between MRD and risks for relapse, and the prognostic significance of MRD measurements during and after initial induction therapy.[163, 177-180] In an analysis of post-induction MRD (measured by flow cytometry with sensitivity level <0.05%) in adult patients with ALL (N=87), median relapse-free survival was significantly longer among patients with MRD <0.05% at day 35 compared with those with MRD ≥0.05% (42 months vs 16 months; P=0.001).[180] A similar pattern emerged when only the subgroup of patients with morphologic CR at day 35 was included in the MRD evaluation. Additionally, although patient numbers were limited, 90% of patients with MRD <0.03% at an earlier time point (at day 14, during induction therapy) remained relapse-free at 5 years.[180] MRD following induction therapy was also found to be significantly predictive of relapse in a subgroup analysis from the UK MRC/ECOG study. In patients with Ph-negative B-cell lineage ALL (N=161) whose data were analyzed for MRD evaluation (measured by PCR with sensitivity level <0.01%), the 5-year relapse-free survival rate was significantly higher in patients with MRD negativity versus those with MRD ≥0.01% (71% vs 15%; P=0.0002).[179] Post-induction MRD has been shown to serve as a significant independent predictor of relapse even among adult patients considered to be at standard risk based on traditional prognostic factors. In a study of adult patients with Ph-negative ALL (N=116 evaluable), MRD status following induction therapy (measured by flow cytometry with sensitivity level <0.1%) was significantly predictive of relapse regardless of whether the patient was considered at standard risk or high risk at initial evaluation.[178] Among the patients who were initially classified as having standard risk, those with MRD <0.1% after induction had significantly lower risk of relapse at 3 years compared with patients with higher levels of MRD (9% vs 71%; P=0.001). Interestingly, this study also showed that MRD measured during the post-consolidation time point was not significantly predictive of outcomes.[178] In a study by the German Multicenter ALL (GMALL) Study Group, patients with standard risk disease (N=148 evaluable) were monitored for MRD (measured by PCR with sensitivity level <0.01%) at various time points during the first year of treatment (GMALL 06/99 study).[177] Only patients with ALL who met all of the following criteria for standard risk were enrolled in this study: absence of t(4;11) *MLL* translocation or t(9;22) *BCR-ABL* translocation; WBC count <30 × 10^9/L for B-cell lineage ALL or <100 × 10^9/L for T-cell lineage ALL; age 15 to 65 years; and achievement of morphologic CR after phase I of induction treatment. At the end of initial induction therapy (at day 24), patients with MRD ≥0.01% had a 2.4-fold higher risk (95% CI, 1.3-4.2) of relapse compared with patients with MRD <0.01%.[177] Moreover, this study indentified distinct risk groups according to MRD status at various time points. Patients categorized as low risk (10% of study patients) had MRD <0.01% at both day 11 and day 24 (during and after initial induction), and had a 3-year DFS rate

and OS rate of 100% (for both endpoints). Patients in the high-risk group (23%) had MRD ≥0.01% persisting through week 16, and had a 3-year DFS and OS rate of only 6% and 45%, respectively. All other patients (67%) were categorized as having intermediate risk, and had a 3-year DFS and OS rate of 53% and 70%, respectively.[177] Importantly, a multivariate Cox regression analysis that included gender, age, WBC count, B- or T-cell lineage, and MRD in the model demonstrated that MRD was the only independently significant predictor of outcomes in this patient population. Thus, MRD evaluation post-induction may provide further risk stratification information among patients who are otherwise considered standard risk by traditional evaluation of prognostic factors.

