National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Acute Myeloid Leukemia

Version 2.2011

NCCN.org

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NCCN Guidelines™ Version 2.2011 Panel Members
Acute Myeloid Leukemia

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Discussion

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

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

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

See NCCN Categories of Evidence and Consensus

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NCCN Guidelines™ Version 2.2011 Updates
Acute Myeloid Leukemia

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The 2.2011 version of the Acute Myeloid Leukemia Guidelines represents the addition of the updated discussion section - MS-1.

Updates in the 1.2011 version of the Acute Myeloid Leukemia Guidelines from the 3.2010 version include:

AML-1
- CT/MRI added for patients with neurologic symptoms.
- Footnote "a" - sentence added that the diagnosis of AML can be made with < 20% blasts in patients with recurrent cytogenetic abnormalities, eg, t(15;17), t(8;21), t(16;16), inv(16).
- Footnote "e" - the following sentence was added: These are useful for patients with normal karyotype or core binding factor leukemia.

AML-2
- For patients not able to tolerate anthracyclines, the consolidation regimen was modified to Arsenic trioxide 0.15 mg/kg IV daily 5 days/week every other month for 4 cycles, with ATRA 45 mg/m^2 in 2 divided doses daily po during two weeks monthly (for a total of 7 cycles).
- Footnote "j" was revised. In patients with clinical and pathologic features of APL, start ATRA *upon first suspicion of APL, without waiting for genetic confirmation of the diagnosis*. Early initiation of ATRA prevents the lethal complication of bleeding. If *cytogenetic and molecular testing does not confirm APL,* discontinue ATRA and continue treatment as for AML.
- Footnote "l": The following reference was added - Shen, et al. All-trans retinoic acid/As_2O_3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci USA 2004;101(15):5328-35 and Estey, et al. Blood 2006;107:3469-3473.

AML-3
- Dosing schedule added for daunorubicin 50 mg/m^2 x 4 days.
- Dosing added for cytarabine.
- Footnote "r" is new to the page. "Data suggest that lower doses of ATRA (25 mg/m^2) may be used in children and young adults."
- Consolidation for the PETHEMA regimen - idarubicin in the first cycle changed from 7 mg to 5 mg. The reference in footnote "u" updated with the published reference in Blood 2010;115:5137-5146.
- Footnote "w" is new to the page: "All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed prior to each anthracycline/mitoxantrone-containing course." (also on AML-4)

AML-4
- Consolidation treatment recommendations were distinguished by risk category for the PETHEMA regimen. ATRA is now included for low risk. Mitoxantrone changed from 5 days to 3 days for 2nd cycle. The reference in footnote "u" updated with the published reference in Blood 2010;115:5137-5146.

AML-4
- North American Intergroup Protocol C9710 added as a regimen option in consolidation therapy with supporting reference in footnote "s". Powell BL, et al. Arsenic trioxide improves event-free and over-all survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood 2010 (in press).

AML-6
- Dosing schedule added for arsenic and ATRA.
- "Strongly" added to "Consider CNS prophylaxis."
- Footnote "dd" - sentence added "Testing recommended at least 2-3 weeks after the completion of arsenic to avoid false positives."

AML-10
- Dosing for high dose cytarabine changed from 3 g/m^2 to 1.5-3 g/m^2.

AML-11
- The categories in PS 0-2 changed to "Favorable cytogenetics/molecular markers without prior MDS/therapy-related AML" and "Therapy-related AML/prior MDS or unfavorable cytogenetic/molecular markers."

AML-13
- Low intensity regimens clarified as decitabine or 5-azacytidine.

AML-14
- Age < 60, "strongly preferred" added to the clinical trial recommendation.
- Footnote "ggg" modified to now provide a link to a new attachment page, "Salvage Chemotherapy Regimen Options"

AML-A
- Footnote "3" new to the page: "For CEBPA, the double mutation appears to confirm the relatively favorable prognosis."
- Footnote "5" modified to FLT3-ITD mutations are *considered to confer a significantly poorer outcome in patients* with normal karyotype,.."

AML-C 1 of 2
- Rasburicase added as a treatment option for tumor lysis prophylaxis. The following sentence was added: "Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid or with evidence of impaired renal function."
- Footnote "2" was modified. "Patients who are allo-immunized should receive cross match compatible and/or HLA-specific blood products."

AML-C 2 of 2

Clinical coagulopathy and overt bleeding:
- First sub-bullet "and prothrombin time (PT) and partial thromboplastin time (PTT) close to normal values" added to the end of the first sentence.
- Second sub-bullet is new to the page. "Central venous catheter should not be placed until bleeding controlled."

AML-F
- This is a new page providing drug and combination regimens for "Salvage Chemotherapy Regimen Options."

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Acute Myeloid Leukemia

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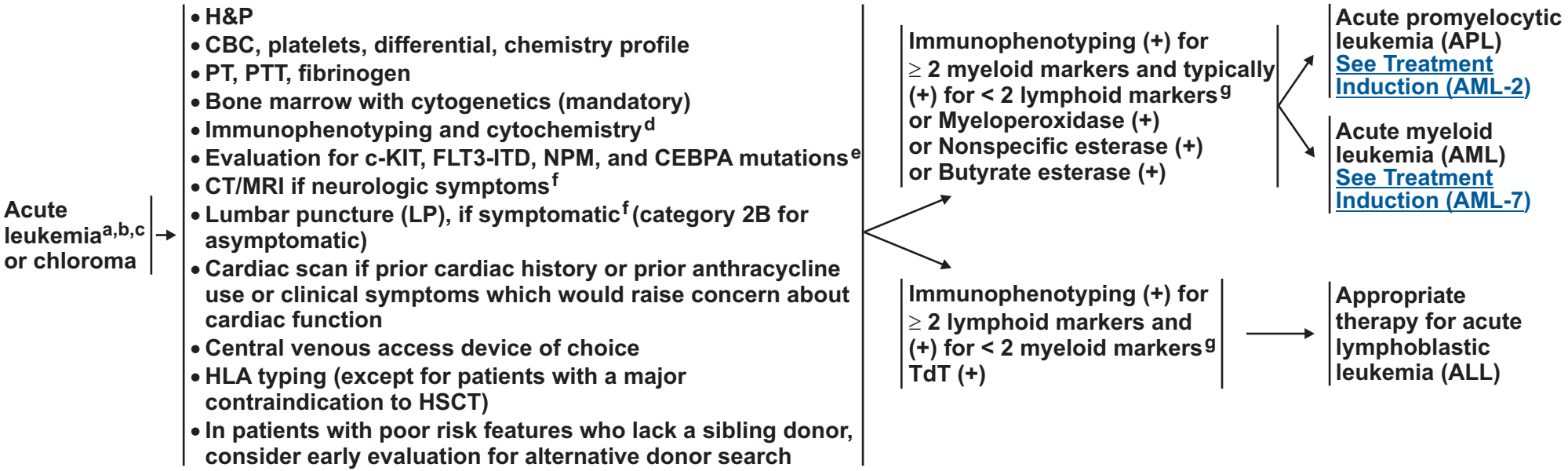

[a] The WHO classification defines acute leukemia as ≥ 20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% blasts in patients with recurrent cytogenetic abnormalities, eg, t(15;17), t(8;21), t(16;16), inv(16). Ongoing clinical trials for AML and high-risk MDS may continue to use FAB criteria of ≥ 30% blasts at least until completion of those trials. AML evolving from MDS (AML-MDS) is often more resistant to cytotoxic chemotherapy than AML which arises without antecedent hematologic disorder and may have a more indolent course. Some clinical trials designed for high-grade MDS may allow enrollment of patients with AML-MDS.

[b] Young adults may be eligible for pediatric trials with more intensive induction regimens and transplant options. AML patients should preferably be managed at experienced leukemia centers where clinical trials may be more available.

[c] Patients who present with isolated extramedullary disease (chloroma) should be treated with systemic therapy. Local therapy (surgery/RT) may be used for residual disease.

[d] Samples for both techniques should be taken at the time of initial sampling. Prioritization of these two complementary diagnostic procedures is left to the discretion of the pathology departments of the individual institutions. M0 can only be diagnosed by immunophenotyping. The role of immunophenotyping in detecting minimal residual disease is being evaluated.

[e] These molecular abnormalities are important for prognostication in a subset of patients (category 2A) and may guide therapeutic intervention (category 2B) (See AML-A). These are useful for patients with normal karyotype or core binding factor leukemia. If test is not available at your institution, consult pathology about preserving material from original diagnostic sample for future use at an outside reference lab after full cytogenetic data available.

[f] For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or CNS bleeding. LP should be performed if no mass/lesion detected on imaging study. Screening LP should be considered at first remission for patients with M5 or M4 morphology or WBC > 100,000/mcL at diagnosis.
See Evaluation and Treatment of CNS leukemia (AML-B).

[g] When presented with rare cases not fitting this algorithm, consultation with an experienced hematopathologist is recommended.

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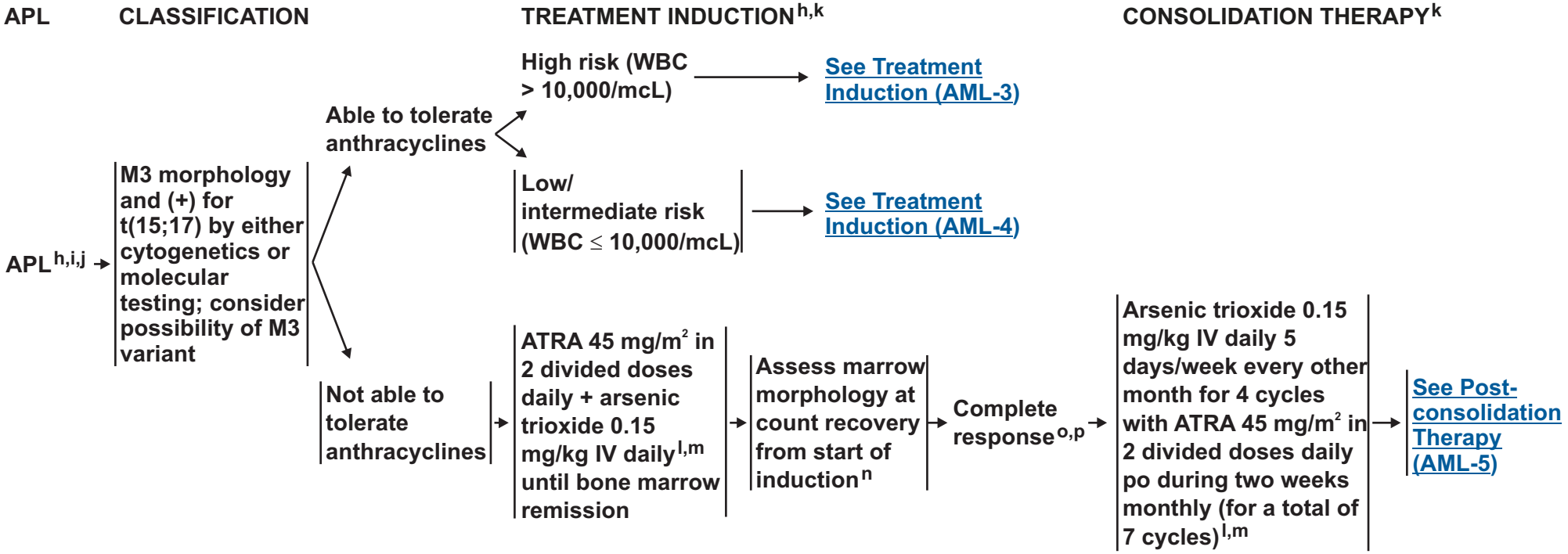

[h] Several groups have published large trials with excellent outcomes. However to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one with consolidation from another.

[i] Therapy-related APL is treated the same as de novo APL.

[j] In patients with clinical and pathologic features of APL, start ATRA upon first suspicion of APL without waiting for genetic confirmation of the diagnosis. Early initiation of ATRA prevents the lethal complication of bleeding. If cytogenetic and molecular testing does not confirm APL, discontinue ATRA and continue treatment as for AML.

[k] Monitor for APL differentiation syndrome and disseminated intravascular coagulation (DIC), see Supportive Care (AML-C 2 of 2).

[l] Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As_2O_3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci USA 2004;101(15):5328-35.
Estey E, Garcia-Manero G, Ferrajoli A, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. Blood 2006;107:3469-3473.

[m] See Arsenic trioxide monitoring, Supportive Care (AML-C 2 of 2).

[n] Assessment of molecular remission should not be made before 4-5 weeks after induction, it should be made after consolidation. Because premature morphologic and molecular assessment (day 10-14 marrow) can be misleading, a nadir marrow is not recommended. Differentiation of the leukemic promyelocytes usually requires more time. Patients often remain molecularly positive at the end of induction even when the marrow shows morphologic remission.

[o] See Response Criteria for Acute Myeloid Leukemia (AML-D).

[p] Primary resistance is rare. The majority of induction failures are related to bleeding or differentiation syndrome. Treatment options include clinical trial, matched sibling or alternative donor HSCT.

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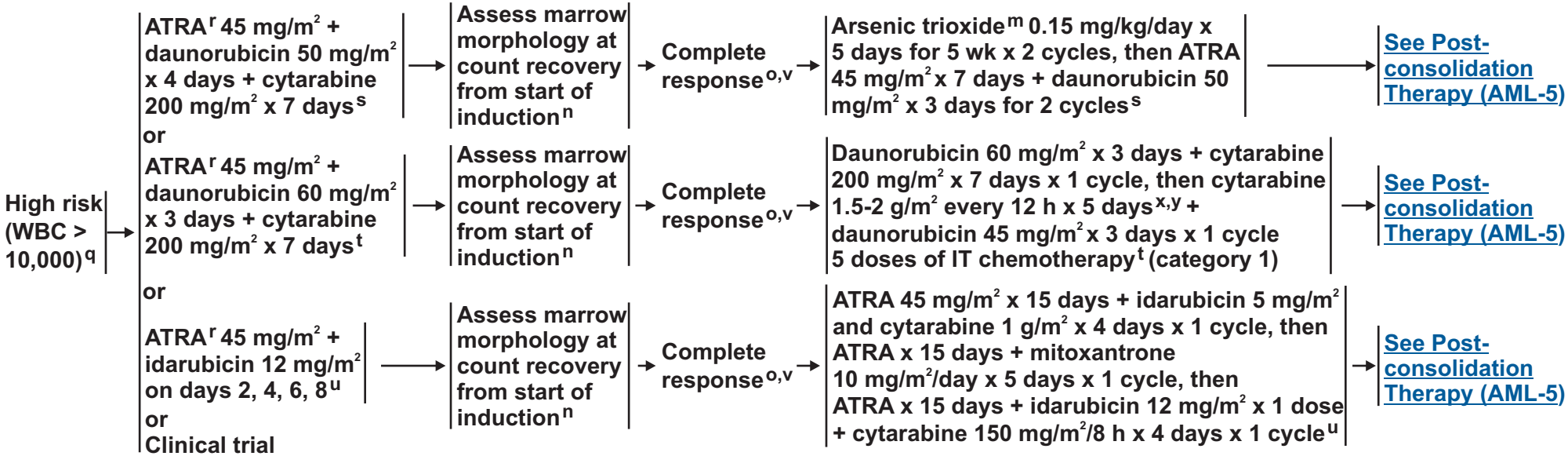

[h] Several groups have published large trials with excellent outcomes. However to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one with consolidation from another.

[k] Monitor for APL differentiation syndrome and disseminated intravascular coagulation (DIC), see Supportive Care (AML-C 2 of 2).

[m] See Arsenic trioxide monitoring, Supportive Care (AML-C 2 of 2).

[n] Assessment of molecular remission should not be made before 4-5 weeks after induction, it should be made after consolidation. Because premature morphologic and molecular assessment (day 10-14 marrow) can be misleading, a nadir marrow is not recommended. Differentiation of the leukemic promyelocytes usually requires more time. Patients often remain molecularly positive at the end of induction even when the marrow shows morphologic remission.

[o] See Response Criteria for Acute Myeloid Leukemia (AML-D).

[q] For patients with a high WBC (> 10,000), consider prophylactic dexamethasone to prevent differentiation syndrome.

[r] Data suggest that lower doses of ATRA (25 mg/m^2) may be used in children and young adults.

[s] Powell BL, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood 2010 (in press).

[t] Ades LA, Sanz MA, Chevret S, et al. Treatment of newly diagnosed acute promyelocytic leukemia (APL): A comparison of French-Belgian-Swiss and PETHEMA results. Blood 2008;111:1078-1086.

[u] Sanz MA, Montesinos P, Rayon C, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high risk patients: further improvements in treatment outcomes. Blood 2010;115:5137-5146.

[v] Induction failure is related to bleeding, differentiation, or infection and not disease progression. See relapse on AML-6.

[w] All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed prior to each anthracycline/mitoxantrone-containing course.

