

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Acute Myeloid Leukemia**

Version 2.2013

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## Acute Myeloid Leukemia

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**Continue**

[NCCN Guidelines Panel Disclosures](#)

### [NCCN Acute Myeloid Leukemia Panel Members](#)

### [Summary of Guidelines Updates](#)

### [Evaluation for Acute Leukemia and Diagnostic Studies \(AML-1\)](#)

### [APL, Treatment Induction \(AML-2\)](#)

### [APL, Post-Consolidation Therapy \(AML-5\)](#)

### [APL, Post-Remission Therapy \(AML-6\)](#)

### [AML, Treatment Induction Age \(<60 y\) \(AML-7\)](#)

### [AML, Post-Induction Therapy After Standard-Dose Cytarabine \(Age <60 y\) \(AML-8\)](#)

### [AML, Post-Induction Therapy After High-Dose Cytarabine \(Age <60 y\) \(AML-9\)](#)

### [AML, Post-Remission Therapy \(AML-10\)](#)

### [AML, Treatment Induction \(Age ≥60 y\) \(AML-11 and AML-12\)](#)

### [AML, Post-Induction Therapy \(Age ≥60 y\) \(AML-13\)](#)

### [AML, Post-Remission Therapy \(Age ≥60 y\) \(AML-14\)](#)

### [AML, Surveillance \(After Completion of Consolidation\) \(AML-15\)](#)

### [AML, Salvage Therapy \(AML-15\)](#)

### [Risk Status Based on Validated Cytogenetics and Molecular Abnormalities \(AML-A\)](#)

### [Evaluation and Treatment of CNS Leukemia \(AML-B\)](#)

### [Supportive Care \(AML-C\)](#)

### [Response Criteria for Acute Myeloid Leukemia \(AML-D\)](#)

### [Monitoring During Therapy \(AML-E\)](#)

### [Salvage Chemotherapy Regimen Options \(AML-F\)](#)

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

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/physician.html](#).

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

See [NCCN Categories of Evidence and Consensus](#).

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Summary of the changes in the 2.2013 version of the NCCN Guidelines for Acute Myeloid Leukemia from the 1.2013 version include:

**MS-1** - The Discussion section was updated to reflect the changes in the algorithm.

Summary of the changes in the 1.2013 version of the NCCN Guidelines for Acute Myeloid Leukemia from the 2.2012 version include:

### **AML-1**

#### Evaluation for Acute Leukemia

- Previous footnote “a” deleted: “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.”
- Page reorganized by moving the recommendation for molecular markers from the diagnosis section to the evaluation section.
- Cardiac evaluation modified: “Evaluate myocardial function (echocardiogram or MUGA scan) in patients with a history or symptoms of cardiac disease or prior exposure to cardiotoxic drugs or radiation to thorax.”

### **AML-2**

- Treatment recommendations are: 1) based on the assessment of risk status; and 2) only high-risk patients proceed to therapy based upon ability to tolerate anthracyclines.
- Footnote “k” added: “New data suggest similar outcomes in patients with low or intermediate risk.”
- Footnote “i” modified: “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 *may* prevents the lethal complication of bleeding. If cytogenetic and molecular testing do not confirm APL, discontinue ATRA and continue treatment as for AML.
- The following sentence was removed from footnote “n”:  
“Differentiation of the leukemic promyelocytes usually requires more time.” (also applies to AML-3 and AML-4)
- Footnote “o” replaced with footnote “u” from AML-3.
- “Assess marrow morphology at count recovery from start of induction” deleted and replaced with “At count recovery, proceed with consolidation.”
- Complete response and footnote with link to the response criteria deleted. (also applies to AML-3 and AML-4)

### **AML-3**

- “Assess marrow morphology at count recovery from start of induction and consider LP” deleted and replaced with “At count recovery, consider LP and proceed with consolidation.”

### **AML-3**

- The following reference was added as footnote “u”: “Breccia M, Carmosino I, Diverio D, et al. Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count. *Br J Haematol* 2003;120:266-270.”
- Footnote “o” modified: “~~Induction failure~~ *Early mortality* is related to bleeding, differentiation syndrome, or infection. *Persistent disease is rare, and not disease progression.* See first relapse on [AML-6](#). (also applies to AML-4)

### **AML-4**

- The following regimen was added for treatment induction: “ATRA 45 mg/m<sup>2</sup> in 2 divided doses daily + arsenic trioxide 0.15 mg/kg daily until bone marrow remission” with the following consolidation “Arsenic trioxide 0.15 mg/kg/day IV 5 days/week for 4 weeks every 8 weeks for a total of 4 cycles, and ATRA 45 mg/m<sup>2</sup>/day for 2 weeks every 4 weeks for a total of 7 cycles” with the reference “y”: “Lo-Coco F, Avvisati G, Orlando SM, et al. ATRA and Arsenic Trioxide (ATO) Versus ATRA and Idarubicin (AIDA) for Newly Diagnosed, Non High-Risk Acute Promyelocytic Leukemia (APL): Results of the Phase III, Prospective, Randomized, Intergroup APL0406 Study by the Italian-German Cooperative Groups Gimema-SAL-AMLSG [abstract]. *Blood* 2012;120:Abstract 6.”
- “Assess marrow morphology at count recovery from start of induction and consider LP” deleted and replaced with “At count recovery, proceed with consolidation.”
- Consolidation Therapy
  - ▶ “Low and intermediate designations and corresponding treatment recommendations” deleted and replaced with “ATRA 45 mg/m<sup>2</sup> x 15 days + idarubicin 5 mg/m<sup>2</sup> x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m<sup>2</sup>/day x 5 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m<sup>2</sup> x 1 dose x 1 cycle (category 1)” and the following reference in footnote “aa”, “Lo-Coco F, Avvisati G, Vignetti M, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adult patients younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. *Blood* 2010;116:3171-3179.”

Summary of the changes in the 1.2013 version of the NCCN Guidelines for Acute Myeloid Leukemia from the 2.2012 version include:

### AML-5

- Previous footnote “bb” divided into 2 footnotes, “Monitoring is to be performed at the discretion of the treating physician (see Discussion).” removed from new footnote “bb”.
- Previous footnote “cc” deleted and incorporated into new footnote “cc”. The following sentence in new footnote “cc” modified: “If molecular relapse is confirmed by a second positive test, ~~intervention should be strongly considered (eg, arsenic trioxide) treat as first relapse (AML-6).~~”

### AML-6

- First relapse: “until count recovery with marrow confirmation of remission” added.
- Footnote “gg” was modified: “There is a *small* randomized trial that suggests that the addition of ATRA does not confer any benefit over arsenic alone.”

### AML-7

- Treatment Induction
  - Standard-dose regimen modified by the removal of the daunorubicin range of 60-90 and recommending 90 mg/m<sup>2</sup>: cytarabine 100-200 mg/m<sup>2</sup> continuous infusion x 7 days with idarubicin 12 mg/m<sup>2</sup> or daunorubicin 60-90 mg/m<sup>2</sup> x 3 days (category 1)
  - The following regimen added: “Standard-dose cytarabine 200 mg/m<sup>2</sup> continuous infusion x 7 days with daunorubicin 60 mg/m<sup>2</sup> x 3 days and cladribine 5 mg/m<sup>2</sup> x 5 days (category 1)” and the following reference in footnote “nn”: “Holowiecki J, Grosicki S, Giebel S, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study. J Clin Oncol 2012;30:2441-2448.”
  - High-dose regimen modified by the removal of the daunorubicin range of 45-60 and recommending 60 mg/m<sup>2</sup>: “High-dose cytarabine (HiDAC) 2 g/m<sup>2</sup> every 12 hours x 6 days or 3 g/m<sup>2</sup> every 12 h x 4 days with idarubicin 12 mg/m<sup>2</sup> or daunorubicin 45-60 mg/m<sup>2</sup> x 3 days (1 cycle) (category 2B).”

### AML-7

- Treatment Induction
  - The following treatment recommendation was deleted: Matched sibling or alternative donor HSCT (category 2B) and corresponding previous footnote “pp”: “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 a 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.”

### AML-8

- Significant residual blast, dosing added for cytarabine: “High-dose cytarabine alone (*HiDAC 2 g/m<sup>2</sup> every 12 hours x 6 days*).” Footnote “vv” added: “For re-induction, no data are available to show superiority with intermediate or high-dose cytarabine.”
- Footnote “ww” added: “For patients with residual blasts after induction with standard-dose cytarabine with daunorubicin and cladribine, a second cycle of the same induction regimen can be given. Holowiecki J, Grosicki S, Giebel S, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized, phase III study. J Clin Oncol 2012;30:2441-2448.”
- Induction failure: “See [AML-F](#) for other salvage regimens” added as an additional treatment option.

### AML-9

- Significant residual blasts: “See [AML-F](#) for salvage regimens” added as an additional treatment option.
- Induction failure: “See [AML-F](#) for salvage regimens” added as an additional treatment option.

Summary of the changes in the 1.2013 version of the NCCN Guidelines for Acute Myeloid Leukemia from the 2.2012 version include:

### AML-10

- Intermediate-risk cytogenetics or molecular abnormalities, footnote “ddd” added to high-dose cytarabine: “There is no evidence that HiDAC is superior to lower doses of cytarabine in intermediate-risk patient subgroup.”
- “Treatment-related disease or poor-risk cytogenetics or molecular abnormalities,” the following treatment recommendation deleted: “1 to 2 cycles of high-dose cytarabine-based consolidation was followed by autologous HSCT if no allogeneic transplant option is available” as this is addressed in footnote “eee”.
- Previous footnote “zz” deleted: “Clinical trials, when available, are strongly recommended in the treatment of patients with poor prognostic features.”