MRD assessment following consolidation therapy has also been shown to have prognostic significance, offering the possibility to adjust post-consolidation treatment approaches. In a recent study that evaluated MRD (measured by PCR with sensitivity level <0.01%) after consolidation therapy (weeks 16 to 22 from initiation of induction) in adult patients with ALL (N=142), patients with MRD <0.01% (n=58) were primarily allotted to receive maintenance chemotherapy for 2 years while those with MRD ≥0.01% (n=54) were eligible to undergo allogeneic HSCT following high-dose therapy.[181] The 5-year DFS rate was significantly higher among patients with MRD negativity versus those with MRD ≥0.01% (72% vs 14%; *P*=0.001); similarly, the 5-year OS rate was significantly higher for patients with MRD negative status post-consolidation (75% vs 33%; *P*=0.001).[181] In a follow-up study of the GMALL 06/99 study mentioned earlier, patients with standard risk ALL (as defined by Bruggemann et al[177]) who achieved MRD negativity (<0.01% leukemic cells by PCR) during the first year of treatment underwent sequential MRD monitoring during maintenance therapy and follow up.[182] Among the patients included in this analysis (N=105), 28 patients (27%) became MRD positive after the first year of therapy; MRD was detected prior to hematological relapse in 17 of these patients.[182] The median relapse-free survival was 18 months (calculated from the end of initial treatment) among the subgroup that became MRD positive, whereas the median has not yet been reached among patients who remained MRD negative. The median time from MRD positivity (at any level, including non-quantifiable cases) to clinical relapse was 9.5 months; the median time from quantitative MRD detection to clinical relapse was even shorter, at 4 months.[182] This study showed that detection of post-consolidation MRD was highly predictive of subsequent hematological relapse and introduced the concept of 'molecular relapse' in ALL. However, the potential advantage of intensifying or modifying treatment regimens (e.g., incorporation of allogeneic HSCT) based on identification of a molecular relapse remains to be investigated.

Studies in children and adult patients with ALL suggest that differences may exist in the kinetics of leukemic cell eradication between these two patient populations. Among children treated on contemporary regimens, about 60% to 75% of patients achieved clearance of MRD (by sensitive flow cytometry or PCR assays) at the end of induction therapy (typically corresponding to 5 to 6 weeks after initiation of induction).[166-170, 183] In one study, nearly 50% of children had MRD clearance (<0.01% by flow cytometry) at day 19 of induction therapy.[166] Adult patients appear to have a slower rate of leukemic cell clearance compared with children, with about 30% to 50% of adult patients having MRD negativity after initial induction.[177, 180] About 50% of patients remained MRD positive at 2 months following initiation of induction, with further reductions in proportion of MRD-positive patients occurring beyond 3 to 5 months.[163, 177] Such differences in the kinetics of leukemic cell reduction in the bone marrow may, at least in part, be attributed to differences in

therapeutic regimens, variations in the distribution of immunophenotypic or cytogenetic/molecular features, and other host factors.

NCCN Recommendations for MRD Assessment

Collectively, the studies above demonstrate the high prognostic value of MRD in assessing risks for relapse in patients with ALL, and the potential role of MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies. As previously discussed, current flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of <1 × 10^{-4} (<0.01%) bone marrow mononuclear cells (MNCs).[184, 185] The concordance rate for detecting MRD between these methods is high. It should be noted, however, that high-sensitivity PCR assays (for analysis of Ig or TCR gene rearrangements) require the identification of patient-specific markers that involve direct sequencing, and may therefore be labor- and resource-intensive for routine application in the clinical practice setting. Recommendations on the minimal technical requirements for MRD assessment (both for PCR and flow cytometry methods) and definitions for response based on MRD results (e.g., MRD negativity, non-quantifiable MRD positivity, quantifiable MRD positivity) have recently been published as a result of a consensus meeting held by ALL study groups across Europe.[184] The recommendations were made in an effort to standardize MRD measurements and reporting of MRD data within the context of clinical trials. The NCCN Guidelines panel strongly recommends that MRD assessments be performed at specialized treatment centers with access to reference laboratories that have expertise in MRD assays.