[x] Although the original regimen included high-dose cytarabine as second consolidation, some investigators recommend using high-dose cytarabine early for CNS prophylaxis, especially for patients not receiving IT chemotherapy.

[y] Dose adjustment of cytarabine may be needed for older patients or patients with renal dysfunction.

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APL
Able to tolerate anthracyclines

TREATMENT INDUCTION[h,k]

Low/ intermediate (Int.) risk (WBC ≤ 10,000)

- **ATRA[r] 45 mg/m² + daunorubicin 50 mg/m² x 4 days + cytarabine 200 mg/m² x 7 days[s,y,z]**
  → **Assess marrow morphology at count recovery from start of induction[n]**
  → **Complete response[o,v]**
  → **Arsenic trioxide[m] 0.15mg/kg/day x 5 days for 5 wk x 2 cycles, then ATRA 45 mg/m² x 7 days + daunorubicin 50 mg/m² x 3 days for 2 cycles[s]**
  → **See Post-consolidation Therapy (AML-5)**

  or

- **ATRA[r] 45 mg/m² + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[t,y,z] (category 1)**
  → **Assess marrow morphology at count recovery from start of induction[n]**
  → **Complete response[o,v]**
  → **Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine 1 g/m² every 12 h x 4 days[y] + daunorubicin 45 mg/m² x 3 days x 1 cycle[t] (category 1)**
  → **See Post-consolidation Therapy (AML-5)**

  or

- **ATRA[r] 45 mg/m² + idarubicin 12 mg/m² on days 2, 4, 6, 8[u,z] (category 1)**
  → **Assess marrow morphology at count recovery from start of induction[n]**
  → **Complete response[o,v]**
  - **Low risk** → **ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/day x 3 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 dose x 1 cycle[u] (category 1)** → **See Post-consolidation Therapy (AML-5)**
  - **Int. risk** → **ATRA 45 mg/m² x 15 days + idarubicin 7 mg/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/day x 3 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 2 doses x 1 cycle[u] (category 1)** → **See Post-consolidation Therapy (AML-5)**

  or
  Clinical trial

CONSOLIDATION THERAPY[w]

[h] Several groups have published large trials with excellent outcomes. However to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one with consolidation from another.
[k] Monitor for APL differentiation syndrome and disseminated intravascular coagulation (DIC), see Supportive Care (AML-C 2 of 2).
[m] See Arsenic trioxide monitoring, Supportive Care (AML-C 2 of 2).
[n] Assessment of molecular remission should not be made before 4-5 weeks after induction, it should be made after consolidation. Because premature morphologic and molecular assessment (day 10-14 marrow) can be misleading, a nadir marrow is not recommended. Differentiation of the leukemic promyelocytes usually requires more time. Patients often remain molecularly positive at the end of induction even when the marrow shows morphologic remission.
[o] See Response Criteria for Acute Myeloid Leukemia (AML-D).
[r] Data suggest that lower doses of ATRA (25 mg/m²) may be used in young adults.
[s] Powell BL, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood 2010 (in press).
[t] Ades LA, Sanz MA, Chevret S, et al. Treatment of newly diagnosed acute promyelocytic leukemia (APL): A comparison of French-Belgian-Swiss and PETHEMA results. Blood 2008;111:1078-1086.
[u] Sanz MA, Montesinos P, Rayon C, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high risk patients: further improvements in treatment outcomes. Blood 2010;115:5137-5146.
[v] Induction failure is related to bleeding, differentiation, or infection and not disease progression. See relapse on AML-6.
[w] All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed prior to each anthracycline/mitoxantrone-containing course.
[y] Dose adjustment of cytarabine may be needed for older patients or patients with renal dysfunction.
[z] Patients who have rapidly escalating WBC or other high risk features during course of induction therapy, see consolidation on AML-3.

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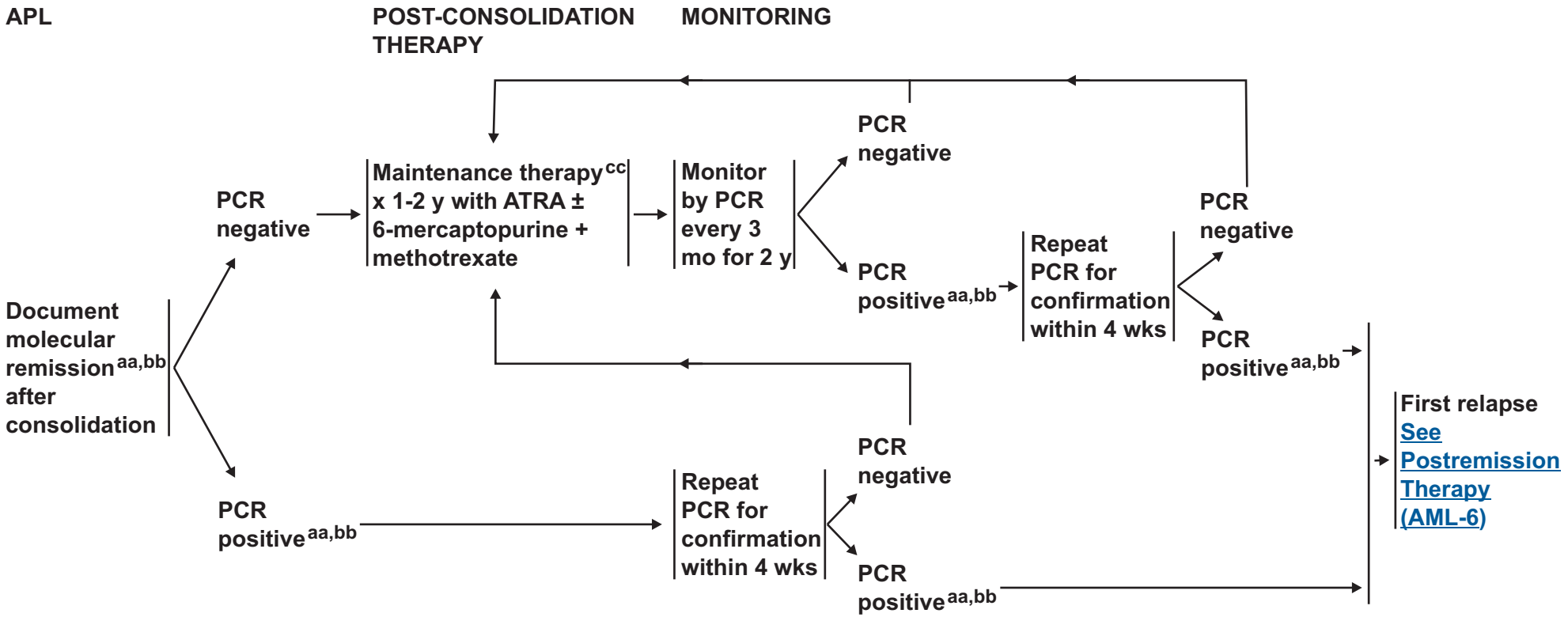

[aa] Polymerase chain reaction (PCR) should be performed on a marrow sample at completion of consolidation to document molecular remission. Subsequent monitoring by PCR can be done with peripheral blood, although using marrow sample is a more sensitive monitoring technique and may give earlier signs of relapse. Prior practice guidelines have recommended monitoring marrow by PCR every 3 mo for 2 y to detect molecular relapse. We continue to endorse this for high risk patients, those over age 60 y or who had long interruptions during consolidation or patients not able to tolerate maintenance. Clinical experience indicates that risk of relapse in patients with low risk disease who are in molecular remission at completion of consolidation is low and monitoring may not be necessary outside the setting of a clinical trial. To confirm PCR positivity, a second marrow sample should be done in 2-4 weeks in a reliable laboratory. If molecular relapse is confirmed by a second positive test, intervention should be strongly considered (eg, arsenic trioxide). If the second test was negative, frequent monitoring (every 3 mo for 2 y) is strongly recommended to confirm that the patient remains negative. The PCR testing lab should indicate level of sensitivity of assay for positivity (most clinical labs have a sensitivity level of 10^{-4}) and testing should be done in the same lab to maintain level of sensitivity. Consider consultation with a physician experienced in molecular diagnostics if results are equivocal.

[bb] If patient confirmed molecularly positive, treat as relapse (AML-6).

[cc] The role of maintenance chemotherapy remains unclear, particularly for patients with low risk disease who achieve a molecular remission at the end of consolidation. The majority of studies showing benefit for maintenance occurred prior to the use of ATRA for consolidation. Trials are evaluating benefits of maintenance in this group.

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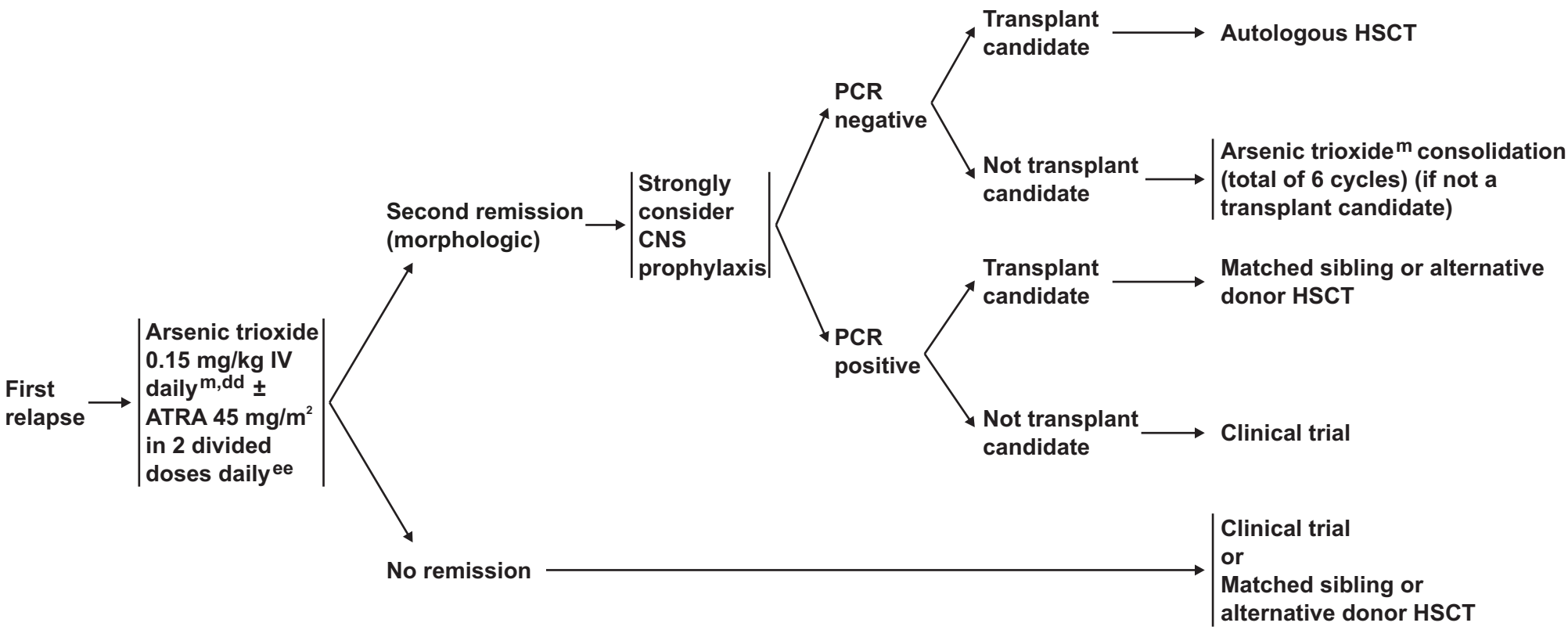
APL **POSTREMISSION THERAPY** **ADDITIONAL THERAPY**



[m] See Arsenic trioxide monitoring, Supportive Care (AML-C 2 of 2).

[dd] At the end of 2 cycles, if patient is not in molecular remission, consider matched sibling or alternative donor HSCT or clinical trial. Testing recommended at least 2-3 weeks after the completion of arsenic to avoid false positives.

[ee] There is a randomized trial that suggests the addition of ATRA does not confer any benefit over arsenic alone. Raffoux E, Rousselot P, Poupon J, et al. Combined treatment with arsenic trioxide and all-trans-retinoic-acid in patients with relapsed acute promyelocytic leukemia. J Clin Oncol 2003;21:2326-2334.

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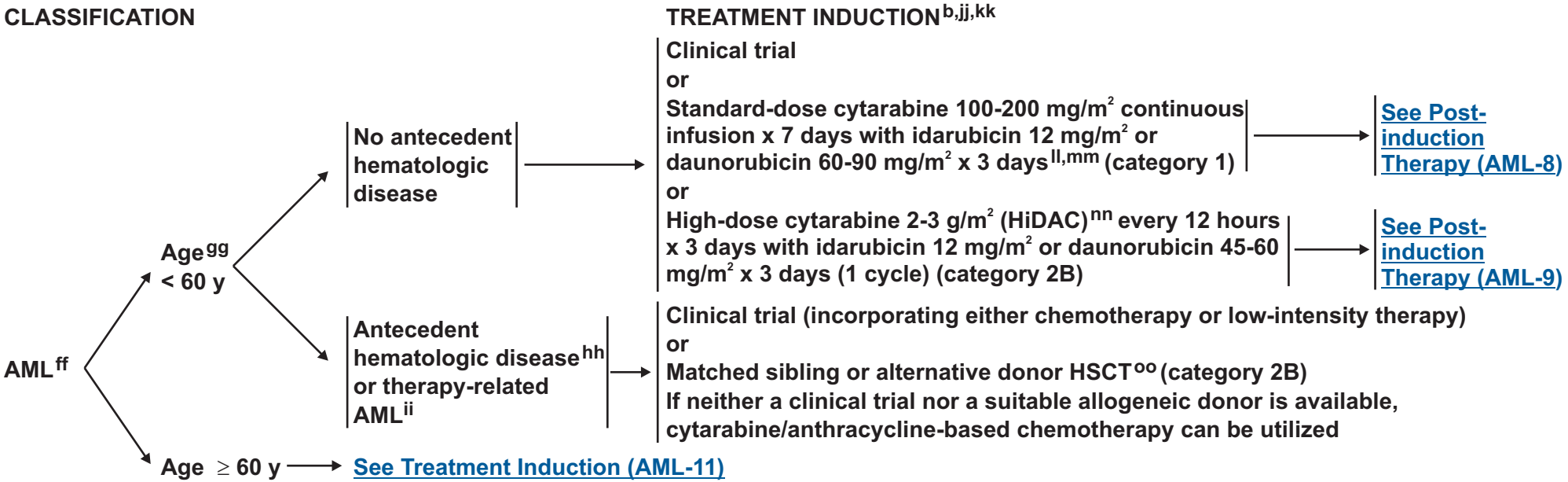

[b] Young adults may be eligible for pediatric trials with more intensive induction regimens and transplant options. AML patients should preferably be managed at experienced leukemia centers where clinical trials may be more available.

[ff] Patients with blast counts > 50,000/mcL are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the white count include apheresis or hydroxyurea. Prompt institution of definitive therapy is essential.

[gg] Poor performance status and comorbid medical condition, in addition to age are factors which influence ability to tolerate standard induction therapy.

[hh] Patients with known poor-prognosis karyotypes prior to treatment may be treated like patients with an antecedent hematologic disorder.

[ii] Patients with favorable karyotypes [inv16, t(8;21), t(16;16)] should be candidates for standard induction therapy, similar to de novo AML.

[jj] See Supportive Care (AML-C 1 of 2).

[kk] See Monitoring During Therapy (AML-E).

[ll] ECOG reported a significant increase in CR rates and OS using daunorubicin 90 mg/m² x 3 days versus 45 mg/m² x 3 days in patients < 60 years of age. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 2009;361:1249-1259. If there is residual disease on day 12-14, additional daunorubicin dose is 45 mg/m² x 3 days.

[mm] For patients with impaired cardiac function, other regimens that combine non-anthracycline (such as fludarabine or topotecan) with cytarabine have been published.

[nn] The use of high-dose cytarabine for induction outside the setting of a clinical trial is still controversial. While the remission rates are the same for standard- and high-dose cytarabine, two studies have shown more rapid marrow blast clearance after one cycle of high dose therapy and a disease-free survival advantage for patients ≤ age 50 who received the high-dose therapy (category 2B). Kern W and Estey EH. High-dose cytarabine arabinoside in the treatment of acute myeloid leukemia: review of three randomized trials. Cancer 2006;107:116-124. There are no data using more than 60 mg of daunorubicin or 12 mg of idarubicin with high-dose cytarabine.

[oo] The benefit of induction chemotherapy prior to allogeneic HSCT versus immediate HSCT is unclear in patients with high grade MDS and low blast count AML evolving from MDS. If donor is available, allogeneic HSCT without prior induction therapy is an option, particularly for patients with poor risk cytogenetics. If the patient has not been previously treated with a hypomethylating agent such as decitabine or 5-azacytidine, a trial of such therapy may also be used to reduce marrow blasts prior to transplant with less toxicity than standard induction.