### AML-11

- Favorable cytogenetic/molecular markers: Standard-dose regimen modified by the removal of the daunorubicin range of 45-60 and recommending 45-90 mg/m<sup>2</sup>: “Standard-dose cytarabine (100-200 mg/m<sup>2</sup> continuous infusion x 7 days) with idarubicin 12 mg/m<sup>2</sup> or daunorubicin 45-60 mg/m<sup>2</sup> x 3 days or mitoxantrone 12 mg/m<sup>2</sup>.”
- Footnote “hh”, the following sentence was removed: “Prompt institution of definitive therapy is essential.”

### AML-12

- Footnote “hh”, the following sentence was removed: “Prompt institution of definitive therapy is essential.”

### AML-13

- Residual blasts: “Consider” deleted before “clinical trial.”

### AML-A

- The title of the page was modified, “Risk Status Based on *Validated* Cytogenetics and Molecular Abnormalities” with footnote “1”: “The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.”

### AML-A

- Better-risk, molecular abnormalities, text modified: “Normal cytogenetics: ~~with~~-NPM1 mutation in the absence of FLT3-ITD or isolated *biallelic* CEBPA<sup>3</sup> mutation.”
- Intermediate-risk, cytogenetics: “alone” added to “+8”
- Poor-risk, cytogenetics: “monosomal karyotype” added.
- Footnote “3” modified: “For Philadelphia+ AML t(9;22), ~~consider managing~~ *manage* as myeloid blast crisis in CML, *with addition of tyrosine kinase inhibitors. See NCCN Guidelines for Chronic Myelogenous Leukemia.*”
- Previous footnote “3” deleted: For CEBPA, the double mutation appears to confirm the relatively favorable prognosis.

### AML-B

- Positive mass effect or increased intracranial pressure: “High-dose cytarabine based therapy + dexamethasone to reduce intracranial pressure” added as a treatment option.
- Footnote “5” modified: “Screening LP should be considered at first remission for patients with M4 or M5 morphology, ~~biphenotypic mixed~~ *phenotype acute* leukemia, or WBC count >100,000/mcL at diagnosis.”

### AML-C 1 of 2

- Last bullet, last sentence deleted: “Azoles should not be given during anthracycline chemotherapy, since azoles impair drug metabolism and can increase toxicity.”

### AML-D

- Bullet 4 (complete remission), sub-bullet 4 modified: “CRi - There are some clinical trials, particularly those that focus on the elderly or those with antecedent myelodysplasia, that include a variant of complete response referred to as ~~CRp~~ or CRi. This has been ~~loosely~~ defined as <5% marrow blasts, *either ANC >1000/mcL or platelets ≥100,000/mcL*, and transfusion independence but with persistence of cytopenia (usually thrombocytopenia).”

### AML-E

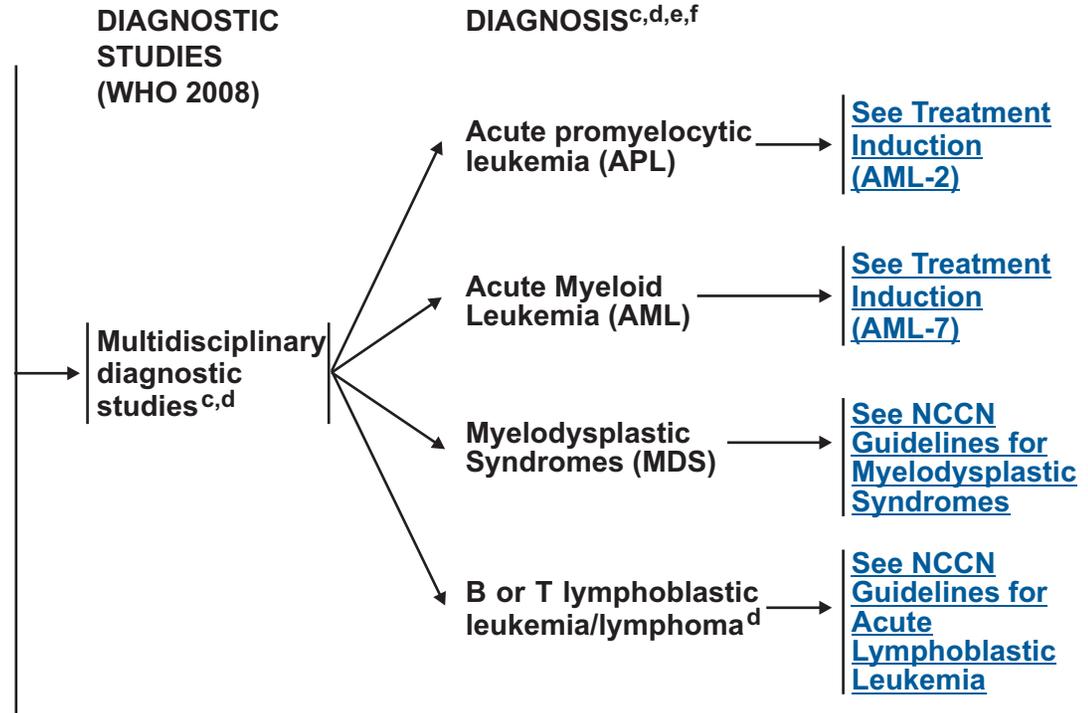
- Induction
  - ▶ Bullet 3 added: “Liver function tests 1-2 times/week.”
  - ▶ Bullet 4 added: “Coagulation panel 1-2 times/week.”

### EVALUATION FOR ACUTE LEUKEMIA

- History and physical (H&P)
- Complete blood count (CBC), platelets, differential, chemistry profile
- Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen
- Bone marrow with cytogenetics (karyotype ± FISH)
  - Cryopreserve samples for evaluation of c-KIT, FLT3-ITD, NPM1, and CEBPA mutations<sup>a</sup>
- Immunophenotyping and cytochemistry
- Human leukocyte antigen (HLA) typing for sibling or unrelated donor (except for patients with a major contraindication to hematopoietic stem cell transplantation [HSCT])
- CT/MRI if neurologic symptoms<sup>b</sup>
- Lumbar puncture (LP), if symptomatic<sup>b</sup> (category 2B for asymptomatic)
- Evaluate myocardial function (echocardiogram or MUGA scan) in patients with a history or symptoms of cardiac disease or prior exposure to cardiotoxic drugs or radiation to thorax
- Central venous access device of choice

<sup>a</sup>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 (especially FLT3-ITD, NPM1 mutations) or core binding factor leukemia (especially c-KIT mutation). If a test is not available at your institution, consult pathology about preserving material from the original diagnostic sample for future use at an outside reference lab after full cytogenetic data are available.

<sup>b</sup>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 is detected on the imaging study. Screening LP should be considered at first remission for patients with M5 or M4 morphology or WBC count >100,000/mcL at diagnosis. [See Evaluation and Treatment of CNS Leukemia \(AML-B\)](#).



<sup>c</sup>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)). AML evolving from MDS (AML-MDS) is often more resistant to cytotoxic chemotherapy than AML that 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.

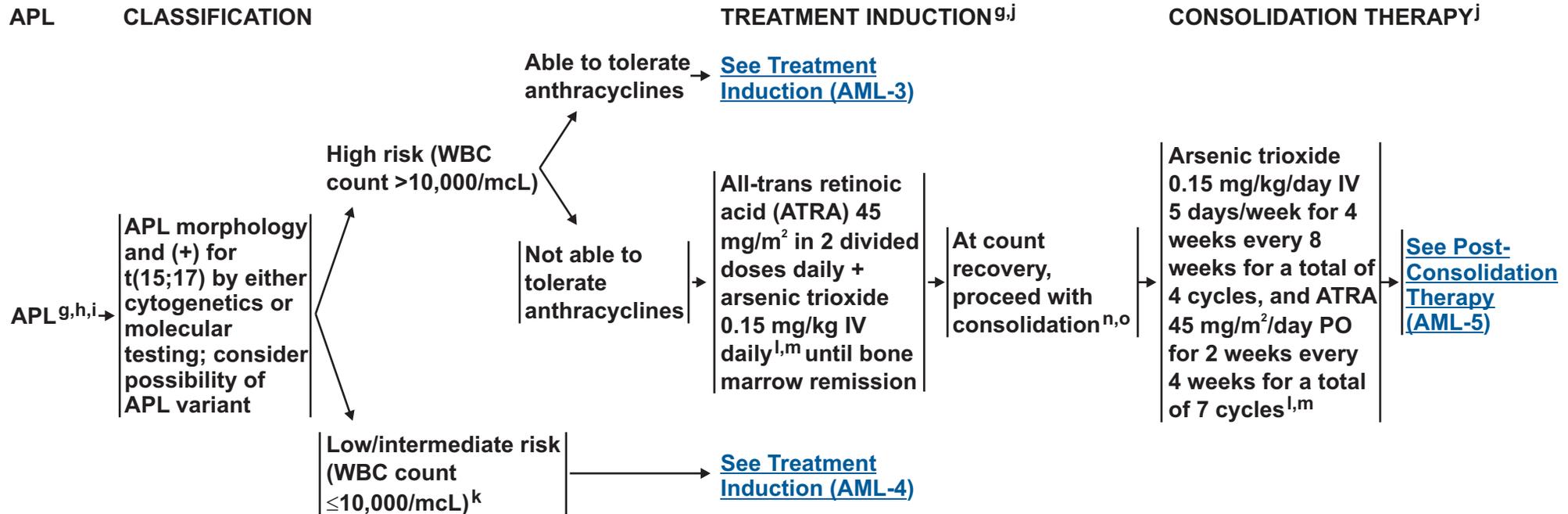
<sup>d</sup>When presented with rare cases such as acute leukemias of ambiguous lineage, including mixed phenotype acute leukemias (according to 2008 WHO classification), consultation with an experienced hematopathologist is strongly recommended.

<sup>e</sup>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.

<sup>f</sup>Patients who present with isolated extramedullary disease (myeloid sarcoma) should be treated with systemic therapy. Local therapy (surgery/radiation therapy [RT]) may be used for residual disease.