The timing of MRD assessment varies depending on the ALL treatment protocol being used, and may occur during or after completion of initial induction therapy. If MRD is being evaluated, the initial measurement should be performed upon completion of induction therapy; additional time points for MRD evaluation may be useful depending upon the specific treatment protocol or regimen used. For MRD evaluation by multicolor flow cytometry, sampling of bone marrow MNCs is preferred over peripheral blood samples. At least 1 × 10^6 MNCs are required for analysis (about 2 mL of bone marrow or 5-10 mL of peripheral blood provides sufficient number of cells for multiple analysis).[184, 185] For MRD evaluation by RQ-PCR, sampling of bone marrow MNC is preferred. At least 1 × 10^7 MNCs are required for initial marker characterization and generation of individual dilution series; 1 × 10^6 MNCs are sufficient for follow-up analysis.[184] The minimal limit of assay sensitivity (to declare MRD negativity) should be <1 × 10-4 (<0.01%).

Supportive Care for Patients with ALL

Given the highly complex and intensive treatment protocols used in the management of ALL, supportive care issues are important considerations to ensure that patients derive the most benefit from ALL therapy. Although differences may exist between institutional standards and practices, supportive care measures for patients with ALL generally include the use of antiemetics for prevention of nausea and vomiting, blood product transfusions or cytokine support for severe cytopenias, nutritional support for prevention of weight loss, gastroenterology support, pain management, prevention and management of infectious complications, and prophylaxis for tumor lysis syndrome. In addition, both short-term and long-term consequences of potential toxicities associated with specific agents used in ALL regimens should also be considered. These include the use of steroids (e.g., risks for hyperglycemia or peptic ulcerations in the acute setting; risks for osteonecrosis or avascular necrosis with long-term use) and asparaginase (e.g., risks for hypersensitivity reactions, hyperglycemia, coagulopathy, hepatotoxicity, and/or pancreatitis). Supportive care

measures should be tailored to meet the individual needs of each patient based on factors such as age, performance status, extent of cytopenias prior to and during therapy, risks for infectious complications, disease status and the specific agents used in the ALL treatment regimen (see Guidelines section on "Supportive Care").

NCCN Recommendations for Supportive Care

Most chemotherapy regimens used in ALL contain agents that are at least moderately emetogenic, which may necessitate antiemetic support prior to initiating emetogenic chemotherapy. Antiemesis prophylaxis may include the use of such agents as serotonin (5-HT3) receptor antagonists, corticosteroids, and/or neurokinin-1 (NK1)–receptor antagonists. Recommendations for antiemetic support for patients receiving chemotherapy are available via the NCCN Guidelines for Antiemesis. For patients with ALL, the routine use of corticosteroids as part of antiemetic therapy should be avoided given that steroids constitute a major component of ALL regimens. For patients experiencing >10% weight loss, enteral or parenteral nutritional support should be considered. Regimens to maintain bowel movement and to prevent the occurrence of constipation may need to be considered for some patients. Daily doses of docusate sodium may be useful, and laxatives should be administered promptly when symptoms arise.

For patients requiring transfusion support for severe or prolonged cytopenias, only irradiated blood products should be used. Growth factor support (G-CSF; filgrastim 5 mcg/kg/day subcutaneously) is recommended during blocks of myelosuppressive therapy or as directed by the treatment protocol being followed for individual patients.