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AML POST-INDUCTION THERAPY AFTER STANDARD-DOSE CYTARABINE

Age < 60 y

Follow-up bone marrow[jj,kk] 7-10 d after induction completed

- **Significant residual blasts[pp]** → **High-dose cytarabine or standard-dose cytarabine with idarubicin or daunorubicin[ll] or See treatment for Induction failure**
- **Significant cyto-reduction[qq] with low % residual blasts** → **Standard-dose cytarabine with idarubicin or daunorubicin[ll]**
- **Hypoplasia[rr]** → **Await recovery**

Marrow to document remission status upon hematologic recovery

- **Complete response[o,ss]** → See Postremission Therapy (AML-10)
- **Induction failure[o]** → **CONSOLIDATION THERAPY**

CONSOLIDATION THERAPY

Clinical trial
or
Matched sibling or alternative donor HSCT
or
High dose cytarabine (if not previously used as treatment for persistent disease at day 15) ± anthracycline (daunorubicin or idarubicin), if clinical trial not available while awaiting identification of a donor
or
Best supportive care

[o] See Response Criteria for Acute Myeloid Leukemia (AML-D).

[jj] See Supportive Care (AML-C).

[kk] See Monitoring During Therapy (AML-E).

[ll] ECOG reported a significant increase in CR rates and OS using daunorubicin 90 mg/m^2 x 3 days versus 45 mg/m^2 x 3 days in patients < 60 years of age. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 2009;361:1249-1259. If there is residual disease on day 12-14, additional daunorubicin dose is 45 mg/m^2 x 3 days.

[pp] Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.

[qq] If ambiguous, consider repeat bone marrow biopsy in 5-7 d before proceeding with therapy.

[rr] Hypoplasia is defined as cellularity < 10-20% and residual blasts < 5-10%.

[ss] Patients with an increased risk of meningeal involvement (initial WBC > 100,000/mcL or monocytic histology) should be considered for CNS evaluation with a lumbar puncture upon achieving complete response. See Evaluation and Treatment of CNS leukemia (AML-B).

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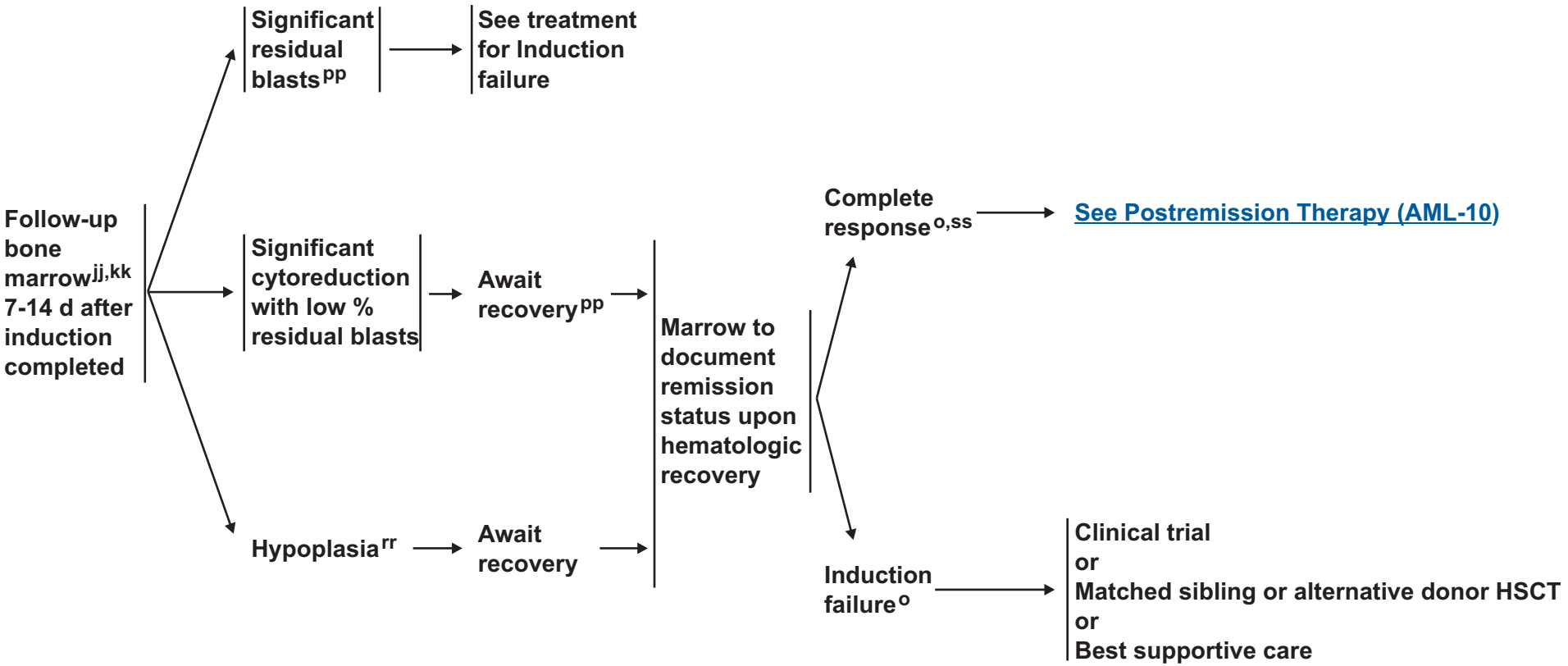
AML POST-INDUCTION THERAPY AFTER HIGH-DOSE CYTARABINE

Age < 60 y

CONSOLIDATION THERAPY



[o] See Response Criteria for Acute Myeloid Leukemia (AML-D).

[jj] See Supportive Care (AML-C).

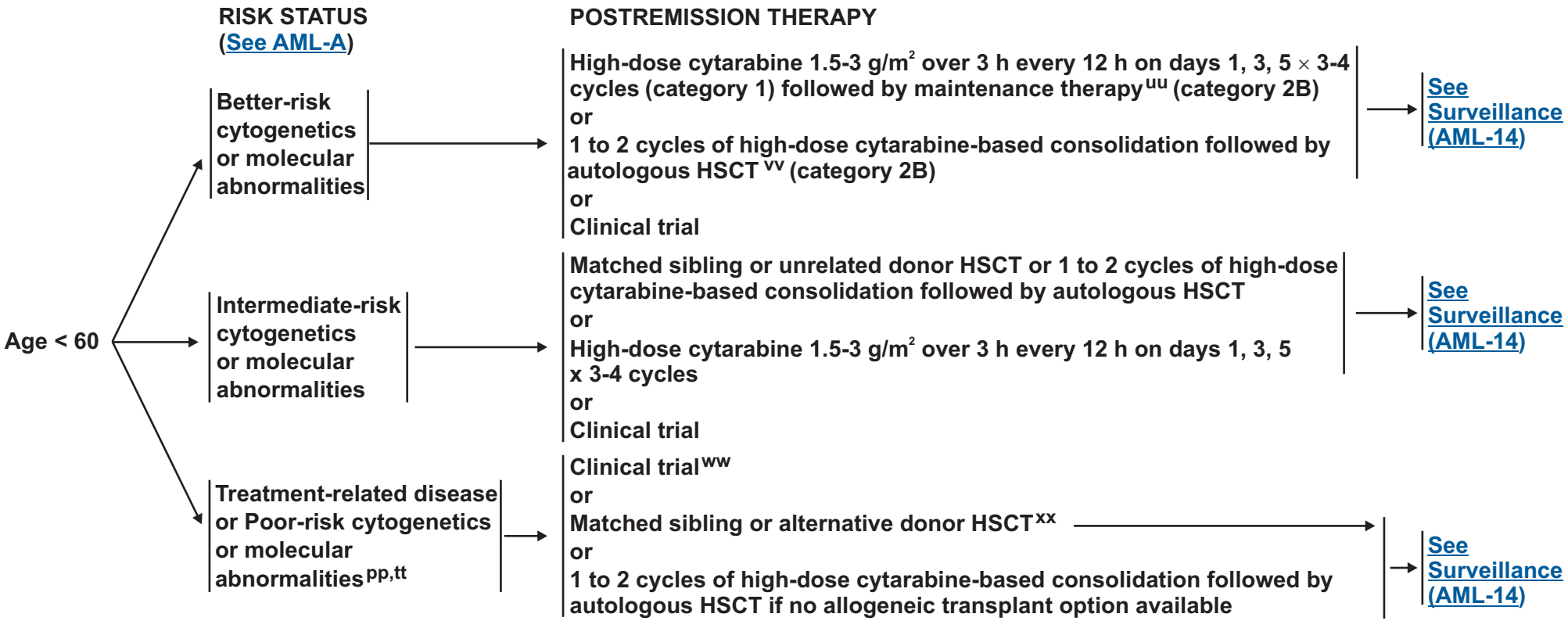
[kk] See Monitoring During Therapy (AML-E).

[pp] Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.

[rr] Hypoplasia is defined as cellularity < 10-20% and residual blasts < 5-10%.

[ss] Patients with an increased risk of meningeal involvement (initial WBC > 100,000/mcL or monocytic histology) should be considered for CNS evaluation with a lumbar puncture upon achieving complete response. See Evaluation and Treatment of CNS leukemia (AML-B).

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.



[pp] Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.

[tt] FLT3-ITD mutations are also emerging as a poor risk feature in the setting of otherwise normal karyotype, and these patients should be considered for clinical trials where available. There is controversy regarding allogeneic transplant for FLT3-ITD only mutations, in the absence of other poor prognostic features.

[uu] While the original study design incorporated maintenance chemotherapy following a planned 4 cycles of consolidation, only a small fraction of the patients who received HiDAC, also received maintenance therapy. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 1994;331:896-903.

[vv] While both options- (1) multiple cycles of dose-intensive consolidation and (2) one cycle of dose-intensive consolidation followed by autologous HSCT- can produce good survival for patients with favorable cytogenetics, there are significant differences in toxicity. Patient age, comorbid conditions, and issues such as fertility and salvage options should be considered when choosing consolidation.

[ww] Clinical trials when available are strongly recommended in the treatment of patients with poor prognostic features (eg, high WBC, or two cycles of induction needed to achieve CR).

[xx] Patients may require at least one cycle of high dose cytarabine consolidation while donor search is in progress to maintain remission. Patients may proceed directly to transplant following achievement of remission if a donor (sibling or alternative) is available.

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National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Acute Myeloid Leukemia

NCCN Guidelines Index
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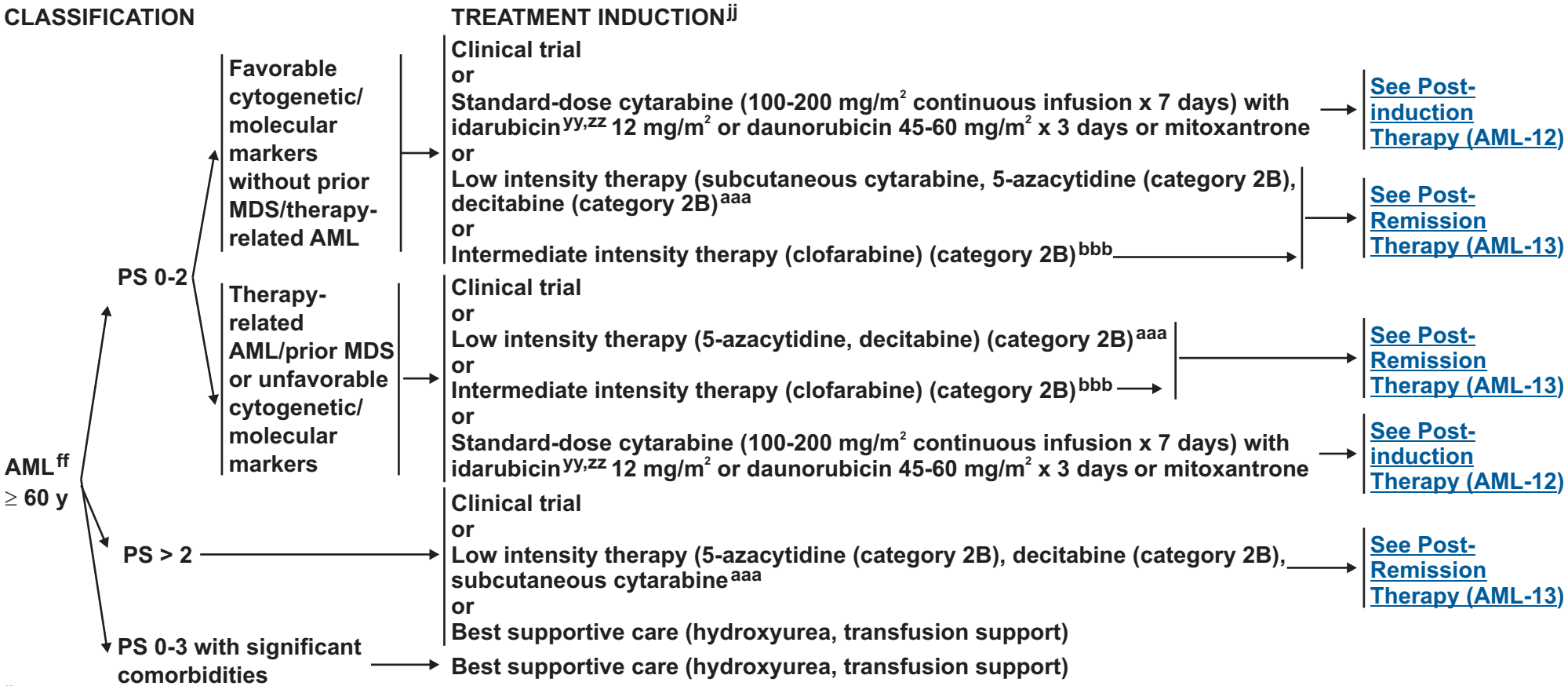
Discussion



[ff] Patients with blast counts > 50,000/mcL are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the white count include apheresis or hydroxyurea. Prompt institution of definitive therapy is essential.

[jj] See Supportive Care (AML-C).

[yy] Idarubicin treatment compared to high doses of daunorubicin up to 80 mg/m² yields higher complete response rate and more complete responses after one course. (Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol 2010;28:808-814). The CR rates and 2 yr overall survival in patients between 60 and 65 treated with daunorubicin 90 mg/m² is also comparable to the outcome for idarubicin 12 mg/m²; the higher dose daunorubicin did not benefit patients over age 65 (Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med. 2009;361:1235-1248).

[zz] Patients over 75 years old with significant comorbidities usually do not benefit from conventional chemotherapy treatment. However, the rare patient with good or normal karyotype and no significant comorbidities may benefit from conventional chemotherapy treatment.

[aaa] Response may not be evident before 3-4 cycles of treatment with hypomethylating agents (5-azacytidine, decitabine). Similar delays in response are likely with novel agents on clinical trial but endpoints will be defined by the protocol.

[bbb] Clofarabine is renally cleared. The recommended treatment dose for patients 60-70 with normal CrCl (≥ 60 mL/min) is 30 mg/m². Clofarabine is not recommended for older patients with impaired renal function.

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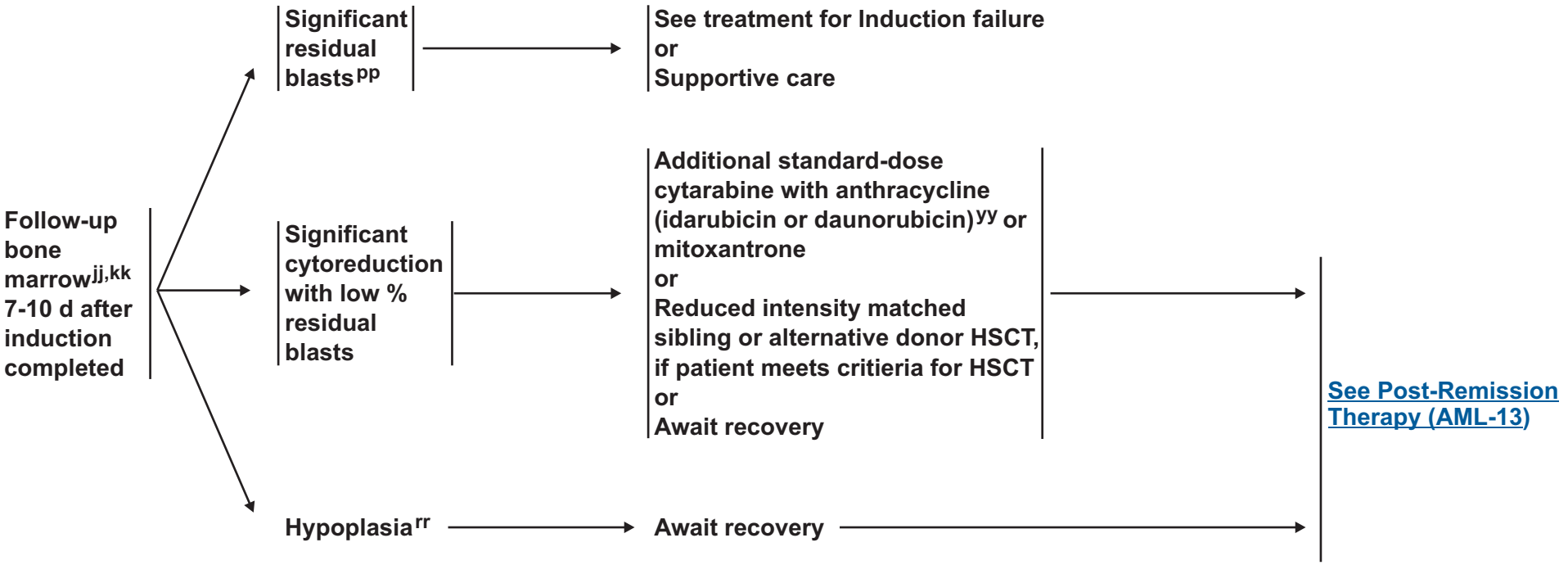
AML POST-INDUCTION THERAPY
Age ≥ 60 y



[jj] See Supportive Care (AML-C).