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

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



<sup>g</sup>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 trial with consolidation from another.

<sup>h</sup>Therapy-related APL is treated the same as de novo APL.

<sup>i</sup>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 may prevent the lethal complication of bleeding. If cytogenetic and molecular testing do not confirm APL, discontinue ATRA and continue treatment as for AML.

<sup>j</sup>Monitor for APL differentiation syndrome and coagulopathy; [see Supportive Care \(AML-C 2 of 2\)](#).

<sup>k</sup>New data suggest similar outcomes in patients with low or intermediate risk.

<sup>l</sup>Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As<sub>2</sub>O<sub>3</sub> combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. *Proc Natl Acad Sci USA* 2004;101(15):5328-35.

Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. *J Clin Oncol* 2009;27:504-510.

<sup>m</sup>See Arsenic trioxide monitoring, [Supportive Care \(AML-C 2 of 2\)](#).

<sup>n</sup>Premature morphologic and molecular assessment (day 10-14 marrow) can be misleading; a nadir marrow is not recommended. Patients often remain molecularly positive at the end of induction, even when the marrow shows morphologic remission. The first assessment of molecular remission should be made after consolidation.

<sup>o</sup>Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare. See first relapse on [AML-6](#).

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

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### TREATMENT INDUCTION (HIGH RISK)<sup>g,j,p</sup>

ATRA<sup>q</sup> 45 mg/m<sup>2</sup> +  
daunorubicin 50 mg/m<sup>2</sup> x 4 days +  
cytarabine 200 mg/m<sup>2</sup> x 7 days<sup>r</sup>

or

ATRA<sup>q</sup> 45 mg/m<sup>2</sup> +  
daunorubicin 60 mg/m<sup>2</sup> x 3 days +  
cytarabine 200 mg/m<sup>2</sup> x 7 days<sup>s</sup>

or

ATRA<sup>q</sup> 45 mg/m<sup>2</sup> + idarubicin  
12 mg/m<sup>2</sup> on days 2, 4, 6, 8<sup>t</sup>

or

At count  
recovery,<sup>n,u</sup>  
consider LP and  
proceed with  
consolidation<sup>o</sup>

At count  
recovery,<sup>n,u</sup>  
consider LP and  
proceed with  
consolidation<sup>o</sup>

At count  
recovery,<sup>n,u</sup>  
consider LP and  
proceed with  
consolidation<sup>o</sup>

### CONSOLIDATION THERAPY<sup>v</sup>

Arsenic trioxide<sup>m</sup> 0.15 mg/kg/day x  
5 days for 5 wks x 2 cycles, then  
ATRA 45 mg/m<sup>2</sup> x 7 days +  
daunorubicin 50 mg/m<sup>2</sup> x 3 days for 2 cycles<sup>r</sup>

Daunorubicin 60 mg/m<sup>2</sup> x 3 days + cytarabine 200  
mg/m<sup>2</sup> x 7 days x 1 cycle, then cytarabine 2 g/m<sup>2</sup>  
(age <50) or 1.5 g/m<sup>2</sup> (age 50-60) every 12 h x 5  
days<sup>w,x</sup> + daunorubicin 45 mg/m<sup>2</sup> x 3 days x 1 cycle  
5 doses of IT chemotherapy<sup>s</sup> (category 1)

ATRA 45 mg/m<sup>2</sup> x 15 days + idarubicin 5 mg/m<sup>2</sup>  
and cytarabine 1 g/m<sup>2</sup> x 4 days x 1 cycle, then  
ATRA x 15 days + mitoxantrone  
10 mg/m<sup>2</sup>/day x 5 days x 1 cycle, then  
ATRA x 15 days + idarubicin 12 mg/m<sup>2</sup> x 1 dose  
+ cytarabine 150 mg/m<sup>2</sup>/8 h x 4 days x 1 cycle<sup>t</sup>

[See Post-Consolidation Therapy \(AML-5\)](#)

[See Post-Consolidation Therapy \(AML-5\)](#)

[See Post-Consolidation Therapy \(AML-5\)](#)

### Clinical trial

<sup>g</sup>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 trial with consolidation from another.

<sup>j</sup>Monitor for APL differentiation syndrome and coagulopathy; [see Supportive Care \(AML-C 2 of 2\)](#).

<sup>m</sup>See Arsenic trioxide monitoring, [Supportive Care \(AML-C 2 of 2\)](#).

<sup>n</sup>Premature morphologic and molecular assessment (day 10-14 marrow) can be misleading; a nadir marrow is not recommended. Patients often remain molecularly positive at the end of induction, even when the marrow shows morphologic remission. The first assessment of molecular remission should be made after consolidation.

<sup>o</sup>Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare. See first relapse on [AML-6](#).

<sup>p</sup>For patients with (or who develop) a high WBC count (>10,000), consider prophylactic dexamethasone to prevent differentiation syndrome.

<sup>q</sup>Data suggest that lower doses of ATRA (25 mg/m<sup>2</sup>) may be used in children and adolescents.

<sup>r</sup>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;116:3751-3757.

<sup>s</sup>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.

<sup>t</sup>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.

<sup>u</sup>Breccia M, Carosino I, Diverio D, et al. Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count. *Br J Haematol* 2003;120:266-270.

<sup>v</sup>All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed prior to each anthracycline/mitoxantrone-containing course.

<sup>w</sup>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.

<sup>x</sup>Dose adjustment of cytarabine may be needed for older patients or patients with renal dysfunction.

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

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

### TREATMENT INDUCTION (LOW/INTERMEDIATE RISK)<sup>g,j,p</sup>

ATRA 45 mg/m<sup>2</sup> in 2 divided doses daily + arsenic trioxide<sup>m</sup> 0.15 mg/kg IV daily until bone marrow remission<sup>y</sup>  
or

ATRA<sup>q</sup> 45 mg/m<sup>2</sup> + daunorubicin 50 mg/m<sup>2</sup> x 4 days + cytarabine 200 mg/m<sup>2</sup> x 7 days<sup>r,z</sup>  
or

ATRA<sup>q</sup> 45 mg/m<sup>2</sup> + daunorubicin 60 mg/m<sup>2</sup> x 3 days + cytarabine 200 mg/m<sup>2</sup> x 7 days<sup>s,z</sup> (category 1)  
or

ATRA<sup>q</sup> 45 mg/m<sup>2</sup> + idarubicin 12 mg/m<sup>2</sup> on days 2, 4, 6, 8<sup>t,z</sup> (category 1)  
or

Clinical trial

At count recovery,<sup>n,o</sup> proceed with consolidation

### CONSOLIDATION THERAPY<sup>v</sup>

Arsenic trioxide<sup>m</sup> 0.15 mg/kg/day IV 5 days/week for 4 weeks every 8 weeks for a total of 4 cycles, and ATRA 45 mg/m<sup>2</sup>/day for 2 weeks every 4 weeks for a total of 7 cycles<sup>y</sup>

Arsenic trioxide<sup>m</sup> 0.15 mg/kg/day x 5 days for 5 wks x 2 cycles, then ATRA 45 mg/m<sup>2</sup> x 7 days + daunorubicin 50 mg/m<sup>2</sup> x 3 days for 2 cycles<sup>r</sup>

Daunorubicin 60 mg/m<sup>2</sup> x 3 days + cytarabine 200 mg/m<sup>2</sup> x 7 days x 1 cycle, then cytarabine 1 g/m<sup>2</sup> every 12 h x 4 days + daunorubicin 45 mg/m<sup>2</sup> x 3 days x 1 cycle<sup>s</sup> (category 1)

ATRA 45 mg/m<sup>2</sup> x 15 days + idarubicin 5 mg/m<sup>2</sup> x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m<sup>2</sup>/day x 5 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m<sup>2</sup> x 1 dose x 1 cycle (category 1)<sup>aa</sup>

[See Post-Consolidation Therapy \(AML-5\)](#)

[See Post-Consolidation Therapy \(AML-5\)](#)

[See Post-Consolidation Therapy \(AML-5\)](#)

<sup>g</sup>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 trial with consolidation from another.

<sup>j</sup>Monitor for APL differentiation syndrome and coagulopathy; [see Supportive Care \(AML-C 2 of 2\)](#).

<sup>m</sup>See Arsenic trioxide monitoring, [Supportive Care \(AML-C 2 of 2\)](#).

<sup>n</sup>Premature morphologic and molecular assessment (day 10-14 marrow) can be misleading; a nadir marrow is not recommended. Patients often remain molecularly positive at the end of induction, even when the marrow shows morphologic remission. The first assessment of molecular remission should be made after consolidation.

<sup>o</sup>Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare. See first relapse on [AML-6](#).

<sup>p</sup>For patients with (or who develop) a high WBC count (>10,000), consider prophylactic dexamethasone to prevent differentiation syndrome.

<sup>q</sup>Data suggest that lower doses of ATRA (25 mg/m<sup>2</sup>) may be used in adolescents.

<sup>r</sup>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;116:3751-3757.

<sup>s</sup>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.

<sup>t</sup>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.

<sup>v</sup>All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed prior to each anthracycline/mitoxantrone-containing course.

<sup>y</sup>Lo-Coco F, Avvisati G, Orlando SM, et al. ATRA and arsenic trioxide (ATO) versus ATRA and idarubicin (AIDA) for newly diagnosed, non high-risk acute promyelocytic leukemia (APL): results of the phase III, prospective, randomized, intergroup APL0406 study by the Italian-German Cooperative Groups Gimema-SAL-AMLSG [abstract]. *Blood* 2012;120:Abstract 6.

<sup>z</sup>For patients who have rapidly escalating WBC counts or other high-risk features during course of induction therapy, see Consolidation Therapy on [AML-3](#).