Patients with ALL undergoing intensive chemotherapy or allogeneic HSCT are highly susceptible to infections. Immunosuppression due to the underlying disease and therapeutic regimens can predispose patients to common bacterial and viral infections, as well as to various opportunistic infections (e.g., candidiasis, invasive mold infections, *P.jirovecii*, CMV reactivation and infection), particularly during periods of prolonged neutropenia. Patients with ALL should be closely monitored for any signs or symptoms of infections. Cases of febrile neutropenia should be managed promptly with empiric antiinfectives and inpatient admission. Recommendations for the prevention and management of infections in patients with cancer are available via the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections. For patients with ALL, antibacterial prophylaxis with a fluoroquinolone (levofloxacin is preferred) should be considered in those with expected duration of neutropenia (ANC <1000/mcL) of more than 7 days. Antiviral prophylaxis (acyclovir, valacyclovir, or famciclovir) is recommended in HSV-seropositive patients receiving induction/consolidation chemotherapy, and during neutropenia and at least 30 days after allogeneic HSCT. A longer period of prophylaxis may need to be considered in allogeneic HSCT recipients with GVHD or with frequent HSV reactivations before transplantation. In addition, VZV prophylaxis with acyclovir during the 12-month period after allogeneic HSCT may be recommended in patients who are VZV-seropositive pretransplant; agents used for HSV prophylaxis are generally also active against VZV. Antifungal prophylaxis with fluconazole (category 2A) or amphotericin B agents (category 2B) should be considered for all patients with ALL treated with chemotherapy (see the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections). If an amphotericin B product is used for antifungal prophylaxis, a lipid formulation is generally preferred because of less infusional and renal toxicity compared to conventional amphotericin B. Antifungal prophylaxis with posaconazole, itraconazole, and voriconazole should be avoided in patients receiving vinca alkaloids (e.g., vincristine, which is included as a component of nearly

all treatment regimens for ALL) because of the potential of these azoles to inhibit the cytochrome P450 3A4 isoenzyme, potentially reducing clearance of vinca alkaloids. Fluconazole prophylaxis has been shown to be effective in controlling yeast colonization and decreasing the rate of mucosal candidiasis and invasive *Candida* infections in patients receiving allogeneic HSCT.[186-188] For patients undergoing allogeneic HSCT, antifungal prophylaxis with fluconazole or micafungin (both category 1) should be considered until at least day 75 after HSCT; other azoles or amphotericin B agents in this setting are considered category 2B recommendations (see the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections).Trimethoprim/sulfamethoxazole (TMP-SMX) for *P.jirovecii* prophylaxis is effective in preventing *Pneumocystis* pneumonia in patients with acute leukemias,[189, 190] and should be considered for all patients receiving chemotherapy for ALL. CMV monitoring and pre-emptive therapy anti-CMV therapy with IV ganciclovir, IV foscarnet or oral valganciclovir should also be considered for all patients; in particular, routine CMV monitoring and pre-emptive therapy is strongly recommended for patients undergoing allogeneic HSCT until at least 6 months after transplantation. Additional CMV surveillance should be strongly considered during chronic GVHD requiring immunosuppressive therapy and until the CD4+ count is 100/mcL or greater (see the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections). It is important to note that the local susceptibility and resistance patterns of pathogens must be considered in the choice of antiinfective agents used for the prevention or treatment of infections.

Patients with ALL may be at high risk for developing acute tumor lysis syndrome (TLS), particularly those with highly elevated WBC counts prior to induction chemotherapy. TLS is characterized by metabolic abnormalities stemming from the sudden release of intracellular contents into the peripheral blood due to cellular disintegration induced by chemotherapy. If left untreated, TLS can result in profound metabolic changes leading to cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death. Recommendations for the management of TLS are available under the “Tumor Lysis Syndrome” section of the NCCN Guidelines for NHL. The standard prophylaxis for TLS includes hydration with diuresis, alkalinization of the urine, and treatment with allopurinol or rasburicase. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or with evidence of impaired renal function. Although relatively uncommon in patients with ALL, symptomatic hyperleukocytosis (leukostasis) constitutes a medical emergency and requires immediate treatment, as recommended in the NCCN Guidelines for AML. Leukostasis is characterized by highly elevated WBC count (usually >100 × 10^9/L) and symptoms of decreased tissue perfusion that often affects respiratory and CNS function. Although leukapheresis is not typically recommended in the routine management of patients with high WBC counts, it can be considered with caution in cases of leukostasis unresponsive to other interventions.