[kk] See Monitoring During Therapy (AML-E).

[pp] Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.

[rr] Hypoplasia is defined as cellularity < 10-20% and residual blasts < 5-10%.

[yy] Idarubicin treatment compared to high doses of daunorubicin up to 80 mg/m^2 yields higher complete response rate and more complete responses after one course. (Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol 2010;28:808-814). The CR rates and 2 yr overall survival in patients between 60 and 65 treated with daunorubicin 90mg/m^2 is also comparable to the outcome for idarubicin 12mg/m^2; the higher dose daunorubicin did not benefit patients over age 65 (Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med. 2009;361:1235-1248).

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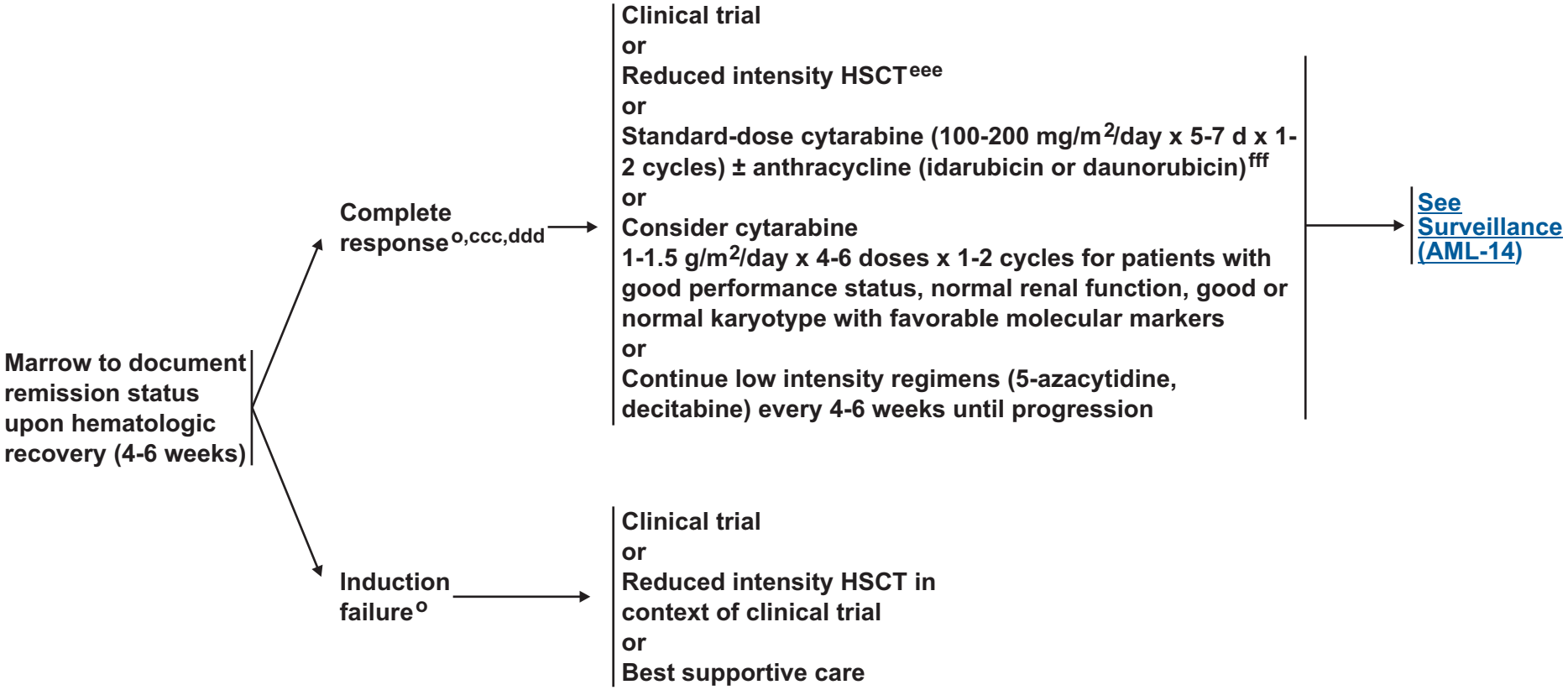
AML POST-REMISSION THERAPY
Age ≥ 60 y



[o] See Response Criteria for Acute Myeloid Leukemia (AML-D).
[ccc] Patients in remission may be screened with LP if initial WBC > 100,000/mcL or monocytic histology. See Evaluation and Treatment of CNS leukemia (AML-B).
[ddd] HLA-typing for patients considered strong candidates for allogeneic transplantation.
[eee] Patients who are deemed as strong candidates for stem cell transplant and who have an available donor should be transplanted in first remission.
[fff] An excellent outcome was reported for outpatient consolidation which provides another option for elderly patients. Gardin C, Turlure P, Fagot T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. Blood 2007;109(12):5129-5135.

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SURVEILLANCE (AFTER COMPLETION OF CONSOLIDATION)

- CBC, platelets every 1-3 mo for 2 y, then every 3-6 mo up to 5 y
- Bone marrow aspirate only if peripheral smear abnormal or cytopenias develop
- Alternative donor search (including cord blood) should be initiated at first relapse in appropriate patients concomitant with institution of other therapy if no sibling donor has been identified

→ Relapse[o]

SALVAGE THERAPY

Age < 60

Early (< 12 mo) →
Clinical trial (strongly preferred)
or
Salvage chemotherapy[ggg] followed by matched sibling or alternative donor HSCT

Late (> 12 mo) →
Clinical trial (strongly preferred)
or
Salvage chemotherapy[ggg] followed by matched sibling or alternative donor HSCT
or
Repeat initial successful induction regimen[hhh]

Age ≥ 60

Early (< 12 mo) →
Clinical trial (strongly preferred)
or
Best supportive care
or
Salvage chemotherapy[ggg] followed by matched sibling or alternative donor HSCT[iii]

Late (> 12 mo) →
Clinical trial (strongly preferred)
or
Treatment with initial successful regimen
or
Salvage chemotherapy[ggg] followed by matched sibling or alternative donor HSCT[iii]
or
Best supportive care

[o] See Response Criteria for Acute Myeloid Leukemia (AML-D).
[ggg] See Salvage Chemotherapy Options (AML-F).
[hhh] Reinduction therapy may be appropriate in certain circumstances, such as patients with long first remission. If a second CR is achieved, then consolidation with allogeneic HSCT should be considered.
[iii] Transplant should only be considered in the context of a clinical trial or if a remission achieved.

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RISK STATUS BASED ON CYTOGENETICS AND MOLECULAR ABNORMALITIES

RISK STATUS	CYTOGENETICS	MOLECULAR ABNORMALITIES
Better-risk	inv(16)[1] or t(16;16)[1] t(8;21)[1] t(15;17)	Normal cytogenetics: with NPM1 mutation or isolated CEBPA[3] mutation in the absence of FLT3-ITD
Intermediate-risk	Normal cytogenetics +8 t(9;11) Other non-defined	t(8;21), inv (16), t(16;16): with c-KIT[4] mutation
Poor-risk	Complex (≥ 3 clonal chromosomal abnormalities) -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[2]	Normal cytogenetics: with FLT3-ITD mutation[5]

[1] Other cytogenetic abnormalities in addition to these findings do not alter better risk status.
[2] Philadelphia+ AML t(9;22) consider managing as myeloid blast crisis in CML. See NCCN Chronic Myelogenous Leukemia Guidelines.
[3] For CEBPA, the double mutation appears to confirm the relatively favorable prognosis.
[4] Emerging data indicates that the presence of c-KIT mutations in patients with t(8;21) and to a lesser extent Inv(16) confers a higher risk of relapse. These patients should be considered for clinical trials, if available.
[5] FLT3-ITD mutations are considered to confer a significantly poorer outcome in patients with normal karyotype, and these patients should be considered for clinical trials where available. There is controversy as to whether FLT3-TKD mutations carry an equally poor prognosis.

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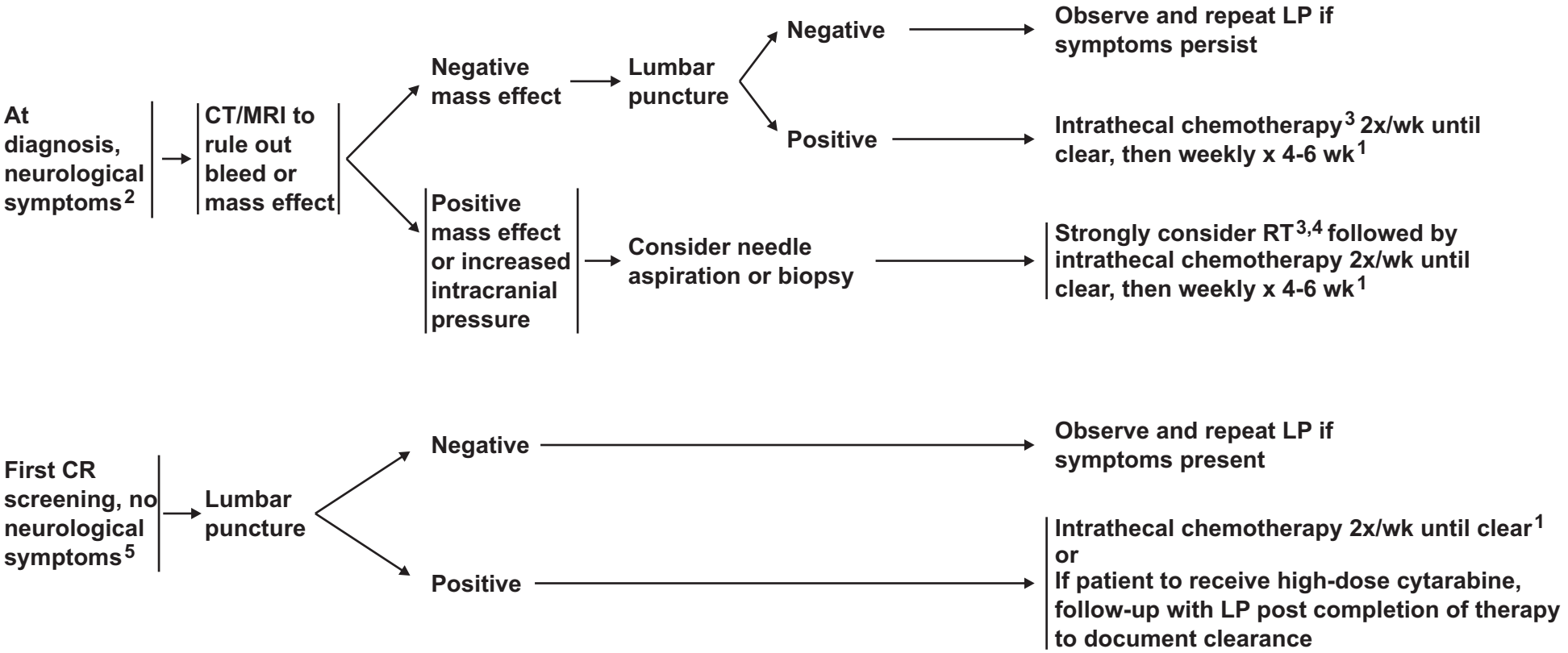
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

EVALUATION AND TREATMENT OF CNS LEUKEMIA[1]



[1] Further CNS surveillance per institutional practice.
[2] For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or CNS bleeding. LP should be performed if no mass, lesion, or hemorrhage detected on imaging study.
[3] Induction chemotherapy should be started concurrently. However, for patients receiving high dose cytarabine, since this agent crosses the blood brain barrier, IT therapy can be deferred until induction is completed.
[4] Concurrent use of CNS RT with high-dose cytarabine, IT methotrexate, or IT liposomal cytarabine may increase risk of neurotoxicity.
[5] Screening LP should be considered at first remission for patients with M4 or M5 morphology, or biphenotypic leukemia, or WBC > 100,000/mcL at diagnosis.

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SUPPORTIVE CARE (1 of 2)

There are variations between institutions but the following issues are important to consider in the management of patients with AML.

General

- **Blood products:**
  - **Leukocyte-depleted products used for transfusion**
  - **Irradiated blood products for patients receiving immunosuppressive therapy (fludarabine, HSCT).**
  - **Transfusion thresholds-- RBCs for Hgb ≤ 8 g/dL or per institutional guidelines or symptoms of anemia; platelets for patients with platelets < 10,000/mcL or with any signs of bleeding.[1]**
  - **CMV screening for potential HSCT candidates may be considered.**
- **Tumor lysis prophylaxis: hydration with diuresis, and urine alkalinization (may be contraindicated with increased phosphate) and 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.**
- **Patients receiving high-dose cytarabine therapy (particularly those with impaired renal function), are at risk for cerebellar toxicity. Neurologic assessments including tests for nystagmus, slurred speech, and dysmetria should be performed before each dose of cytarabine.**
  - **In patients exhibiting rapidly rising creatinine due to tumor lysis, high-dose cytarabine should be discontinued until creatinine normalizes.**
  - **In patients who develop cerebellar toxicity, cytarabine should be stopped. The patient should not be rechallenged with high-dose cytarabine in future treatment cycles. (Smith GA, Damon LE, Rugo HS, et al. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. J Clin Oncol 1997;15(2):833-839).**
- **Saline or steroid eye drops to both eyes four times daily for all patients undergoing high-dose cytarabine therapy until 24 h post completion of cytarabine.**
- **Growth factors may be considered in the elderly after chemotherapy is complete. Note that such use may confound interpretation of the bone marrow. Patient should be off GM-CSF or G-CSF for a minimum of 7 days before obtaining bone marrow to document remission.**
- **Decisions regarding use and choice of antibiotics, should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns. Posaconazole has been shown to significantly decrease fungal infections when compared to fluconazole.[2] Outcomes with other azoles, such as voriconazole, echinocandins, or amphotericin B, may produce equivalent results. Azoles should not be given during anthracyline chemotherapy, since azoles impair drug metabolism and can increase toxicity.**

[1] Patients who are allo-immunized should receive cross match compatible and/or HLA-specific blood products.

[2] Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348-359.