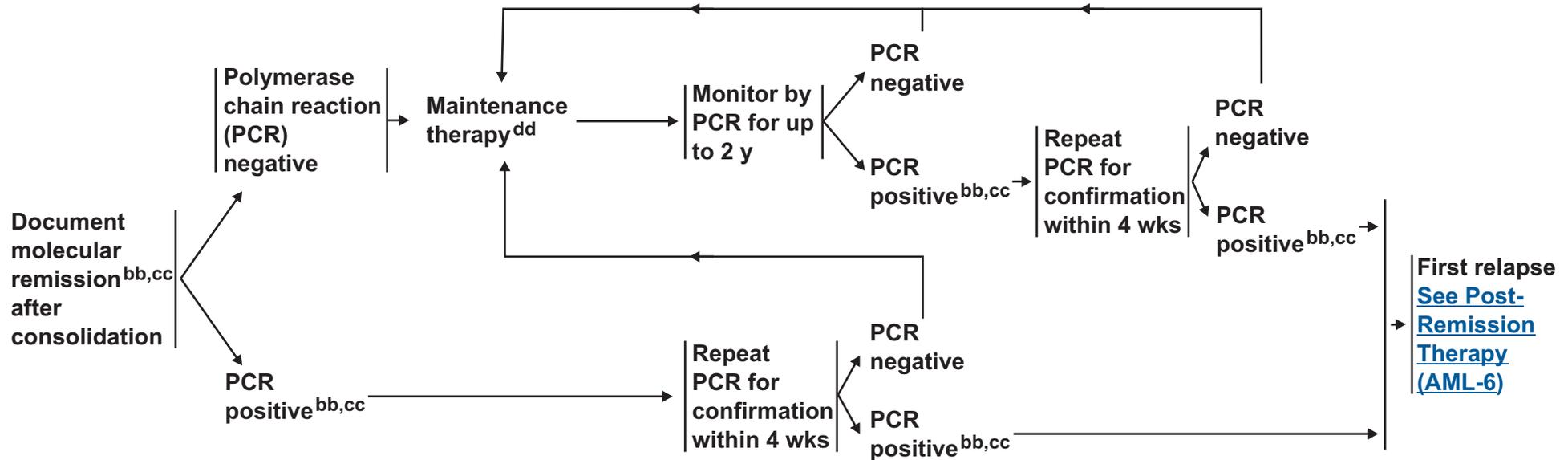
<sup>aa</sup>Lo-Coco F, Avvisati G, Vignetti M, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adult patients younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. *Blood* 2010;116:3171-3179.

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

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### APL

### POST-CONSOLIDATION MONITORING THERAPY



<sup>bb</sup>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 marrow 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 >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.

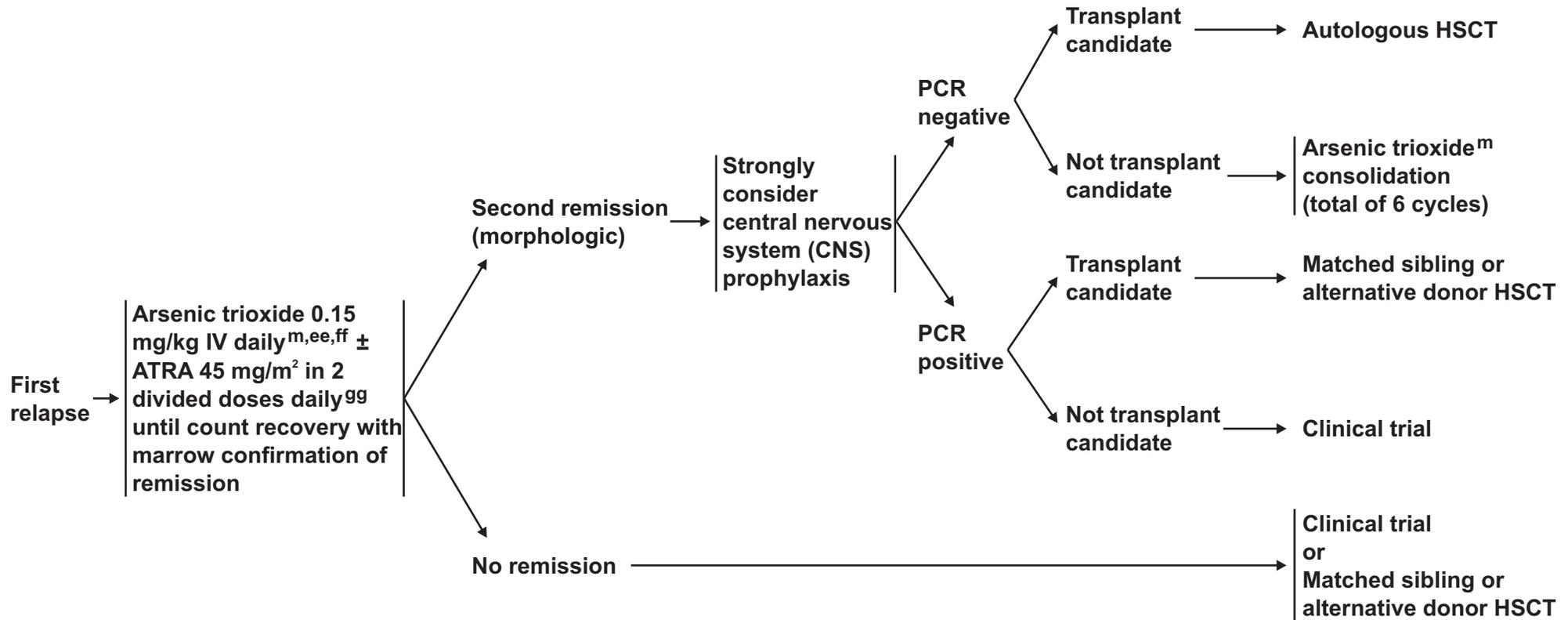
<sup>cc</sup>To confirm PCR positivity, a second marrow sample should be done in 2-4 weeks in a reliable laboratory. If molecular relapse is confirmed by a second positive test, treat as first relapse ([AML-6](#)). If the second test was negative, frequent monitoring (every 3 mo for 2 y) is strongly 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 the same level of sensitivity. Consider consultation with a physician experienced in molecular diagnostics if results are equivocal.

<sup>dd</sup>The majority of studies showing benefit with maintenance occurred prior to the use of ATRA and/or arsenic trioxide and/or cytarabine for consolidation. Maintenance therapy should follow the initial treatment protocol. The role of maintenance chemotherapy remains unclear, particularly for patients with low-risk disease who achieve a molecular remission at the end of consolidation. Avvisati G, Lo-Coco F, Paoloni FP, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. *Blood* 2011;117:4716-4725.

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**APL POST-REMISSION THERAPY ADDITIONAL THERAPY**



<sup>m</sup>See Arsenic trioxide monitoring, [Supportive Care \(AML-C 2 of 2\)](#).

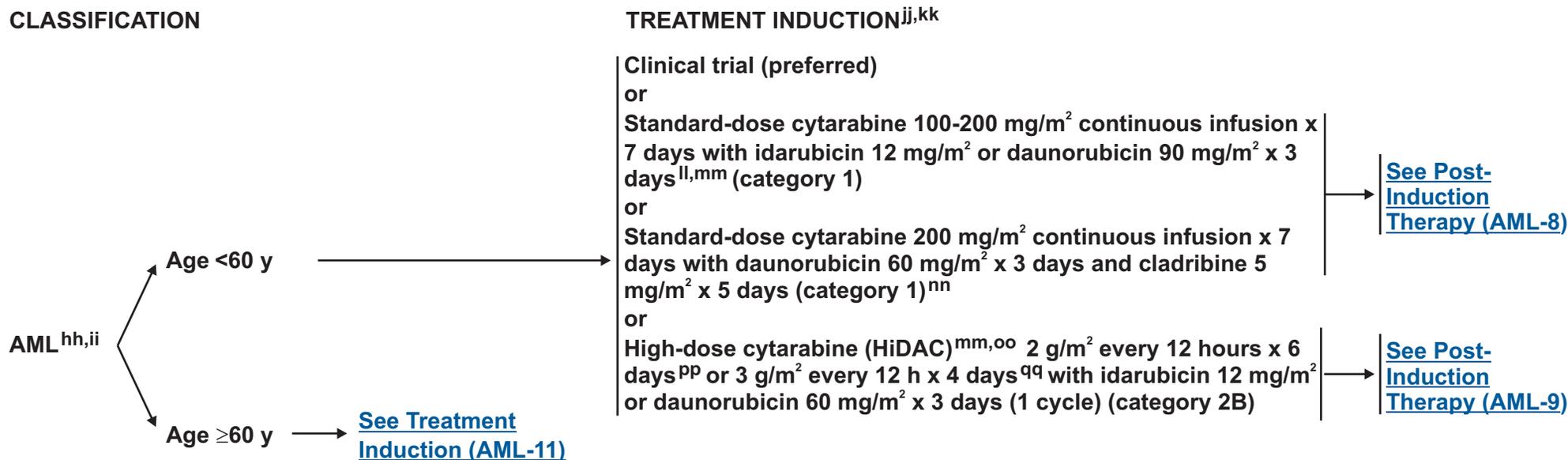
<sup>ee</sup>At the end of 2 cycles, if the patient is not in molecular remission, consider matched sibling or alternative donor HSCT or clinical trial. Testing is recommended at least 2-3 weeks after the completion of arsenic to avoid false positives.

<sup>ff</sup>Outcomes are uncertain in patients who received arsenic trioxide during initial induction/consolidation therapy.

<sup>gg</sup>There is a small randomized trial that suggests that 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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**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

### CLASSIFICATION



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

<sup>ii</sup>Poor performance status and comorbid medical condition, in addition to age, are factors that influence ability to tolerate standard induction therapy.

<sup>jj</sup>[See Supportive Care \(AML-C 1 of 2\).](#)

<sup>kk</sup>[See Monitoring During Therapy \(AML-E\).](#)

<sup>ll</sup>ECOG reported a significant increase in complete response rates and overall survival using daunorubicin 90 mg/m<sup>2</sup> x 3 days versus 45 mg/m<sup>2</sup> 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 days 12-14, the additional daunorubicin dose is 45 mg/m<sup>2</sup> x 3 days.