Key components of the ALL treatment regimen, such as corticosteroids and asparaginase, are associated with unique toxicities that require close monitoring and management. Corticosteroids such as prednisone and dexamethasone constitute a core component of nearly all ALL induction regimens, and are also frequently incorporated into consolidation and/or maintenance regimens. Acute side effects of steroids may include hyperglycemia and steroid-induced diabetes mellitus. Patients should be monitored for glucose control using the Insulin Sliding Scale (ISS) to minimize the risks for developing infectious complications. Another acute side effect of steroid therapy includes peptic ulceration and dyspeptic symptoms; the use of

histamine-2 (H2) receptor antagonist or proton pump inhibitors are recommended during steroid therapy to reduce these risks. A potential long-term side effect associated with steroid therapy includes osteonecrosis/avascular necrosis. Osteonecrosis most often affects weight-bearing joints such as the hip and/or the knee, and appears to have a higher incidence among adolescents (presumably due to the period of skeletal growth) than in younger children or adults.[191-193] Routine measurements for vitamin D and calcium levels should be obtained, and periodic radiographic evaluation (using plain films or MRI) should be considered in order to monitor the risks for osteonecrosis.

Asparaginase is also a core component of ALL regimens, most often given during induction and consolidation for Ph-negative disease. Several different formulations of the enzyme are available, including the native asparaginase derived from *E. coli*, a pegylated form of the *E. coli*-derived asparaginase, polyethylene glycol (PEG)-asparaginase, and *Erwinia* asparaginase derived from a different Gram-negative bacteria *Erwinia chrysanthemi*. These formulations differ in their pharmacologic properties, and may also differ in terms of immunogenicity.[194-196] Regardless of the formulation, asparaginase can be associated with potentially severe hypersensitivity reactions (including anaphylaxis) arising from the production of anti-asparaginase antibodies. PEG-asparaginase appears to be associated with a lower incidence of neutralizing antibodies compared with native asparaginase.[197] However, cross reactivity between neutralizing antibodies against native *E. coli* asparaginase and PEG-asparaginase have been reported.[198, 199] Moreover, a recent study showed that high anti-asparaginase antibody level following initial therapy with native *E. coli* asparaginase was associated with decreased asparaginase activity during subsequent therapy with PEG-asparaginase.[200] In contrast, no cross reactivity between antibodies against native *E. coli* asparaginase and *Erwinia* asparaginase was reported,[198, 199] and enzyme activity of *Erwinia* asparaginase was not affected by the presence of anti-*E. coli* asparaginase antibodies.[200] A study from the DFCI ALL Consortium demonstrated the feasibility and activity of using *Erwinia* asparaginase in pediatric and adolescent patients who developed hypersensitivity reactions to *E. coli* asparaginase during frontline therapy; importantly, treatment with *Erwinia* asparaginase did not negatively impact EFS outcomes in these patients.[201] Thus, for patients who develop severe hypersensitivity reactions during treatment with *E. coli* asparaginase (either to the native or pegylated formulation), the use of *E. coli*-derived formulations should be stopped and *Erwinia* asparaginase should be substituted (see Guidelines section on “Supportive Care: Asparaginase Toxicity Management”). *Erwinia* asparaginase is currently approved by the FDA for patients with ALL who have developed hypersensitivity to *E. coli*-derived asparaginase.[202] Asparaginase can also be associated with various toxicities including pancreatitis (e.g., ranging from asymptomatic cases with amylase or lipase elevation, to symptomatic cases with vomiting or severe abdominal pain), hepatotoxicity (e.g., increase in alanine or glutamine aminotransferase), and coagulopathy (e.g., thrombosis, hemorrhage). Detailed recommendations for the management of asparaginase toxicity in AYA and adult patients have recently been published,[196] and have been incorporated into the NCCN Guidelines for ALL (see Guidelines section on “Supportive Care: Asparaginase Toxicity Management”).

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