See APL Supportive Care (AML-C 2 of 2)

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

SUPPORTIVE CARE (2 of 2)

APL

- **Clinical coagulopathy and overt bleeding:**
  - **Management of clinical coagulopathy and overt bleeding: Aggressive platelet transfusion support to maintain platelets ≥ 50,000/mcL, fibrinogen replacement with cryoprecipitate and fresh frozen plasma to maintain a level over 150 mg/dL and prothrombin time (PT) and partial thromboplastin time (PTT) close to normal values. Monitor daily until coagulopathy resolves.**
  - **Central venous catheter should not be placed until bleeding controlled.**
- **Leukapheresis is not recommended in the routine management of patients with a high WBC count in APL because of the difference in leukemia biology; however, in life threatening cases with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution.**
- **APL differentiation syndrome:**
  - **Maintain a high index of suspicion of APL differentiation syndrome (fever, often associated with increasing WBC > 10,000/mcL usually at initial diagnosis or relapse, shortness of breath, hypoxemia, pleural or pericardial effusions). Close monitoring of volume overload and pulmonary status is indicated. Initiate dexamethasone at first signs or symptoms of respiratory compromise (hypoxia, pulmonary infiltrates, pericardial or pleural effusions) (10 mg BID for 3-5 days with a taper over 2 wks). Consider interrupting ATRA therapy until hypoxia resolves.**
- **Arsenic trioxide monitoring[1]**
  - **Prior to initiating therapy**
    - **ECG for prolonged QTc interval assessment**
    - **Serum electrolytes (Ca, K, Mg) and creatinine**
  - **During therapy**
    - **Maintain K concentrations above 4 mEq/dL**
    - **Maintain Mg concentrations above 1.8 mg/dL**
    - **Reassess patients with absolute QTc interval > 500 millisec (weekly during induction therapy and before each course of post-remission therapy)**
- **Myeloid growth factors should not be used.**
- **Patients with relapsed APL or with hyperleukocytosis after ATRA may be at increased risk of CNS disease. Prophylactic intrathecal therapy (IT) is being evaluated in this group.**

[1]Package insert for arsenic trioxide (http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=22624)

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RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA[1]

- **Morphologic leukemia-free state**
  - **Bone marrow < 5% blasts in an aspirate with spicules**
  - **No blasts with Auer rods or persistence of extramedullary disease**
- **If there is a question of residual leukemia, a bone marrow aspirate/biopsy should be repeated in one week.**
- **A bone marrow biopsy should be performed if spicules are absent from the aspirate sample.**
- **Complete remission**
  - **Morphologic CR - patient independent of transfusions**
    - **Absolute neutrophil count > 1000/mcL**
    - **Platelets ≥ 100,000/mcL**
    - **No residual evidence of extramedullary disease**
  - **Cytogenetic CR - cytogenetics normal (in those with previously abnormal cytogenetics)**
  - **Molecular CR - molecular studies negative[2]**
  - **CRi - There are some clinical trials, particularly in the elderly or those with antecedent myelodysplasia, which includes a variant of CR referred to as CRp or CRi. This has been loosely defined as < 5% marrow blasts and transfusion independence but with persistence of cytopenia (usually thrombocytopenia).**
- **Partial remission[3]**
  - **Decrease of at least 50% in the percentage of blasts to 5 to 25% in the bone marrow aspirate and the normalization of blood counts, as noted above.**
- **Patients failing to achieve a complete response are considered treatment failures.**
- **Relapse following complete response is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause (eg, bone marrow regeneration after consolidation therapy) or extramedullary relapse.**

[1] Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21(24):4642-4649.

[2] This is clinically relevant only in APL and Ph+ leukemia at the present time.

[3] PR's are only useful in assessing potential activity of new investigational agents, usually in Phase I trials, and should not be considered a therapy goal for standard therapy.

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MONITORING DURING THERAPY

Induction:

- **CBC, platelets daily (differential daily during chemotherapy and every other day after recovery of WBC > 500/mcL until either normal differential or persistent leukemia is documented), platelets every day while in hospital until platelet-transfusion independent.**
- **Chemistry profile, including electrolytes, BUN, creatinine, uric acid, and PO_4, at least daily during active treatment until risk of tumor lysis is past. If patient is receiving nephrotoxic agents, closer monitoring is required through the period of hospitalization.**
- **Bone marrow aspirate/biopsy 7-10 days after completion of cytarabine-based chemotherapy to document hypoplasia. If hypoplasia is not documented or indeterminate, repeat biopsy in 7-14 days to clarify persistence of leukemia. If hypoplasia, then repeat biopsy at time of hematologic recovery to document remission. If cytogenetics were initially abnormal, include cytogenetics as part of the remission documentation.**

Post–remission therapy:

- **CBC, platelets 2x/wk during chemotherapy**
- **Chemistry profile, electrolytes daily during chemotherapy**
- **Outpatient monitoring post chemotherapy: CBC, platelets, differential and electrolytes 2-3x/wk until recovery**
- **Bone marrow only if peripheral blood counts abnormal or failure to recover counts within 5 wk**
- **Patients with high risk features, including poor-prognosis cytogenetics, therapy-related AML, prior MDS, or patients who require 2 or more inductions to achieve a CR, are at increased risk for relapse and may be considered for early unrelated donor search, as indicated on AML-7**

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SALVAGE CHEMOTHERAPY REGIMEN OPTIONS

- **Cladribine + cytarabine + GCSF ± mitoxantrone or idarubicin**[1,2]
- **High dose cytarabine + anthracycline (if not received previously in treatment)**
- **Fludarabine + cytarabine + GCSF ± idarubicin**[3,4]
- **Mitoxantrone + etoposide + cytarabine (MEC)**[5]

[1]Martin MG, Welch JS, Augustin K, et al. Cladribine in the treatment of acute myeloid leukemia: a single-institution experience. Clin Lymphoma Myeloma 2009;9(4):298-301.

[2]Wierzbowska A, Robak T, Pluta A, et al. Cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group. Eur J Haematol 2008;80(2):115-126.

[3]Montillo M, Mirto S, Petti MC, et al. Fludarabine, cytarabine, and G-CSF (FLAG) for the treatment of poor risk acute myeloid leukemia. Am J Hematol 1998; 58: 105–109.

[4]Parker JE, Pagliuca A, Mijovic A, et al. Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukaemia. Br J Haematol 1997 Dec;99(4):939-944.

[5]Amadori S, Arcese W, Isacchi G, et al. Mitoxantrone, etoposide, and intermediate-dose cytarabine: an effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. J Clin Oncol 1991 Jul;9(7):1210-1214.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Approximately 12,330 people will be diagnosed with acute myeloid leukemia (AML) in 2010, and 8,950 patients will die from the disease.[1] As the population ages, the incidence of AML, along with myelodysplasia, appears to be rising. Equally disturbing is the increasing incidence of treatment-related myelodysplasia and leukemia in survivors of tumors of childhood and young adulthood such as Hodgkin's disease, sarcomas, breast and testicular cancers, and lymphomas. Ionizing radiation and occupational exposure to benzene and petrochemicals are also associated with AML.[2]

The clinicians comprising the NCCN AML panel convene annually to update guidelines for the diagnosis and treatment of AML in adults.

Clinical trials have led to significant improvements in treatment in some areas, primarily in acute promyelocytic leukemia (APL). However, recent large clinical trials have highlighted the need for new, innovative strategies since outcomes for AML patients, particularly the older patients, have not substantially changed in the last three decades.

The NCCN AML panel has focused on outlining reasonable treatment options based on recent clinical trials and data from basic science, which may identify new risk factors and treatment approaches. In some areas, panel members have divergent opinions about the relative risks and benefits of various treatment options. Therefore, these guidelines include an effort to provide a rationale for the inclusion of several of the treatment options in some categories.

Initial Evaluation

The initial evaluation has two objectives. The first is to characterize the disease process including factors such as 1) prior toxic exposure, 2) myelodysplasia, and 3) karyotypic or molecular abnormalities which may provide prognostic information that may have an impact on responsiveness to chemotherapy and risk of relapse. The second objective focuses on patient-specific factors including comorbid conditions that may affect an individual's ability to tolerate chemotherapy. Both disease-specific and individual patient information factors are taken into consideration for treatment decisions.

There are two systems commonly used by pathologists to define hematopoietic malignancies. The French American British (FAB) classification is based on morphology relying on cytochemical stains and also incorporates flow cytometry to define an immunophenotype which separates myeloid from lymphoid blasts. Acute myeloid leukemia is then subcategorized into eight entities based on degree of

differentiation. The FAB classification (1976) sets the threshold between high-grade myelodysplasia (MDS) and AML at 30% blasts.

The 1999 World Health Organization (WHO) classification was designed to include newer prognostic factors such as chromosome translocations, and evidence of dysplasia either by morphology or history which might predict biologic responsiveness, allowing physicians to identify subgroups of patients who might benefit from specific treatment strategies.[3] This classification created a minimum of 17 subclasses of AML. Based on epidemiologic data that indicated equivalently poor survival for MDS patients with 20-30% blasts as for AML patients with >30% blasts, the WHO lowered the threshold for the diagnosis of AML to >20% blasts and abolished the MDS category of refractory anemia with excess blasts in transformation (RAEB-T). In addition, WHO allows the diagnosis of AML regardless of the percentage of marrow blasts in patients with abnormal hematopoiesis and characteristic clonal structural cytogenetic abnormalities in patients with t(15;17), t(8;21), and inv(16) or t(16;16). In 2003 the International Working Group for the Diagnosis and Standardization of Response Criteria accepted the cytochemical and immunophenotypic criteria of WHO as the standard for diagnosis of AML including the reporting of dysplasia by morphology.[4] As yet, however, there is no evidence that dysplasia represents an independent risk factor as it is frequently linked to poor risk cytogenetics.

Based on the recommendations of the International Working Group, some cooperative group and most institutional phase II and pharmaceutical trials have adopted the WHO threshold for percentage marrow blasts as the criterion for the diagnosis of AML as well as their definitions of CR (complete remission) and other categories of response. At the present time, some of the large cooperative group trials retain the FAB criteria for purposes of comparability of study populations in large phase III trials in which the control arm of a current trial is based on the outcome of a prior trial that used FAB definitions.

The WHO most recently revised diagnostic and response criteria for AML in 2008 to include additional recurrent genetic abnormalities created by reciprocal translocations as well as a new provisional category for some of the molecular markers which have been found to have prognostic impact.[5]

Although roughly 75% of patients with acute leukemia can be categorized as myeloid or lymphoid lineage based on routine cytochemistries, immunophenotyping is necessary for proper diagnosis in a subset of patients, particularly those with undifferentiated or minimally differentiated (AML-MO) morphology that may be negative for cytochemical myeloperoxidase (MPO) or combined esterases. A diagnosis of acute lymphoblastic leukemia (ALL) requires the presence of at least two lymphoid markers; most are also terminal deoxynucleotidyl transferase (TdT) positive. The guidelines suggest that either of these complementary techniques can be used at the discretion of the pathology departments of the individual institutions. Some cases may still show evidence of both myeloid and lymphoid antigen expression on the leukemic cells. These cases will require consultation with an experienced hematopathologist. Aberrant expression of differentiation antigens present at diagnosis may allow tracking of residual abnormal cells by flow cytometry in follow-up samples that may appear normal by conventional morphology. However, the role of immunophenotyping and molecular markers to monitor minimal residual disease in adult AML remains an area of research interest at present.

Although cytogenetic information is usually unknown when treatment is initiated in patients with de novo AML, karyotype represents the single most important prognostic factor for predicting remission rate, relapse, and overall survival. In a retrospective review, of 1,213 AML patients treated on CALGB protocols, the 5-year survival rate was 55% for patients with favorable cytogenetics, 24% for patients with intermediate risk, and 5% for those with poor risk cytogenetics.[6] Therefore the importance of obtaining adequate samples on marrow or peripheral blood at diagnosis to do full karyotyping as well as FISH probes for the most common abnormalities cannot be overemphasized. In addition to basic cytogenetic analysis, new molecular markers are helping to refine prognostics groups particularly in patients with a normal karyotype. These include FMS-like tyrosine kinase 3 (FLT3), c-kit, nucleophosmin member 1 (NPM1), and CEBP-A (CCAAT/enhancer binding protein alpha) mutations.[7-15] At present tests for these molecular markers are not commonly available in the community; it is important to preserve additional aliquots of cryopreserved marrow from the time of diagnosis for molecular diagnostic tests in patients with normal karyotype. The two most frequent molecular mutations with prognostic impact are mutations of the FLT3 gene encoding a transmembrane growth factor receptor and mutations of the NPM1 gene which encodes a shuttling protein within the nucleolus. Each of these mutations may be found in 40-50% of patients with normal cytogenetics either as isolated or double mutations A single NPM1 mutation which localizes to the cytoplasm confers a higher complete remission rate (CR) an improved event free survival (EFS) as well as overall survival (OS) to patients with normal karyotype similar to patients with favorable cytogenetics.[9,15] Two major classes of activating FLT3 mutations have been identified in AML patients- internal-tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations. Several large studies have shown that isolated FLT3-ITD mutations carry a poor prognosis with a disease free survival (DFS) of 20-25% at two years particularly if both alleles are mutated.[7, 10] Patients who have both NPM1 and FLT3-ITD mutations have an outcome intermediate between those two groups.[15-18]

Internal tandem duplications of the mixed lineage leukemia (MLL) gene have also been associated with a poor prognosis. In patients with favorable karyotypes; t(8;21) or inv(16), the presence of a mutation in c-kit significantly increases the risk of relapse.[8,13,14] While none of these abnormalities affect the initial treatment, they provide information which may influence subsequent treatment decisions. Research into basic leukemia biology using banked samples from clinical trials may provide keys to altered cellular pathways which may lead to new treatment options. The new risk stratification which incorporates the molecular data along with cytogenetics is summarized in the NCCN treatment algorithms.

Extramedullary presentation, including CNS disease is uncommon events in AML. Patients with significant CNS signs or symptoms at presentation should be evaluated using appropriate imaging techniques such as radiography, computed tomography (CT), or magnetic resonance imaging (MRI) for intracranial bleeding, leptomeningeal disease or mass lesions in either the brain or spinal cord.

If symptoms persist, and bleeding and mass lesions are excluded, the patient should have a lumbar puncture (LP) for diagnostic and possible therapeutic purposes once coagulopathy has been corrected and adequate platelet support is available. Routine screening LP's are not warranted in AML at diagnosis. However, for patients at high risk for CNS disease such as those with monocytic differentiation (M4 or M5) or high WBC (>100,000/mcL) at presentation, a diagnostic LP should be included as part of the documentation of remission status.

Coagulopathy is fairly common at presentation in many leukemias; it is good clinical practice to screen for this problem with prothrombin time (PT), partial thromboplastin time (PTT) and fibrinogen as part of the initial work-up and before any invasive procedure. The need for a cardiac evaluation should be determined by individual risk factors such as patient and family history or previous malignancy treated with cardiotoxic drugs or thoracic radiation. Human leukocyte antigen (HLA) typing should be performed in all newly diagnosed AML patients for whom allogeneic hematopoietic stem cell transplantation (HSCT) would be considered. HLA typing of family members is recommended for patients under age 55 who do not have favorable risk cytogenetics. Tissue typing should be broadened to include unrelated donors searches in patients under 55 with karyotypes or molecular abnormalities deemed high risk or antecedent MDS/therapy related AML. In the high risk group a donor search should begin while the patient is recovering from induction chemotherapy rather than waiting for remission to be achieved. Many institutions also use HLA typing to select platelet donors for allogeneic transplantation. For patients who present with solitary extramedullary disease (often referred to as granulocytic sarcoma or chloroma) without overt marrow disease, the initial treatment should still be based on systemic induction chemotherapy. Radiation or surgical resection may be incorporated at time of systemic chemotherapy in emergent situations, but these modalities, if needed at all, should optimally be deferred until count recovery to avoid excess toxicity.

Principles of Treatment

Treatment of acute leukemia has been divided into induction chemotherapy and post-remission (or consolidation) therapy. Although obtaining a remission is the first step in controlling the disease, it is also important that the patient emerge from the induction phase in condition to tolerate subsequent more intensive treatments during consolidation to achieve durable disease control. Patients who do not receive post-remission therapy will relapse, usually within 6 to 9 months. The induction strategy is influenced by individual patient characteristics, such as age, presence of comorbid conditions affecting performance status, and pre-existing myelodysplasia. This is particularly true of elderly patients with AML. Patients whose performance status would make them poor candidates for the standard anti-neoplastic regimens may still be able to participate in clinical trials using epigenetic agents designed to target this underserved patient population. If a clinical trial is not an option then low intensity therapy or supportive care may be the appropriate choice. In the younger patients, strategies for consolidation are based on the potential risk of relapse, with higher risk patients receiving more aggressive therapy. Cytogenetic and molecular mutations are the most significant prognostic indicator, with failure to achieve remission following 1 cycle of induction therapy and tumor burden (WBC ≥ 100,000/mcL) included as poor risk factors for long term remission. At several points during the course of treatment, response is assessed, based on bone marrow morphology as well as cytogenetic and molecular responses. See “Monitoring during Therapy” in the NCCN Guidelines and also the page on “Response Criteria for Acute Myeloid Leukemia” for definitions of complete and partial response and disease relapse

Finally, all patients require attentive supportive care related both to the underlying leukemia (i.e. tumor lysis syndrome) and the side effects of chemotherapy. These measures are summarized in the NCCN Guidelines under “Supportive Care”.

Management of Acute Promyelocytic Leukemia (APL)

APL has a distinctive morphology, and clinical presentation with coagulopathy which sets it apart from the other FAB morphologic subgroups. The translocation of the promyelocytic leukemia (PML) gene on chromosome 15 adjacent to the retinoic acid receptor (RAR) alpha gene on chromosome 17 produces a fusion protein which can be quantitatively monitored using polymerase chain reaction (PCR) to document disease burden and to ultimately confirm “molecular remission”. The unique ability of all-trans retinoic acid (ATRA) to produce differentiation in APL blasts can reverse the coagulopathy which is the major cause of death during induction. To minimize early induction mortality due to coagulopathy, patients with a presumptive diagnosis of APL based on morphology, immunophenotype and /or coagulopathy with positive disseminated intravascular coagulation (DIC) screen should promptly start ATRA and anthracycline without waiting for molecular confirmation. If the initial clinical diagnosis of APL is not confirmed by FISH or PCR, ATRA will be discontinued and standard AML induction continued.