<sup>mm</sup>For patients with impaired cardiac function, other regimens that combine a non-anthracycline (such as fludarabine or topotecan) with cytarabine have been published.

<sup>nn</sup>Holowiecki J, Grosicki S, Giebel S, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study. *J Clin Oncol* 2012;30:2441-2448.

<sup>oo</sup>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.

<sup>pp</sup>Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. *Blood* 1996;88:2841-2851.

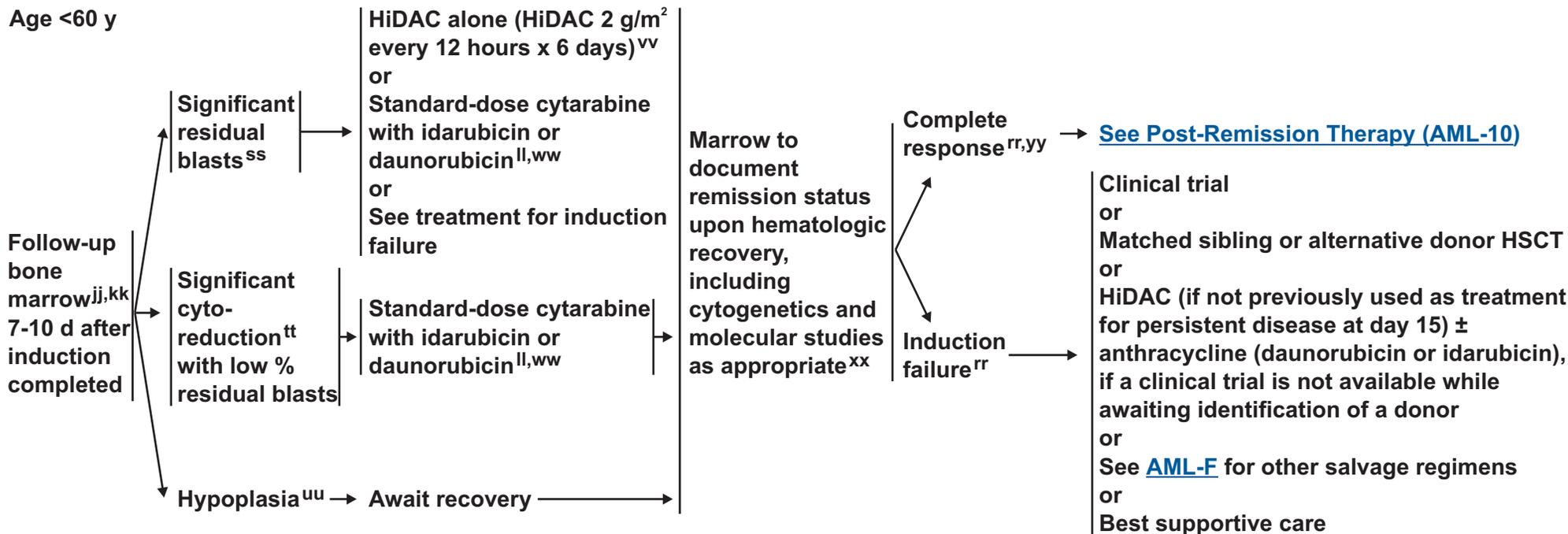
<sup>qq</sup>Bishop JF, Matthews JP, Young GA, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. *Blood* 1996;87:1710-1717.

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### AML POST-INDUCTION THERAPY AFTER STANDARD-DOSE CYTARABINE

Age <60 y



<sup>jj</sup> See [Supportive Care \(AML-C 1 of 2\)](#).

<sup>kk</sup> See [Monitoring During Therapy \(AML-E\)](#).

<sup>ll</sup> ECOG reported a significant increase in complete response rates and overall survival using daunorubicin 90 mg/m<sup>2</sup> x 3 days versus 45 mg/m<sup>2</sup> 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 days 12-14, the additional daunorubicin dose is 45 mg/m<sup>2</sup> x 3 days.

<sup>rr</sup> See [Response Criteria for Acute Myeloid Leukemia \(AML-D\)](#).

<sup>ss</sup> Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and the patient is a candidate for an allogeneic HSCT.

<sup>tt</sup> If ambiguous, consider repeat bone marrow biopsy in 5-7 days before proceeding with therapy.

<sup>uu</sup> Hypoplasia is defined as cellularity <10%-20% and residual blasts <5%-10%.

<sup>vv</sup> For re-induction, no data are available to show superiority with intermediate or high-dose cytarabine.

<sup>ww</sup> For patients with residual blasts after induction with standard-dose cytarabine with daunorubicin and cladribine, a second cycle of the same induction regimen can be given. Holowiecki J, Grosicki S, Giebel S, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study. *J Clin Oncol* 2012;30:2441-2448.

<sup>xx</sup> The role of immunophenotyping in detecting minimal residual disease is being evaluated.

<sup>yy</sup> Patients with an increased risk of meningeal involvement (initial WBC count >100,000/mcL or monocytic histology) should be considered for CNS evaluation with a LP upon achieving complete response. See [Evaluation and Treatment of CNS Leukemia \(AML-B\)](#).

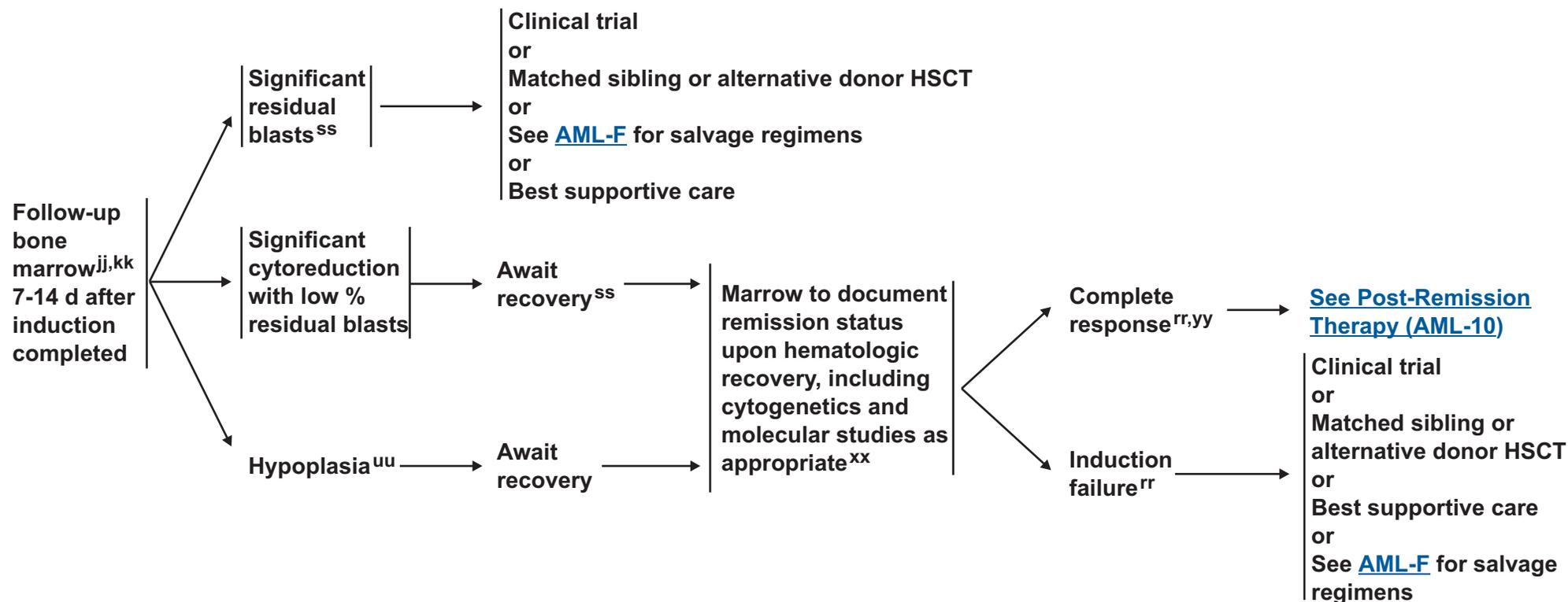
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### AML POST-INDUCTION THERAPY AFTER HIGH-DOSE CYTARABINE

Age <60 y

### CONSOLIDATION THERAPY



<sup>jj</sup> See [Supportive Care \(AML-C 1 of 2\)](#).

<sup>kk</sup> See [Monitoring During Therapy \(AML-E\)](#).

<sup>rr</sup> See [Response Criteria for Acute Myeloid Leukemia \(AML-D\)](#).

<sup>ss</sup> Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and the patient is a candidate for an allogeneic HSCT.

<sup>uu</sup> Hypoplasia is defined as cellularity <10%-20% and residual blasts <5%-10%.

<sup>xx</sup> The role of immunophenotyping in detecting minimal residual disease is being evaluated.

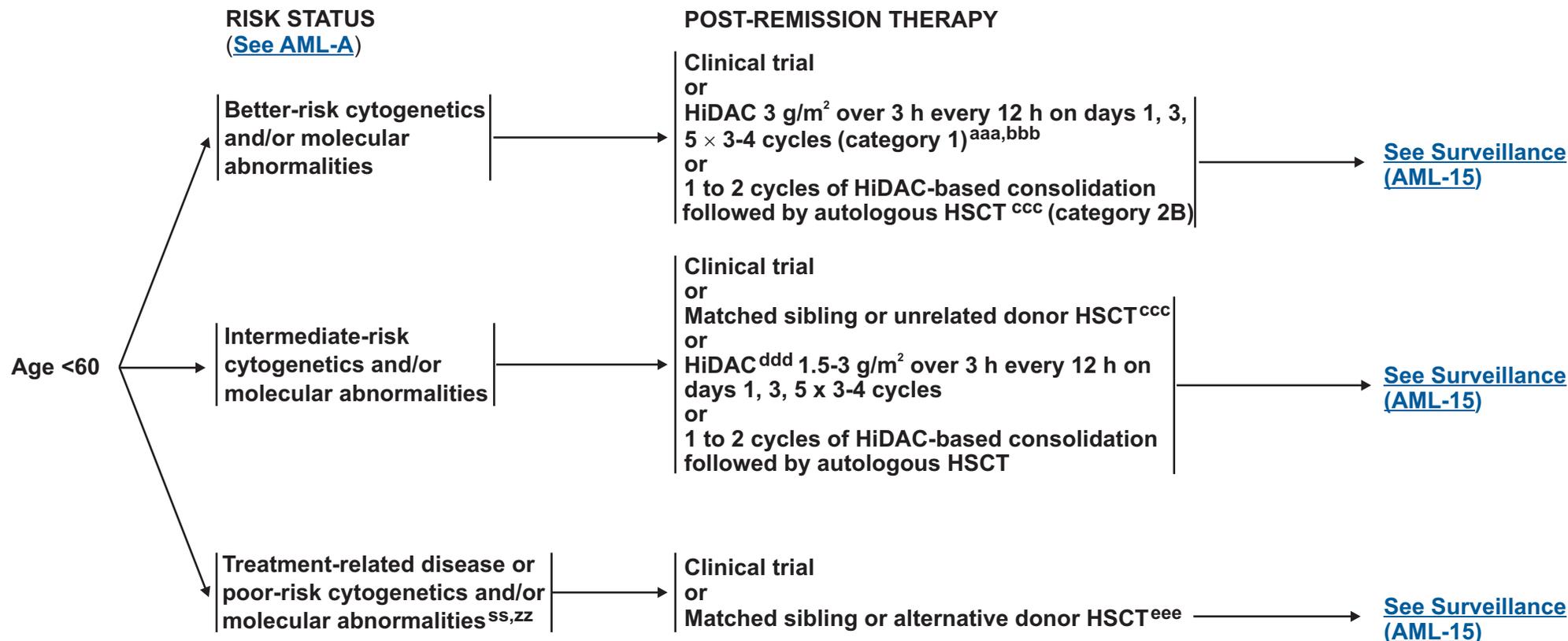
<sup>yy</sup> Patients with an increased risk of meningeal involvement (initial WBC count >100,000/mcL or monocytic histology) should be considered for CNS evaluation with a LP upon achieving complete response. See [Evaluation and Treatment of CNS Leukemia \(AML-B\)](#).

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# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia



<sup>ss</sup>Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and the patient is a candidate for an allogeneic HSCT.

<sup>zz</sup>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.

<sup>aaa</sup>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.

<sup>bbb</sup>Alternate dosing of cytarabine for postremission therapy has been reported (see [Discussion](#)). Lowenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. N Engl J Med 2011;364:1027-1036.

<sup>ccc</sup>While both options--multiple cycles of dose-intensive consolidation and 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.

<sup>ddd</sup>There is no evidence that HiDAC is superior to lower doses of cytarabine in intermediate-risk patient subgroup.

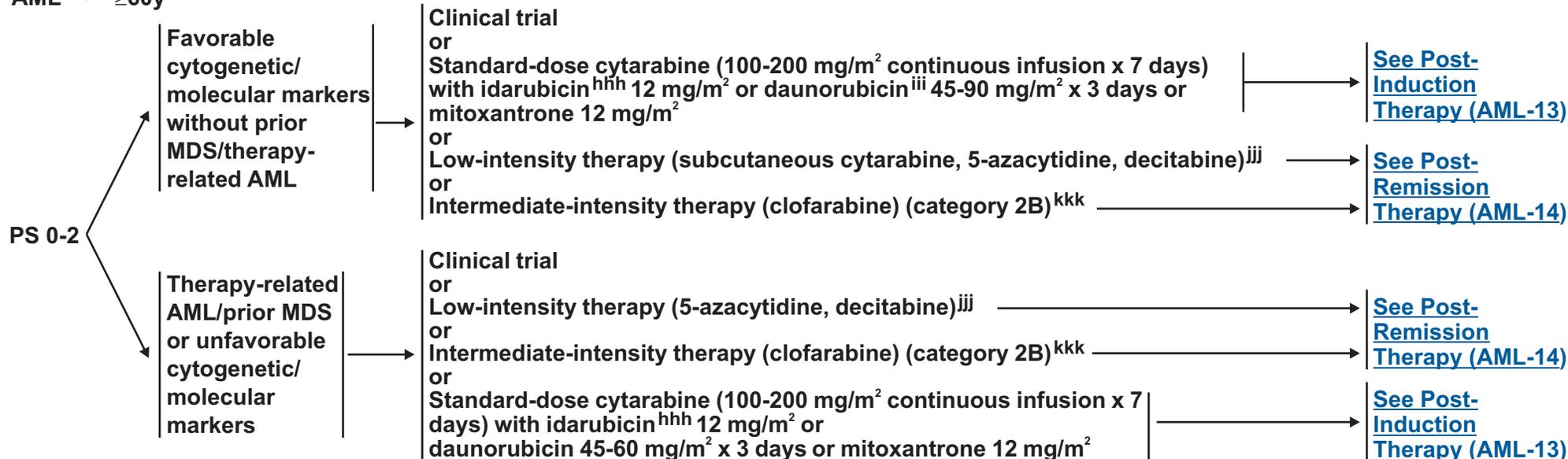
<sup>eee</sup>Patients may require at least one cycle of high-dose cytarabine consolidation while donor search is in progress to maintain remission. Patients may proceed directly to transplant following achievement of remission if a donor (sibling or alternative) is available.

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### CLASSIFICATION

AML<sup>hh,fff</sup> ≥60y



### [PS >2 or PS 0-3 with Significant Comorbidities - See AML-12](#)

<sup>hh</sup>Patients with blast counts >50,000/mcL are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include apheresis or hydroxyurea.

<sup>jj</sup>[See Supportive Care \(AML-C 1 of 2\).](#)

<sup>fff</sup>There is a web-based scoring tool available to evaluate the probability of complete response and early death after standard induction therapy in elderly patients with AML: <http://www.aml-score.org/>. Krug U, Rollig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet* 2010;376:2000-2008.

<sup>999</sup>Patients >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 chemotherapy.

<sup>hhh</sup>Idarubicin treatment compared to high doses of daunorubicin up to 80 mg/m<sup>2</sup> yields a 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).

<sup>iii</sup>The complete response rates and 2-yr overall survival in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m<sup>2</sup> is also comparable to the outcome for idarubicin 12 mg/m<sup>2</sup>; the higher dose daunorubicin did not benefit patients > 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).

<sup>jjj</sup>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 a clinical trial, but endpoints will be defined by the protocol.

<sup>kkk</sup>Clofarabine is renally cleared. The recommended treatment dose for patients 60-70 with normal creatinine clearance (≥60 mL/min) is 30 mg/m<sup>2</sup>. Clofarabine is not recommended for older patients with impaired renal function. It is immunosuppressive and unusual infections similar to those seen post stem cell transplant should be considered in the setting of febrile neutropenia.

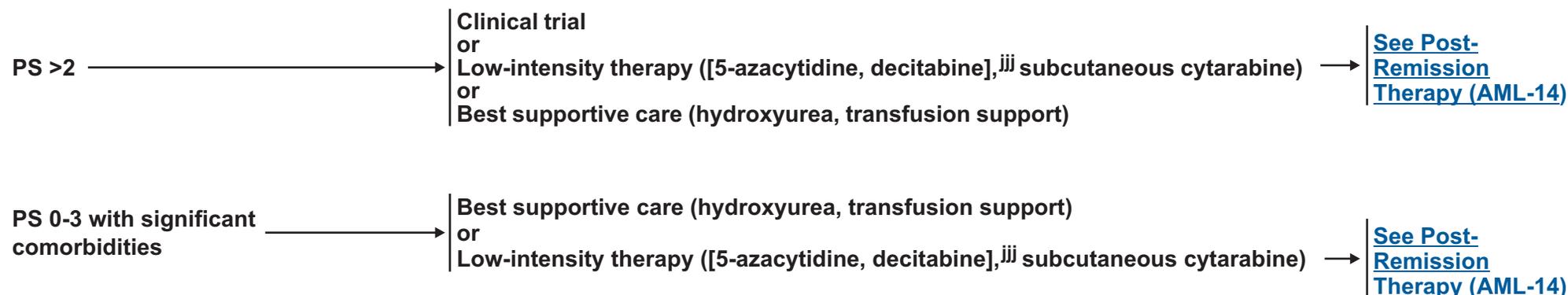
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### CLASSIFICATION

### TREATMENT INDUCTION<sup>jj</sup>

AML<sup>hh,fff</sup> ≥60 y



<sup>hh</sup>Patients with blast counts >50,000/mcL are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include apheresis or hydroxyurea.