Induction Therapy for patients with APL

The evolution of treatment strategies for APL built on clinical observation and well constructed clinical trials is one of the most rewarding sagas of modern hematology. As a single agent ATRA was reported to induce CR rates of 85% by the group in Shanghai in 1988.[19] The first North American Intergroup study confirmed a 70% CR rate with single agent ATRA which was equivalent to rates obtained with conventional doses of cytarabine (Ara-C) and daunorubicin.[20, 21]

The French APL 93 trial compared ATRA followed by chemotherapy (Ara-C and daunorubicin) with ATRA plus chemotherapy. CR rates were 92% in both arms but the relapse rate at 2 years was 6% in combined ATRA plus chemotherapy group versus 16% for the sequential group.[22, 23]

Induction regimens were pared down to ATRA and idarubicin in both the Italian GIMEMA 93 trial and the Spanish PETHEMA LPA 94 trial which produced CR rates of 95% which raised the question of whether there was a need for Ara-C in APL induction.[24, 25] It had been commonly observed that patients with elevated WBC had high risk disease based on both higher deaths during induction and from increased rates of relapse. As an outgrowth of the PETHEMA LPA 94 trials, Sanz et al devised a risk stratification based solely on WBC and platelet count at presentation. In this study the induction regimen remained then same (idarubicin and ATRA) but ATRA was added to consolidation cycles 1-3 for all but low risk patients (those with WBC (≤10,000/mcL and platelets >40,000/mcL). The CR rate in this trial was 91% with almost all the failure attributed to hemorrhage, infection, or differentiation syndrome. Factors predictive of death during induction were WBC >10,000/mcL, age >60, creatinine ≥1.4 and male sex).[26, 27] In 2006, Ades et al reported the outcome of the French APL 2000 trial in which 340 patients under age 60 with WBC < 10,000/mcL were randomized to receive ATRA (45 mg/m^2) and daunorubicin (60 mg/m^2 per day for 3 days) as induction therapy with or without Ara-C (200 mg/m^2 per day for 7 days). Those randomized to Ara-C in induction also received Ara-C in consolidation.[28] Patients with WBC >10,000/mcL or over age 60 all received Ara-C. While the complete remission rates were similar in the randomized groups, (99% with and 94% without Ara-C), those receiving Ara-C had a lower 2 year cumulative incidence of relapse that translated into an improved event free survival rate (93% at 2 years with Ara-C and 79% with no Ara-C). In patients with WBC > 10,000/mcL the CR rate was 97% and the 2 year disease free survival was 89% for those under 60 years and 79% for those over 60 years of

age. A report of a joint analysis of the outcomes in the PETHEMA 99 and the French APL 2000 trial in patients <65 years of age showed that in patients with WBC <10,000/mcL, CR rates were similar but the relapse rates at 3 yrs were lower (4.2%) in the PETHEMA trial which used ATRA during consolidation than in the APL 2000 Ara-C containing regimen (14.3%) (*P* = 0.03).[29] However, for patients with WBC >10,000/mcL, the Ara-C containing protocol gave better CR rate (95% compared with 84%) and a better 3 year survival (92% vs. 81%) (*P* = 0.18).[29] The second North American Intergroup trial (NAIT) also used ATRA (45 mg/m^2), daunorubicin (50 mg/m^2 per day for 4 days) and cytarabine (200 mg/m^2 per day for 7 days) with similar initial CR rates.[30] Consolidation in this trial differed in that two cycles of a novel agent, arsenic trioxide were given following induction and prior to the final two cycles of anthracycline.

All three regimens offer excellent outcomes. Choices of regimen will be influenced by risk group, age and cardiovascular risks. The panel recommends that APL patients should be treated according to one of the regimens established from the clinical trials and that one should use a regimen consistently through all components and not mix induction from one trial with consolidation from a second trial. The guidelines are broken down by 1) ability to tolerate anthracyclines and 2) the PETHEMA risk classification using WBC at diagnosis. APL patients who can tolerate anthracyclines are stratified into risk groups based on WBC counts. In general the panel has preferentially listed regimens of equivalent efficacy for a given risk group based on ease of administration. For low or intermediate risk patients (WBC lesser than 10,000/mcL), the panel recommends initial induction with ATRA plus idarubicin alone [31] (category 1); or ATRA plus daunorubicin and cytarabine [21, 29, 30] (category 1 for those on French APL 2000 protocol[29]); or enrollment in a clinical trial.

For high risk patients (WBC greater than 10,000/mcL) the panel had a preference for regimens which include cytarabine along with ATRA plus daunorubicin over ATRA plus idarubicin because of a higher disease free survival at 2 years with the cytarabine containing regimen although the CR rates reported in the trials were very comparable.[21, 29, 31]

Arsenic trioxide has also been found to be a potent promoter of apoptosis in APL cells.[32, 33] In 2004 Shen et al first published outcomes on single agent ATRA; single agent arsenic trioxide (ATO); or the combination of both drugs. While CR rates exceed 90% in all three arms, the decline in quantity of PML/RAR alpha fusion protein as measured by quantitative PCR was significantly higher with the combination. Hematologic recovery was more rapid and relapse free survival was improved at 18 months.[34] Subsequently Estey et al used a similar combination of ATRA and ATO to treat 25 patients with low/intermediate risk APL.[35] Nineteen high risk patients in the same study were treated using the ATRA and ATO combined with gemtuzumab ozogamicin 9 mg/m^2 on day 1 of induction therapy. Complete remission was achieved in 24 of 25 patients with low risk disease and 15 of 19 patients with high risk disease. The authors suggest that ATRA plus ATO may be an alternative to chemotherapy in patients with low and intermediate risk untreated APL and when combined with gemtuzumab ozogamicin, may improve outcome in high risk patients. As of October 2010 gemtuzumab ozogamicin is no longer commercially available in the US after the FDA withdrew its prior approval of the drug for treatment of older patients with relapsed acute myeloid leukemia. However, due to a lack of clinical benefit in this. The NCCN guidelines indicate that ATRA plus ATO is an alternative for patients who cannot tolerate anthracycline therapy.

Consolidation Therapy for Patients with APL

Because the differentiating action of ATRA occurs over a longer time period than the cytoreduction of conventional chemotherapy, early marrow evaluations for hematologic response at day 7-14 post induction are misleading and may lead to over treatment. Marrow evaluation is not recommended until recovery of blood counts usually 4-6 weeks post therapy. Cytogenetics is usually normal by this point but molecular remission often requires at least two cycles of consolidation. All consolidation regimens have high cumulative doses of cardiotoxic agents. Therefore, cardiac function of the patient should be assessed prior to initiating each anthracycline or mitoxantrone containing consolidation cycle.

The goal of consolidation therapy for APL is the conversion of a morphologic and cytogenetic remission into a durable molecular remission. The data from the two sequential PETHEMA trials[25-27] which produced the current risk model was used to construct subsequent trials which intensify therapy for the high risk groups. In the second PETHEMA trial (LPA 99) 15 days of ATRA (45 mg/m^2) were added to each of three cycles of anthracycline consolidation. For the low risk group there was no difference in relapse rate (3-6%) or in 3 year disease free progression (DFS) (93-97%) with the ATRA group compared to a similar consolidation without ATRA in trial LPA 94.[27] For the intermediate risk group, the relapse rate was 2.5% versus 14% in the historic control with a 3 year DFS of 97% versus 82%. Although the addition of ATRA to the high risk group did improve relapse and DFS, there is room for improvement with a relapse rate of 21% and a 3 year DFS of 77%. The new AIDA-2000 trial of the Italian GIMEMA group has confirmed that inclusion of ATRA in consolidation significantly improves outcome.[36]

In the French APL 2000 which randomized cytarabine with daunorubicin consolidation without ATRA, the low and intermediate groups had a 2 year DFS with cytarabine of 93% versus 77% for the group without it.[28] Thus the outcomes for consolidation with anthracycline plus ATRA or anthracycline plus cytarabine are comparable for patients with intermediate risk APL. In the French APL 2000 all the high risk patients under age 60 received cytarabine which does appear to offer some benefit with a 2 year DFS of 89%.[29] In the new nonrandomized Spanish trial (LPA 2005), cytarabine (1 g/m^2/day for 4 days) was added to the combination of ATRA (45 mg/m^2/day for 15 days) and idarubicin (7 mg/m^2/day for 4 days) for consolidation in high risk patients younger than 60 years of age. In the high risk patients the relapse rate at 3 years was significantly lower (11%) compared to 21% without cytarabine.[36, 37] The LPA 2005 trial also began to approach the question of how to reduce toxicity during consolidation therapy in low and intermediate risk patients by a dose reduction of mitoxantrone (from 10 mg/m^2/day for 5 days to 10 mg/m^2/day for 3 days) for low and intermediate risk groups and a small reduction of idarubicin dose between low and intermediate (from 7 mg/m^2/day for 4 days to 5 mg/m^2/day for 4 days). According to the results, in low and intermediate risk groups, lowering the dose of mitoxantrone resulted in reduction of toxicity and hospital stay while maintaining the anti-leukemic activity.

The North American Intergroup trial (NAIT) also approached the topic of decreasing toxicity during consolidation by incorporating arsenic trioxide(ATO) into the consolidation schema directly after achieving remission.[30, 38] In this trial, patients who were randomized to received two courses of 25 days of ATO (5 days a week for 5 weeks) immediately after entering CR and followed by standard post remission regimen with two more courses of ATRA plus daunorubicin had a significantly better event-free and overall survival than those who

received only the two courses of ATRA plus chemotherapy particularly in high risk patients.[30, 38] The overall outcomes do not appear to be superior to the less complex consolidation schedules in either of the two most recent European trials for patients in the low and intermediate risk groups but did appear to offer improved survival for high risk disease. The consolidation period in the North American Intergroup protocol is longer and maybe difficult for some patients. The potential benefits of the use of ATO in consolidation may rest in a lesser risk of long term cardiovascular complications and perhaps a lower risk of secondary myelodysplasia.

For patients with high risk disease, the panel suggests the inclusion of cytarabine as used in the French APL 2000 trial[28] and PETHEMA LPA2005 [31] or 2 cycles of ATO followed by 2 additional cycles of standard chemotherapy as used in the US Intergroup trial for consolidation.[30, 38] When using a cytarabine containing regimen, dose adjustments of cytarabine may be needed for older patients or patients with renal dysfunction.[29, 30] For low risk patients the panel has positioned the revised PETHEMA 2005 regimen slightly higher than either the French APL 2000 or the NAIT because of ease of administration and decreasing toxicity. However all three regimens will yield excellent results. For the intermediate risk group, outcomes are very similar as long as one regimen is followed consistently from induction through consolidation.

In patients who could not tolerate anthracyclines who received ATRA and ATO for induction therapy, the reported trials continued with repeated cycles of these two agents post induction. For patients who cannot tolerate anthracyclines, who received ATRA and ATO as induction therapy, the NCCN panel recommends for consolidation therapy, ATO (0.15 mg/Kg IV daily for 5 days/week every other month for 4 cycles) with ATRA (45 mg/m^2 in divided doses daily PO during one week monthly for 7 cycles).

Post-Consolidation or Maintenance Therapy for Patients with APL

Following consolidation therapy, patients are assessed for molecular remission using RT-PCR techniques on bone marrow samples. For those that are PCR negative a 1-2 year course of ATRA maintenance therapy has been recommended which may be combined with 6-mercaptopurine (6-MP) and methotrexate. The recommendations for maintenance ATRA arose from several early trials which showed superior relapse free survival for patients receiving ATRA alone or in combination as maintenance. The French APL 93 trial showed decreased relapse rates at 2 years for ATRA (21%), 6-MP, and methotrexate (13%), and ATRA plus 6-MP, and methotrexate (8%), versus no maintenance (35%).[22] Results of a longer follow-up of the APL93 study patients show a beneficial effect of maintenance treatment with intermittent ATRA and continuous 6-MP and methotrexate, with an additive effect of the 2 modalities.[39] The study data showed that that maintenance treatment reduced the incidence of early relapses without increasing incidence late relapses. Patients with WBC count higher than 5000/µL benefitted most from maintenance therapy. The relapse rate dropped from 68.4% with no maintenance to 20.6% with combined ATRA plus chemotherapy maintenance. In patients with WBC counts lower than 5000/µL, the 10-year relapse rate reduced from 29.2% without maintenance to 11.5% with combined maintenance.[39]

The first US Intergroup trial showed superiority of disease-free survival for patients receiving maintenance ATRA versus no maintenance.[21, 22] However there are data from the AIDA trial which suggest that there was no benefit to maintenance in patients who are molecularly negative at end of consolidation.[40] However as consolidation regimens have evolved to incorporate ATRA or ATO into consolidation, the role of

maintenance chemotherapy is less clear, particularly for patients with low risk disease who achieve a molecular remission at the end of consolidation. An international cooperative group trial (SWOG 0521) is designed to examine the need for maintenance in low/intermediate patients. The studies showing benefit for maintenance were carried out prior to the use of ATRA for consolidation.[21, 22] The conflicting data indicate that benefit of maintenance depends upon prior induction and consolidation therapy. Therefore, it would be appropriate to use maintenance in conjunction with protocols in which it has been shown to confer benefit.

Monitoring by RT-PCR should be performed on a marrow sample at completion of consolidation to document molecular remission. Subsequent monitoring of patients by PCR can be done with peripheral blood, although using marrow sample is a more sensitive monitoring technique and may give earlier signs of relapse. Monitoring is recommended at a minimum of every 3 months for 2 years during maintenance to detect molecular relapse in patients with intermediate and high risk disease. Clinical experience indicates that risk of relapse in patients with low risk disease who are in molecular remission at completion of consolidation is low and monitoring may not be necessary outside the setting of a clinical trial. At the current level of resolution, a change from PCR negative to positive should be confirmed by bone marrow in a reliable laboratory within 4 weeks. If molecular relapse is confirmed by a second positive test, intervention should be strongly considered. If the second test was negative, maintenance therapy and frequent monitoring every 2-3 months for an additional 2 years is strongly suggested to assure that the patient remains negative. Testing should be done in the same laboratory to maintain a consistent level of sensitivity. In patients who develop cytopenias and who have a negative RT-PCR, a marrow is recommended to look for new cytogenetics abnormalities as secondary MDS and AML have occurred following APL therapy.

Management of Relapsed APL

Arsenic trioxide is the recommended therapy for patients who remain molecularly positive at completion of consolidation or who subsequently demonstrate molecular relapse. As a single agent it produced CR rates of 80-90% in patients with hematologic relapse and achieved molecular remissions in 70-80% of those patients. ATRA and ATO appear to be synergistic and one could consider using the combination in patients who had not received ATRA during consolidation.[32-34] However a small randomized study of 20 patients with relapsed APL all previously treated with ATRA containing chemotherapy showed no improvement in response by adding ATRA to ATO compared to ATO alone.[41]

A small percentage of relapsed APL has a CNS component.[42, 43] Therefore for patients who are in second morphologic remission, the NCCN panel strongly recommends intrathecal therapy as CNS prophylaxis.

Patients who achieve a molecular remission after second line therapy should be considered for autologous HSCT, if they do not have contraindications to high dose therapy. Patients who received a PCR-negative autograft had a 75% 7-year overall survival in a recent retrospective study published by the European APL Group, compared to a 52% overall survival for patients receiving allogeneic HSCT.[44] The differences in survival are accounted for by higher treatment-related mortality in the allogeneic group, which influences the guideline recommendations to reserve allogeneic transplant for those who have persistent disease despite salvage therapy. For patients in second CR who have contraindications to HSCT, continued therapy with ATO for six cycles is recommended in the absence of a clinical trial.

Supportive Care for Patients with APL

Specific supportive care issues should be considered when treating patients with APL. Therapy for APL is often associated with a constellation of symptoms and physiologic abnormalities, including fluid retention, dyspnea, episodic hypotension, pulmonary infiltrates, and pulmonary or pericardial effusions now referred to as “differentiation syndrome”. Early in treatment with either ATRA or arsenic as single agents or in combination, patients may begin to develop evidence of “differentiation syndrome”. These patients develop fever, fluid retention, and rapidly rising WBC >10,000. These patients should be closely monitored for hypoxia and the development of pulmonary infiltrates or pleural effusion. Differentiation syndrome along with hemorrhage, are the leading causes of death during induction. Early recognition and prompt initiation of steroids are the keys to dealing with this complication. In some studies, low mortality and morbidity rates were seen when corticosteroids were administered prophylactically in patients presenting with high WBC counts.[27, 45] Kelaidi et al assessed the outcomes of patients with high WBC (greater than 10,000/mcL) enrolled in APL93 and APL2000.[46] The factor in supportive care which had an effect on the early induction deaths was the use of dexamethasone 10mg/12 hour beginning on day 1 for patients on APL2000. The early death rate from differentiation syndrome dropped from 8/139 in APL 93 trial to 2/133 in APL 2000 trial. The NCCN panel recommends addition of prophylactic steroids in patients with WBC greater than 10,000/mcL to prevent differentiation syndrome. The NCCN panel has provided management recommendations in the “Supportive Care” section. For patient with WBC over 10,000 or symptoms of “differentiation syndrome”, the panel recommends treating with dexamethasone 10 mg twice a day for 3 to 5 days, the dose is then tapered over two weeks. ATRA may need to be held during the initial acute symptomatic period but may be restarted when symptoms improve. Other factors which have been reported to increase the risk of differentiation syndrome are: a high body mass index and age over 40.