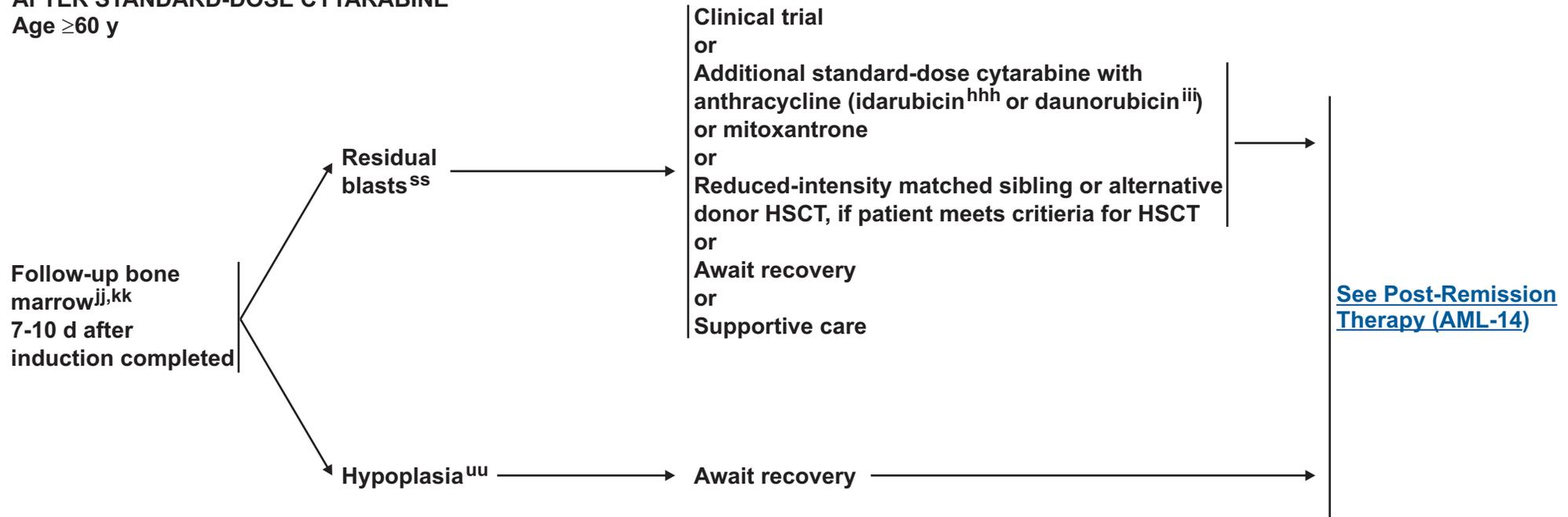
<sup>jj</sup>[See Supportive Care \(AML-C 1 of 2\)](#).

<sup>fff</sup>There is a web-based scoring tool available to evaluate the probability of complete response and early death after intensive induction therapy in elderly patients with AML: <http://www.aml-score.org/>. Krug U, Rollig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. Lancet 2010;376:2000-2008.

<sup>jjj</sup>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 a clinical trial, but endpoints will be defined by the protocol.

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**AML POST-INDUCTION THERAPY  
AFTER STANDARD-DOSE CYTARABINE  
Age ≥60 y**



<sup>jj</sup> See [Supportive Care \(AML-C 1 of 2\)](#).

<sup>kk</sup> See [Monitoring During Therapy \(AML-E\)](#).

<sup>ss</sup> Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and the patient is a candidate for an allogeneic HSCT.

<sup>uu</sup> Hypoplasia is defined as cellularity <10%-20% and residual blasts <5%-10%.

<sup>hhh</sup> Idarubicin treatment compared to high doses of daunorubicin up to 80 mg/m<sup>2</sup> 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).

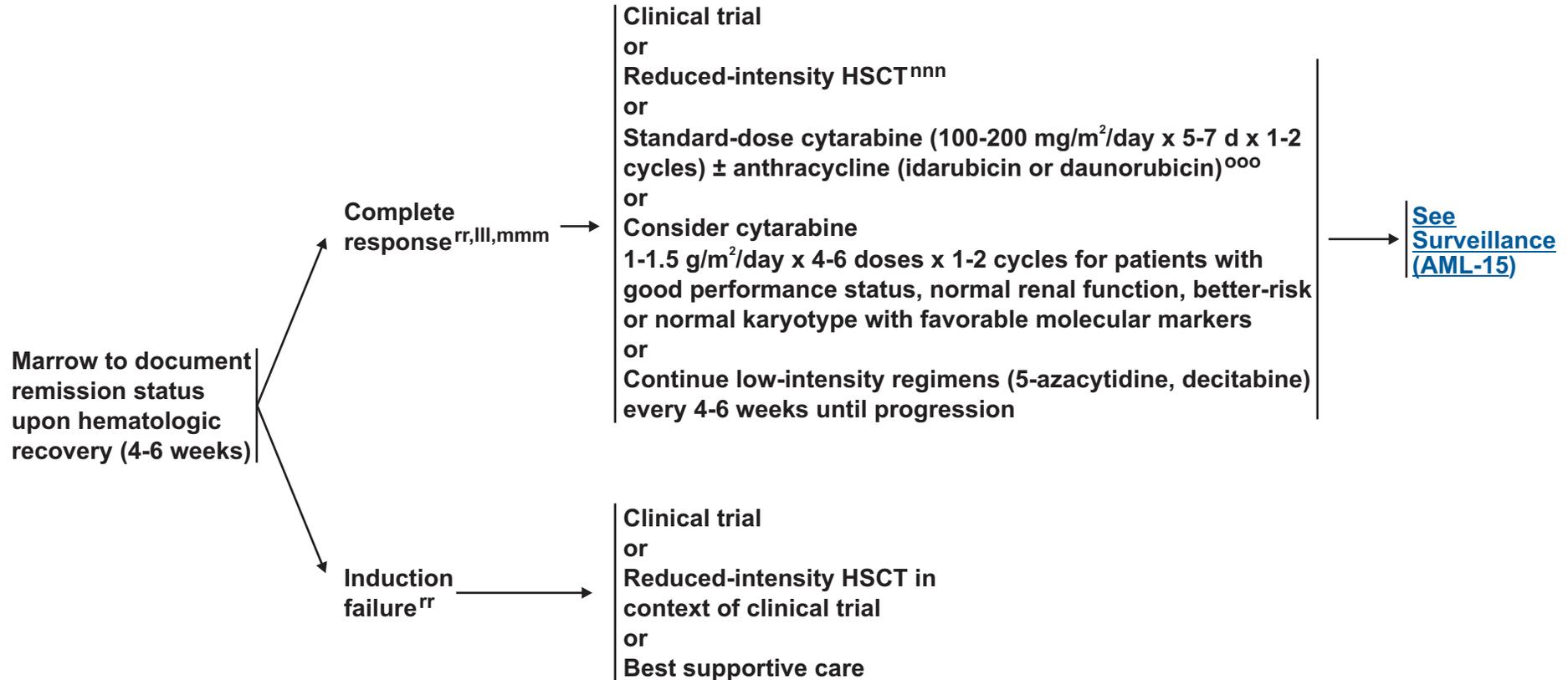
<sup>iii</sup> The complete response rates and 2-yr overall survival in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m<sup>2</sup> is also comparable to the outcome for idarubicin 12 mg/m<sup>2</sup>; the higher dose daunorubicin did not benefit patients > age 65 (Lowenberg 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



<sup>rr</sup>See Response Criteria for Acute Myeloid Leukemia (AML-D).

<sup>III</sup>Patients in remission may be screened with LP if initial WBC count >100,000/mcL or monocytic histology. See Evaluation and Treatment of CNS Leukemia (AML-B).

<sup>mmm</sup>HLA-typing for patients considered strong candidates for allogeneic transplantation.

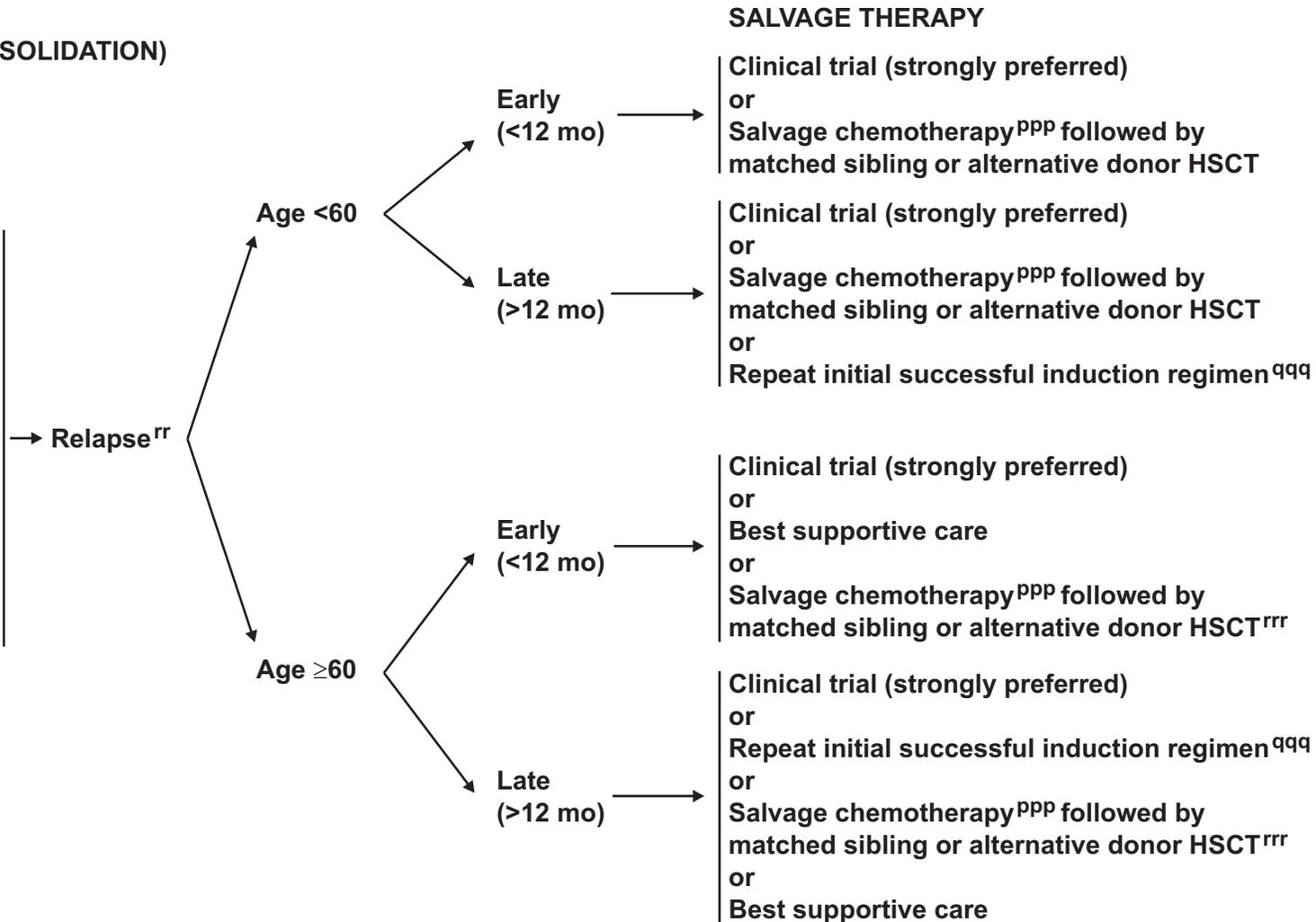
<sup>nnn</sup>Patients who are deemed as strong candidates for stem cell transplant and who have an available donor should be transplanted in first remission.