Leukapheresis is not recommended in the routine management of patients with high white blood cell counts in APL because of the difference in leukemia biology. However, in a life threatening case with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution.

Since coagulopathy is common in patients with APL, it is good clinical practice to screen for this problem with prothrombin time (PT), partial thromboplastin time (PTT) and fibrinogen as part of the initial work-up and before any invasive procedure. Clinical coagulopathy is managed by aggressive transfusion support to maintain platelets ≥ 50,000/mcL, by fibrinogen replacement with cryoprecipitate and frozen plasma to maintain a level of 150 mg/dL and levels of PT and PTT close to normal. Patients with clinical coagulopathy need to be monitored daily until it resolves.

Arsenic trioxide therapy may prolong the QT interval, making patients susceptible to ventricular arrhythmias. Therefore, prior to each cycle of therapy an electrocardiogram (ECG or EKG) is recommended to assess prolonged QT interval. Routine monitoring weekly during therapy is also suggested for older patients. Serum electrolytes should also be monitored prior to and during therapy to maintain electrolytes (Ca ≥9.0, K ≥4.0, Mg ≥1.8) in the upper normal range. Other drugs that prolong the QT interval should be avoided during ATO to minimize the risk of cardiac arrhythmias. Patients with an absolute QT interval greater than 500 m/sec should be reassessed.

In the French APL 93 trial there was a 4 % incidence of CNS relapse in patients with WBC > 10,000. In APL 2000 that high risk population

received five doses of intrathecal chemotherapy using a combination of methotrexate, cytarabine, and steroids upon count recovery following induction. They also received a higher dose of cytarabine (2 gm/m^2) during consolidation cycle 2 as compared with 1 gm/m^2 in APL 93. There were no CNS relapses in APL 2000 versus 5 cases in APL 93. While the original trial used high dose cytarabine as the second consolidation, some investigators are suggesting the use of high dose cytarabine earlier, particularly in those who are not receiving intrathecal therapy for prophylaxis.

Management of Acute Myeloid Leukemia

Most initial treatment decisions for AML are based on age, history of prior myelodysplasia or cytotoxic therapy and performance status. Although karyotype is the most powerful predictor of disease-free survival, in most instances induction chemotherapy will be initiated before this information is available. The intent of traditional induction chemotherapy is to produce a major reduction in the leukemic burden and to restore normal hematopoiesis.

Recommendations for induction chemotherapy for patients with AML consider age 60 as a therapeutic divergence point. This is based on the higher prevalence of unfavorable cytogenetics and antecedent myelodysplasia, along with a higher incidence of multidrug resistance in patients over 60 years of age, as well as an increased frequency of comorbid medical conditions that affect the ability to tolerate intensive treatment.[47] Because complete remission rates rarely exceed 70% in younger patients and 50% in older patients, there is substantial opportunity for innovative clinical trials for both patient populations. These guidelines consider patients older or younger than 60 years old separately.

Management AML Patients Younger than 60

Induction Therapy

Standard induction regimens are appropriate for patients younger than age 60 who have no antecedent hematologic disease, such as myelodysplastic syndrome or treatment related secondary AML. These regimens are based on a backbone of cytarabine and an anthracycline and have changed little in the last 25 years. Historically, in most large cooperative group trials, daunorubicin has been the most commonly used anthracycline at doses of 45-60 mg/m^2. Idarubicin which has a longer intracellular retention time used at doses of 12 mg/ m^2 x 3 days has had comparable remission rates with fewer patients requiring additional therapy at day 15 to achieve remission. CR rates for patients who are 50 years or younger have consistently been in the 60-70% range for most large cooperative group trials of infusional cytarabine and anthracycline. A recent ECOG study reported a significant increase in CR (71% versus 57%) rates and OS using daunorubicin 90 mg/m^2 x 3 days versus 45 mg/m^2 x 3 days in patients younger than 60 years of age.[48] The survival benefit was restricted to patients with favorable- and intermediate-risk cytogenetic profiles and those under the age of 50 years. In a European trial which compared idarubicin 12mg/m^2 x either 3 or 4 days versus daunorubicin 80mg/m^2 x 3 days in patients between ages 50-70 showed CR rates of 83% for the idarubicin 12 mg/m^2 for 3 days versus 70% for daunorubicin 80mg/ m^2 x 3 days (p = 0.024).[49] There was no difference in relapse rate, event free survival (EFS), or OS among the arms. According to the NCCN AML panel, infusional cytarabine x 7 days combined with either idarubicin or escalated daunorubicin is a category 1 recommendation.

For patients with impaired cardiac function, other regimens that combine non-anthracycline (such as fludarabine[50] or topotecan[51]) with cytarabine have been published.

Dose-intensive cytarabine therapy during induction has been explored previously in two large cooperative clinical trials. In an Australian Leukemia Study Group trial,[52] 301 patients under age 60 years were randomized to receive either high dose cytarabine (3 g/m^2 every 12 hours on days 1, 3, 5, and 7 for a total of 24 g/m^2) or standard cytarabine therapy (100 mg/m^2/d x 7 days via continuous infusion); both arms received daunorubicin (50 mg/m^2 on days 1 to 3) and etoposide (75 mg/m^2/day x 7 days). The CR rates were equivalent in both arms (71% and 74%, respectively), although treatment-related morbidity and mortality were higher in the high dose arm. Patients in both arms of the study received only two cycles of standard dose cytarabine, daunorubicin, and etoposide for consolidation. Median remission duration was 45 months for the dose-intensive arm, compared with 12 months for the standard treatment arm.

In a Southwestern Oncology Group (SWOG) study,[53] patients were randomized to receive high-dose cytarabine (2 g/m^2 every 12 hours x 6 days for a total of 24 g/m^2) or standard-dose cytarabine (200 mg/m^2/d x 7 days); patients in both treatment arms also received daunorubicin (45 mg/m^2/d x 3 days). Patients receiving high dose cytarabine induction therapy received a second high-dose cycle for consolidation, and patients in the standard-dose treatment arm were randomized to receive either two cycles of standard dose cytarabine consolidation or one cycle of high-dose cytarabine plus daunorubicin consolidation. The complete response rates were again equivalent: 55% for the high-dose cytarabine treatment arm compared with 58% for the standard-dose arm for patients younger than 50 years; and 45% for high-dose cytarabine versus 53% for standard-dose therapy for patients 50 to 65 years of age. Patients in the high dose cytarabine arm experienced higher treatment-related mortality (12% vs. 5%) and neurologic toxicity. Younger patients who received both high dose cytarabine induction and consolidation in the SWOG trial had the best survival (52%) and disease-free survival (34%) rates at 4 years, when compared with standard induction and consolidation (34% survival and 24% disease-free survival) or standard induction with high dose consolidation (23% survival and 14% disease-free survival). However, the percentage of patients achieving a CR who did not proceed to consolidation was twice as high in the high dose cytarabine induction arm. The risks for neurotoxicity and renal insufficiency are increased with high dose cytarabine and both renal and neurologic function should be closely monitored in patients receiving such treatment. In a Cancer and Leukemia Group B (CALGB) trial,[54] patients who received standard-dose cytarabine-daunorubicin induction therapy or three to four courses of high-dose cytarabine consolidation also achieved a 4-year disease-free interval of 44% with similar rates of neurotoxicity and treatment-related mortality.

Since the overall survival for the high-dose arm in the SWOG trial (HiDAC induction and two cycles of HiDAC consolidation) is comparable to the CALGB trial with standard-dose infusional cytarabine induction and four cycles of HiDAC consolidation, the use of high-dose cytarabine in induction outside a clinical trial remains controversial. The decision to use high-dose cytarabine versus standard-dose cytarabine for induction might be influenced by consolidation strategies; fewer high-dose consolidation cycles may be needed for patients induced with high-dose cytarabine or for patients who will undergo early autologous stem cell transplantation. While the remission rates are the same for standard- and high-dose cytarabine, two studies have shown more rapid marrow blast clearance after one cycle of high-dose therapy and a disease-free survival advantage for patients less than or equal to age 50 who received the high-dose therapy.[55] There are no data using

more than 60 mg of daunorubicin or 12 mg of idarubicin with high-dose cytarabine. High-dose cytarabine plus an anthracycline as induction therapy is considered a category 2B recommendation for patients younger than 60 years.

With either high- or standard-dose cytarabine based induction for younger patients, between 20% and 45% of these patients will not enter remission. In a recent report of 122 patients treated with high dose cytarabine and daunorubicin, the remission rates were strongly influenced by cytogenetics, with complete remission rates of 87%, 79%, and 62% for favorable, intermediate, and poor risk groups, respectively.[56]

Patients with antecedent hematologic disease or treatment related secondary leukemia are considered poor risk patients, unless they have favorable cytogenetics such as t(8;21), inv(16), t(16;16), or t(15;17) In addition, patients with unfavorable karyotypes such as -7, -5, 11q23 abnormalities or complex cytogenetic abnormalities are also considered poor risk and are treated similarly. This group of patients should be entered into a clinical trial (incorporating either chemotherapy or low-intensity therapy), if available, since only 40% to 50% of these patients achieve CR with standard induction therapy, and response durations are short. In addition, HLA testing should be done promptly in those who may be candidates for either fully ablative or reduced intensity allogeneic HSCT from a sibling or an unrelated donor, which constitutes the best option for long-term disease control. Due to the decreased probability of achieving remission through induction chemotherapy, transplantation without induction chemotherapy may be considered for patients with antecedent myelodysplasia or treatment-related leukemia who have an available sibling donor and who have relatively low percentage marrow involvement. In an EBMT (European Blood and Marrow Transplantation) trial,[57] patients with high risk myelodysplasia or AML evolving from myelodysplasia who received allogeneic transplantation without prior cytarabine based chemotherapy had a 34% 3-year disease-free survival. Patients who received antecedent chemotherapy and achieved a CR had a 45% disease-free survival, compared with 10% for patients who did not respond to chemotherapy before transplantation. An alternative strategy for patients with antecedent myelodysplasia who have not received a hypomethylating agent would be a trial of either decitabine or azacytidine while a rapid donor search is initiated.

Post-Induction Therapy for AML Patients Younger than 60 Years

To judge the efficacy of the induction therapy, a bone marrow aspirate and biopsy should be done 7 to 10 days after completion of induction therapy. In patients who have received standard-dose cytarabine induction and have residual blasts without hypoplasia, additional therapy with standard-dose cytarabine and anthracycline should be considered. For those with significant residual blasts or clear cut induction failure, escalation to high dose cytarabine with or without an anthracycline is the most common salvage strategy. Other options include an allogeneic HSCT, if a matched sibling or alternative donor has been identified, or participation in a clinical trial. For those patients whose clinical condition has deteriorated such that active treatment is no longer appropriate, best supportive care should be continued. If the marrow is hypoplastic (defined as cellularity <10-20% and residual blasts <5-10%), additional treatment selection may be deferred until marrow recovery when the remission status can be assessed.

Patients initially treated with high dose cytarabine and who have significant residual blasts 7-10 days after completion of chemotherapy are considered to have induction failure. Additional high dose cytarabine is unlikely to induce remission. If a sibling or HLA matched unrelated donor has been identified, an allogeneic HSCT may salvage

25% to 30% of patients with induction failure. If no donor is immediately available, patients should be considered for a clinical trial.

Occasionally, patients with both myeloid and lymphoid markers at diagnosis (biphenotypic leukemia) may respond to acute lymphoblastic leukemia (ALL) therapy if they failed an AML induction regimen. Treatment decisions for patients with significant reduction without hypoplasia or those with hypoplasia are deferred until the blood counts recover and a repeat marrow is performed to document remission status. Response is then categorized as complete response or induction failure.

Post-remission or Consolidation Therapy for AML Patients Younger than 60 Years

While successful induction therapy clears the visible signs of leukemia in the marrow and restores normal hematopoiesis in patients with de novo AML, additional therapy (consolidation) is needed to first reduce the residual abnormal cells to a level that can be contained by immune surveillance.

Since 1994, multiple (3-4) cycles of high dose cytarabine therapy have been the non-protocol standard consolidation regimen for patients under 60 years of age with either good- or intermediate-risk cytogenetics. This therapy is based on a CALGB trial comparing 100 mg/m^2, 400 mg/m^2, and 3 g/m^2 doses.[54] The 4-year disease-free survival rate for patients receiving 3 g/m^2 was 44%, with a 5% treatment-related mortality rate and a 12% incidence of severe neurologic toxicity. Although the initial report did not break down disease-free survival rates by cytogenetic subgroups, subsequent analysis showed a disease-free survival rate of 60% for good-risk cytogenetics, 30% for intermediate-risk cytogenetics, and 12% for poor-risk cytogenetics in patients receiving high dose cytarabine consolidation; these outcomes are similar to those on the high dose cytarabine treatment arm in the SWOG trial in which patients received high dose cytarabine induction and two cycles of high dose cytarabine consolidation.[53] The CALGB trail also included maintenance chemotherapy following the consolidation, however only a small fraction of patients ever received maintenance and subsequent trials have not included this aspect of the trial.

Other options for consolidation strategies include one or more cycles of high dose cytarabine followed by autologous HSCT or allogeneic HSCT from sibling or unrelated donors. When choosing among these options, decisions are influenced by the (1) expected relapse rate with high dose cytarabine consolidation chemotherapy, (2) the additional morbidity and mortality associated with the transplant procedure, which in turn are strongly influenced by patient-specific comorbidity, and (3) salvage options. Factors such as patient age, comorbid conditions, and features of the disease at diagnosis, including elevated leukocyte counts (≥50,000/mcL) or number of cycles of induction to achieve remission, should play a role in choosing a consolidation strategy, as should issues regarding fertility and salvage options. Patients who require two cycles of chemotherapy to achieve a remission are at very high risk for relapse and should be considered for either clinical trial or allogeneic transplant as initial consolidation whenever possible.

Previous guidelines have used cytogenetics as the major defining criteria for risk of relapse. In this update we have tried to incorporate emerging data on the influence of mutations in specific genes such as c-KIT, FLT3, CEBPA and NPM-1 on subsets of patients within a cytogenetic category. When the data on the Cancer and Leukemia Group B (CALGB) trial was analyzed by cytogenetic groups, the dose intensive cytarabine consolidation produced relapse free survival of 50-60% overall in patients with inv(16) or t(8, 21) with treatment related

mortality cumulative of 8-10%.[6, 54, 56] The data was subsequently re-analyzed to include information on the effects of c-kit mutations which occur in 20-30% of these favorable risk patients on relapse rates and outcomes. In patients with inv16 the relapse rate increased from 29% for wild type c-kit to 56% for patients with c-kit mutations which also translated into a decreased overall survival at 2 years of 56% vs. 76%. In patients with t(8:21) the risk of relapse increased from 30% to 70% and the overall survival decreased to 42% at 2 years.[48]

In the EORTC/GIMEMA trial comparing autologous vs. allogeneic HSCT, disease free survival for patients with good risk cytogenetics (t(8;21) or inv16) was 66% for autologous and 62% for allogeneic HSCT.[58] Treatment related mortality was 6% and 17% respectively. Small single institution studies have reported DFS of 88% for patients undergoing autologous HSCT.[59] These data suggest that in this subgroup of patients with AML, allogeneic HSCT may be restricted to salvage therapy or those with c-kit mutations.

Therefore the panel has provided the following options for consolidation therapy for patients with better risk cytogenetics 1) 3-4 cycles of high dose Ara-C (HiDAC) (category 1) followed by maintenance therapy (category 2B) or one to two cycles of dose intensive cytarabine followed by autologous HSCT (category 2B) for CBF leukemia patients lacking c-kit mutation. However patients who have c-kit mutations have an outcome more similar to those with intermediate risk karyotype and should either be considered for clinical trials targeted toward the molecular abnormality or consolidation strategies similar to the intermediate risk group. A well thought out plan for salvage with either sibling or unrelated donor HSCT should form an important part of the decision for these patients.

Panel members were in accord that transplant based options (either matched sibling or alternate donor HSCT or one to two cycles of dose intensive cytarabine followed by autologous stem cell transplantation) afforded a lesser risk of relapse and a somewhat higher disease free survival as consolidation for most patients with intermediate risk cytogenetics. In the EORTC/GIMEMA trial, the 4-year DFS was 48.5% for allogeneic and 45% for autologous HSCT in patients with normal cytogenetics (with NN and – Y only).[58] Other options for this group include clinical trials or multiple courses (3-4) of high dose cytarabine consolidation.[60] Alternative regimens incorporating intermediate doses of cytarabine (1.5-2.0 gm/m^2) are also acceptable in this group. Comparable 5-year DFS were reported in AML patients <60 years with normal karyotype after either four cycles of intermediate or high dose cytarabine (41%) or autologous HSCT (45%).[60]

However in the last 3-5 years we have learned that “normal” cytogenetics encompasses several molecular mutations with divergent risk behaviors. A large German trial[16] has revealed additional molecular prognostic markers for patients with “normal” karyotype. The presence of an isolated mutant NPM1 cytoplasmic shuttle protein improves prognosis to that comparable to patients with better risk cytogenetics. For this subset of patients, therapy with multiple cycles of HiDAC is a reasonable option and transplantation should be reserved until relapse. In contrast, patients with an isolated FLT3-ITD (internal tandem duplication) mutation and normal karyotype have an outlook similar to those with poor risk cytogenetics[14] and should be considered for a clinical trial or early allogeneic transplantation. Preliminary trials incorporating FLT-3 inhibitors have been disappointing. The NCCN AML panel members strongly recommend clinical trials as standard therapy for patients with poor prognostic features, which include FLT-3 abnormalities in the setting of otherwise normal karyotype, high WBC

(>50,000/ul) at diagnosis or two cycles of induction therapy needed to achieve CR.

Sibling allogeneic HSCT produced a 43% DFS rate in group of patients with poor risk cytogenetics in the EORTC/GIMEMA trial, with similar outcomes for unrelated donor recipients reported by the International Bone Marrow Transplant Registry (IBMTR). The outcome for autologous HSCT was comparable to chemotherapy with 18% DFS.[58] The panel uniformly endorsed allogeneic sibling HSCT or HLA matched unrelated donors (including cord blood) or clinical trial as consolidation therapy for patients with poor risk cytogenetics or molecular abnormalities or patients with therapy-related AML or prior myelodysplasia. Another option for this group is 1 to 2 cycles of high-dose cytarabine based consolidation followed by autologous HSCT if no allogeneic transplant option available (category 2B).

Management of AML Patients 60 and Older

Induction Therapy for patients aged 60 and older

The creation of separate algorithms for patients older than 60 recognizes the poor outcomes in this group with standard cytarabine and an anthracycline, particularly for those 75 or older, or those 60 to 75 years old with significant comorbidities or with an ECOG performance status greater than 2.[47, 51] Treatment related mortality frequently exceeds any expected transient response in this group. The British MRC AML 14 trial randomized 217 older patients unfit for chemotherapy to receive either 20 mg cytarabine by subcutaneous injection twice daily for 10 consecutive days each month or hydroxyurea.[61] CR was achieved in 18% of the cytarabine patients and produced a survival benefit in patients with favorable or normal karyotype. Even this “low intensity” approach had a 30 day mortality of 26%.

The majority of leukemia patients seen by hematologists and oncologists are comprised of the “robust” baby boomers of 60-75 years of age. Many of these patients will present with pancytopenia with modest marrow infiltration (20-40%). If they are clinically stable, it is helpful in the decision making process to know the cytogenetic prognostic group.[62]

For older patients (> 60 years) with AML, the panel recommends using patient performance status, in addition to adverse features (such as unfavorable cytogenetics and therapy related AML or prior MDS) and comorbid conditions to select treatment rather than using their chronological age alone.

Older adults with good functional status (ECOG score 0-2), minimal comorbidity, and good risk cytogenetic or molecular mutations, may benefit from standard therapies regardless of chronologic age. A reasonable treatment regimen for these patients is 7 days of continuous infusion standard dose cytarabine (100-200 mg/m^2 per day) along with 3 days of anthracycline. Patients over 75 years old with significant comorbidities usually do not benefit from conventional chemotherapy treatment. However, the rare patient with good or normal karyotype and no significant comorbidities may benefit from conventional chemotherapy treatment. For patients with normal karyotype, the remission rates are 40-50% with cytarabine combined with idarubicin, daunorubicin or mitoxantrone. The study by Pautas et al published in 2007 ASH annual meetings abstract has shown that idarubicin treatment compared to high doses of daunorubicin up to 80 mg/m^2 yields higher complete response rate and more complete responses after one course.[49] Study by Löwenberg et al[63] shows that the CR rates and 2 year overall survival in patients between 60 and 65 treated with daunorubicin 90mg/m^2 is also comparable to the outcome with idarubicin (12mg/m^2)[64] and that the benefit in overall survival in the

high-dose daunorubicin group was observed only in patients who were under the age of 65 years and in patients with core-binding factor (CBF) leukemia.[63]

Several encouraging therapeutic leads have emerged that hold promise for the treatment of elderly patients with AML who are deemed unfit to receive intensive chemotherapy.

The study by Burnett et al established low-dose cytarabine as an accepted standard of care in elderly patients with AML who are unfit for chemotherapy.[61] The study demonstrated that low-dose cytarabine therapy was associated with a higher CR rate (18% vs. 1%) and longer overall survival compared with hydroxyurea.

The study by Fenaux et al[65] compared 5-azacytidine to conventional care (best supportive care; or low dose cytarabine; or intensive chemotherapy). This study was designed for evaluation of treatment options in high-risk MDS patients using FAB criteria, however using the 2008 WHO classification, 113 study patients (32%) fulfilled criteria for acute myeloid leukemia with marrow-blast percentage between 20% -30% blasts. In the subgroup of RAEB-T, there was a significant survival benefit with 5-azacytidine when compared with best supportive care or low dose cytarabine which exceeded by 9.5 months in both groups. There was also a better overall survival when 5-azacytadine was compared with standard induction therapy but the difference was not significant due to small sample size.

Decitabine (20 mg/m^2/day for 5 days) has been used as remission induction therapy for older patients with AML.[66] The CR rate was 29% (including 3/10 patients with poor risk cytogenetics). Both azacytidine and decitabine are approved by the FDA as therapy for myelodysplasia. Another drug which has received recent attention as a possible induction therapy for older patients is the purine nucleoside analog, clofarabine. Clofarabine has been approved by the FDA for relapsed pediatric ALL. The results of a single agent Phase II trial indicated that single agent clofarabine showed a combined CR/CRp of 45% with a 30 day mortality of 10%. In a group of 115 patients with a median age of 71 years, median overall survival was 59 weeks for the responders versus. 41 weeks for non-responders. Confirmatory Phase III trials are in progress for clofarabine.[67]

The NCCN panel has included subcutaneous cytarabine, 5-azacytidine, and decitabine as low intensity treatment options and clofarabine as intermediate intensity treatment option for patients with AML who are 60 years or older. Best supportive care includes red cell and platelet transfusions to alleviate symptoms of anemia and thrombocytopenia; prophylactic antibiotic and antifungal drugs to reduce the risk of infection; and hydroxyurea for management of leucocytosis

Older adults with newly diagnosed AML with ECOG score between 0-2 with or without adverse features (such as therapy-related AML/prior MDS or unfavorable cytogenic or molecular markers) may be managed by one of the following options: clinical trial, standard infusional cytarabine and anthracycline; or low intensity/intermediate intensity therapy.

Patients with ECOG score greater than 2, significant comorbidity or poor risk cytogenetics are more likely to experience toxicity and less likely to benefit from standard induction chemotherapy. The panel feels it is reasonable to offer such poor risk patients supportive care a clinical trial investigating novel agents or low intensity therapy.

Post-Induction Therapy for AML Patients aged 60 and Older

Similar to younger patients, older patients who receive standard cytarabine /anthracycline induction are evaluated with a bone marrow 7-10 days after completion of chemotherapy and categorized according to the presence of blasts or hypoplasia. Patients with significant cytoreduction without hypoplasia may receive standard-dose cytarabine with an anthracycline or anthracenedione. A repeat bone marrow is performed in these patients and in those with hypoplasia following induction to document the remission status. Because many older patients have some evidence of antecedent myelodysplasia, full normalization of peripheral blood counts often does not occur even if therapy clears the marrow blasts. Thus many Phase I/II trials for AML in the older patient include categories such as CR incomplete (CRi) for patients who have <5% marrow blast but who have mild residual cytopenia.

Many of the newer treatment strategies are designed to work more gradually using agents which may allow expression of tumor suppressor genes (such as a methyltransferase inhibitor like decitabine or 5-azacytidine) or by increasing apoptosis (such as histone deacetylators). Thus success in these trials may be assessed by indirect measures such as hematologic improvement or decreased transfusion requirements as well as survival without actually achieving CR. Frequently in such trials marrow examination is not performed until completion of one or two cycles of therapy.

Patients who achieve a complete remission (including CRi) with standard induction chemotherapy may receive further consolidation with these agents. The French Acute Leukemia (ALFA) 98 trial randomized patients who achieved remission to consolidation with either one additional course of standard cytarabine 200 mg/m^2 x 7 days plus the anthracycline to which they had been randomized for induction (idarubicin 9 mg/m^2 x 4 days or daunorubicin 45 mg/m^2 x 4 days) or 6 monthly courses at 1 day of anthracycline at the above doses and cytarabine 60 mg/m^2/12 hour as a subcutaneous infusion at home for 5 days each month. Patients receiving the ambulatory arm had a better 2 year DFS (28%) than the single intense consolidation (17%) $P = 0.03$; overall survival, transfusion requirement and days in hospital all favored the ambulatory arm.[68] While the CALGB trial did not show an overall benefit for higher doses of cytarabine consolidation in older patients, a subset of patients with a good performance status, normal renal function and a normal or low risk karyotype might be considered for a single cycle of cytarabine (1-1.5 g/m^2/d x 4-6 doses) without an anthracycline.

The role of myeloablative allogeneic HSCT is limited in older patients due to significant co-morbidities, but there has been ongoing interest in reduced intensity allogeneic HSCT as consolidation therapy.[69, 70] Case series and analysis of registry data have reported encouraging results with 40-60% 2 year overall survival and 20% non-relapse mortality for patients transplanted in remission. However, Estey and colleagues prospectively evaluated a protocol where patients over the age of 50 with unfavorable cytogenetics would be evaluated for a reduced intensity allogeneic HSCT.[71] Of the 259 initial patients, only 14 ultimately underwent transplantation, due to illness, lack of donor, refusal or unspecified reasons. The authors compared the results with matched cases receiving conventional dose chemotherapy. This analysis suggested that the reduced intensity allogeneic HSCT was associated with improved relapse free survival and the authors concluded that this approach remains of interest. For this strategy to be better utilized, potential candidacy should be considered during induction and unrelated donor options explored early.

The guidelines note that reduced intensity allogeneic HSCT is considered an additional option for patients 60 years and older for the following indications: (1) as a post-remission therapy for those achieving a complete response to induction therapy (2) for treatment of induction failure only in patients with low volume disease

Post-Remission Surveillance and Salvage Therapy for AML

Complete blood counts including platelets should be monitored every 1-3 months for the first 2 years after patients have completed consolidation, then every 3-6 months for a total of 5 years. Bone marrow evaluation is recommended only if the hemogram becomes abnormal, rather than routine surveillance at fixed intervals, unless this is being done as part of a research protocol.

A matched unrelated donor search (including cord blood) should be initiated for high risk patients who would be candidates for HSCT in first CR or considered at first relapse in appropriate patients concomitant with initiation of re-induction therapy.

Treatment strategies for relapse are categorized according to the patient's age. For patients younger than 60 years who have experienced a relapse, enrollment in clinical trials is considered an appropriate strategy and is a strongly preferred option by the NCCN panel. If the relapse is after a "long" (> 12 months) remission, retreatment with the previously successful regimen is an option. If the relapse is detected when the tumor burden is low and the patient has a previously identified sibling or unrelated donor, salvage chemotherapy followed by allogeneic HSCT can be considered. Transplant should be considered only if the patient has achieved remission or in the context of a clinical trial.

The NCCN treatment algorithms provide a list of some commonly used salvage regimens under "Salvage Chemotherapy Regimen Options" The regimens included represent purine analog (such as fludarabine and cladribine) regimens which have shown remission rates of 30-40% in several clinical trials and those which have been used as the comparator arms in US co-operative group trials in the last decade. The representative regimens are: 1) cladribine, cytarabine, G-CSF with or without mitoxantrone or idarubicin;[72, 73] 2) Fludarabine, cytarabine, G-CSF with or without idarubicin;[74, 75]; 3) Mitoxantrone, etoposide, and cytarabine (MEC).[76]

Patients 60 years or older who are robust and wish to pursue treatment after relapse may be offered: 1) therapy on clinical trial (strongly preferred option by the NCCN panel); 2) salvage chemotherapy followed by match sibling or alternate donor HSCT (Transplant should be considered only if the patient has achieved remission or in the context of a clinical trial); or 3) repetition of the initial successful induction therapy only if they had a long initial remission (i.e. relapse > 12 months of induction therapy). Best supportive care is always an option for those who do not wish to pursue intensive treatment.

Supportive Care for AML

Growth-factor support may be considered for older patients after chemotherapy administration. This recommendation is based on an Eastern Cooperative Oncology Group (ECOG) study.[77] Recommendations on the use of cytokines for infection or for slow marrow recovery is left to institutional policy. G-CSF should have been discontinued for a minimum 7 days before assessing marrow since it may affect interpretation of pathology.

Leukocyte-depleted blood products should be used for transfusion. CMV screening for potential HSCT candidates is left to institutional policies regarding provision of CMV negative blood products to patients who are CMV negative at time of diagnosis. Radiation of all blood products is advised to reduce the risk of graft-versus-host disease in all immunosuppressed patients.

The standard tumor lysis prophylaxis is hydration with alkalinization of the urine, allopurinol administration or rasburicase treatment. Rasburicase is a genetically engineered recombinant form of urate oxidase enzyme. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or with evidence of impaired renal function.

Patients who receive high dose cytarabine need to be closely monitored for changes in renal function. Renal dysfunction is highly correlated with increased risk of cerebellar toxicity. Patients need to be monitored for nystagmus, dysmetria, and ataxia before each dose of high dose cytarabine; patients exhibiting any neurologic signs should discontinue high dose cytarabine, and all subsequent cytarabine therapy must be standard-dose, rather than high dose. In patients who develop cerebellar toxicity, the patient should not be re-challenged with high dose cytarabine in future treatment cycles.[78] High dose cytarabine should also be discontinued in patients with rapidly rising creatinine caused by tumor lysis.

Decisions regarding use and choice of antibiotics to prevent and treat infections should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns. Cornely et al have shown that in patients undergoing chemotherapy for AML or MDS, posaconazole significantly prevented invasive fungal infections when compared to fluconazole or itraconazole and improved overall survival of the patients.[79] Outcomes with other azoles, such as voriconazole, echinocandins, or amphotericin B, may produce equivalent results. Azoles should not be given during anthracyline chemotherapy, since azoles impair drug metabolism and can increase toxicity.

Evaluation and Treatment of CNS Leukemia

Leptomeningeal involvement is much less frequent (<3%) in AML compared to ALL; therefore, the NCCN panel does not recommend lumbar punctures as part the routine diagnostic work up. However, if there are neurologic symptoms at diagnosis, such as headache, confusion, or altered sensorium, an initial CT/MRI should be performed to rule out a bleed or mass effect. If there is no mass effect, cerebrospinal fluid (CSF) cytology should be sampled by lumbar puncture (LP). If the LP is negative, the patient can be followed with a repeat LP if symptoms persist. If the LP is positive, intrathecal chemotherapy with cytarabine or methotrexate is recommended concurrent with systemic induction therapy. Initially the intrathecal therapy is given twice a week until the cytology shows no blasts, and then weekly for 4-6 weeks. High dose cytarabine induction therapy may substitute for intrathecal chemotherapy since it crosses the blood-brain barrier; the CSF must then be reassessed after induction and further therapy given as appropriate. The use of liposomal cytarabine, which has a longer half life, for intrathecal use offers the benefit of less frequent (once weekly) administration.

If the initial CT/MRI identifies a mass effect or increased intracranial pressure, a needle aspiration or biopsy should be considered. If positive, radiation therapy should strongly be considered followed by intrathecal therapy, as described above. One should not administer intrathecal therapy or high dose cytarabine concurrently with cranial radiation due to increased risks of neurotoxicity.

The panel does not recommend routine screening for occult CNS disease in the majority of patients with AML in remission. The exceptions are patients with M4 or M5 morphology, biphenotypic leukemia, or WBC > 100,000/mcL at diagnosis. For patients with positive cytology, the panel recommends either intrathecal chemotherapy, as outlined above, or documenting clearance of CNS disease after the first cycle of high dose cytarabine chemotherapy. In addition to the recommended evaluation and treatment of CNS leukemia, further CNS surveillance is recommended based upon institutional practice.

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