<sup>ooo</sup>An excellent outcome was reported for outpatient consolidation that 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 is 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



<sup>rr</sup> See Response Criteria for Acute Myeloid Leukemia (AML-D).

<sup>PPP</sup> See Salvage Chemotherapy Regimen Options (AML-F).

<sup>qqq</sup> Reinduction therapy may be appropriate in certain circumstances, such as in patients with long first remission. If a second complete response is achieved, then consolidation with allogeneic HSCT should be considered.

<sup>rrr</sup> Transplant should only be considered in the context of a clinical trial or if a remission is achieved.

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### RISK STATUS BASED ON VALIDATED CYTOGENETICS AND MOLECULAR ABNORMALITIES<sup>1</sup>

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

<sup>1</sup>The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.

<sup>2</sup>Other cytogenetic abnormalities in addition to these findings do not alter better risk status.

<sup>3</sup>Paschka P, Du J, Schlenk RF, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AML5G). Blood 2013;121:170-177.

<sup>4</sup>For Philadelphia+ AML t(9;22), manage as myeloid blast crisis in CML, with addition of tyrosine kinase inhibitors. [See NCCN Guidelines for Chronic Myelogenous Leukemia.](#)

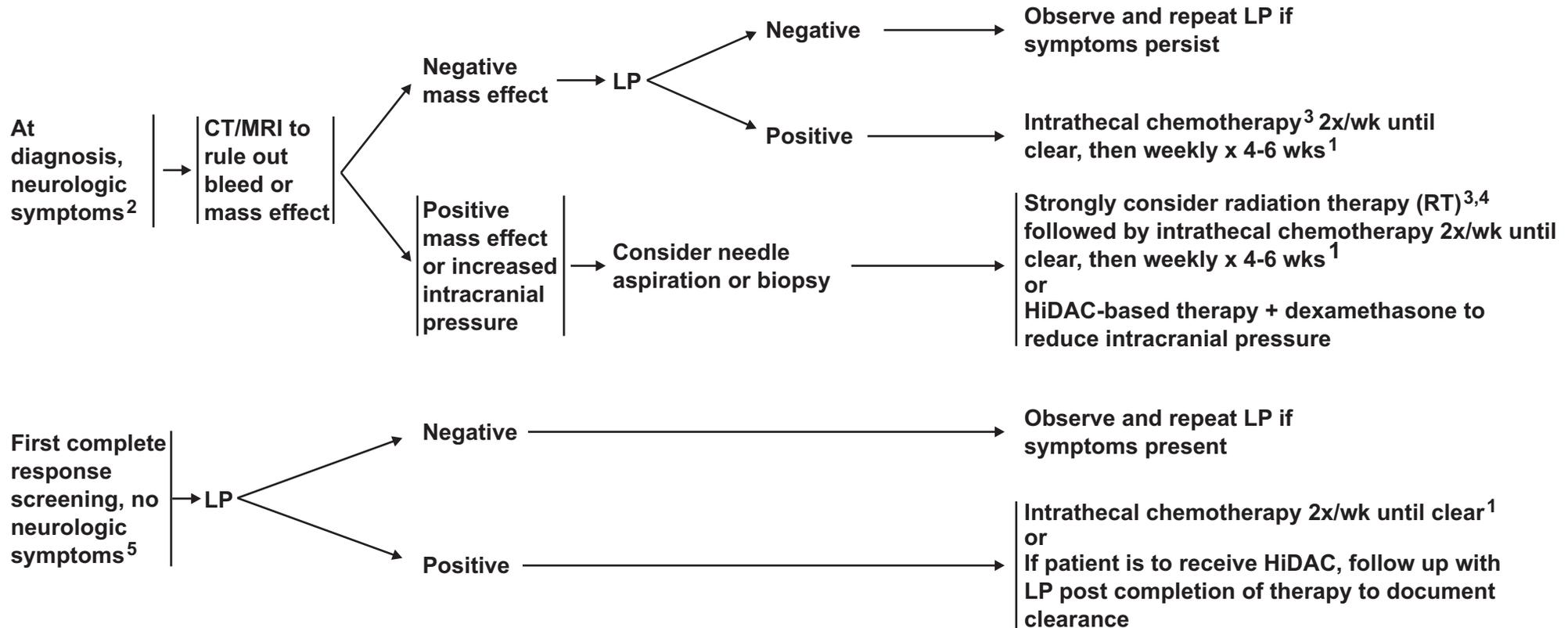
<sup>5</sup>Emerging data indicate that the presence of c-KIT mutations in patients with t(8;21), and to a lesser extent inv(16), confers a higher risk of relapse. These patients should be considered for clinical trials, if available.

<sup>6</sup>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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### EVALUATION AND TREATMENT OF CNS LEUKEMIA<sup>1</sup>



<sup>1</sup> Further CNS surveillance per institutional practice.

<sup>2</sup> 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 was detected on the imaging study.

<sup>3</sup> 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.

<sup>4</sup> Concurrent use of CNS RT with high-dose cytarabine, IT methotrexate, or IT liposomal cytarabine may increase risk of neurotoxicity.

<sup>5</sup> Screening LP should be considered at first remission for patients with M4 or M5 morphology, mixed phenotype acute leukemia, or WBC count >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 (ie, fludarabine, HSCT).
  - ▶ Transfusion thresholds: red blood cell (RBC) counts for Hgb  $\leq 8$  g/dL or per institutional guidelines or symptoms of anemia; platelets for patients with platelets  $<10,000/\text{mCL}$  or with any signs of bleeding.<sup>1</sup>
  - ▶ Cytomegalovirus (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 evidence of impaired renal function.
- Patients receiving HiDAC therapy (particularly those with impaired renal function) are at risk for cerebellar toxicity. Neurologic assessment, 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, HiDAC should be discontinued until creatinine normalizes.
  - ▶ In patients who develop cerebellar toxicity, cytarabine should be stopped. The patient should not be rechallenged with HiDAC 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 should be administered to both eyes four times daily for all patients undergoing HiDAC therapy until 24 hours post completion of cytarabine.
- Growth factors may be considered as a part of supportive care for post-remission therapy. Note that such use may confound interpretation of the bone marrow evaluation. Patients 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.<sup>2</sup> Outcomes with other azoles, such as voriconazole, echinocandins, or amphotericin B, may produce equivalent results.

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

<sup>2</sup>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 Supportive Care \(AML-C 2 of 2\)](#)

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### 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  $\geq 50,000/\text{mCL}$ ; fibrinogen replacement with cryoprecipitate and fresh frozen plasma to maintain a level over 150 mg/dL and PT and PTT close to normal values. Monitor daily until coagulopathy resolves.**
  - ▶ **Central venous catheter should not be placed until bleeding is 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 (ie, fever, often associated with increasing WBC count  $>10,000/\text{mCL}$ , 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 (ie, 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<sup>1</sup>**
  - ▶ **Prior to initiating therapy**
    - ◊ **Electrocardiogram (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.**

<sup>1</sup>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<sup>1</sup>

- **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 complete response - cytogenetics normal (in those with previously abnormal cytogenetics)
  - ▶ Molecular complete response - molecular studies negative<sup>2</sup>
  - ▶ CRi - There are some clinical trials, particularly those that focus on the elderly or those with antecedent myelodysplasia, that include a variant of complete response referred to as CRi. This has been defined as <5% marrow blasts, either ANC >1000/mcL or platelets ≥100,000/mcL, and transfusion independence but with persistence of cytopenia (usually thrombocytopenia).
- **Partial remission<sup>3</sup>**
  - ▶ 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.

<sup>1</sup>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.

<sup>2</sup>This is clinically relevant only in APL and Ph+ leukemia at the present time.

<sup>3</sup>Partial remissions 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 daily (differential daily during chemotherapy and every other day after recovery of WBC count >500/mcL until either normal differential or persistent leukemia is documented); platelets daily while in the hospital until platelet-transfusion independent.**
- **Chemistry profile, including electrolytes, blood urea nitrogen (BUN), creatinine, uric acid, and PO<sub>4</sub>, at least daily during active treatment until risk of tumor lysis is past. If the patient is receiving nephrotoxic agents, closer monitoring is required through the period of hospitalization.**
- **Liver function tests 1-2 times/week.**
- **Coagulation panel 1-2 times/week.**
- **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 are abnormal or if there is failure to recover counts within 5 wks**
- **Patients with high-risk features, including poor-prognosis cytogenetics, therapy-related AML, prior MDS, or possibly 2 or more inductions to achieve a complete response, are at increased risk for relapse and may be considered for early unrelated donor search, as indicated on [AML-10](#).**

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### SALVAGE CHEMOTHERAPY REGIMEN OPTIONS<sup>1</sup>

- Cladribine + cytarabine + granulocyte colony-stimulating factor (G-CSF) ± mitoxantrone or idarubicin<sup>1,2</sup>
- High-dose cytarabine (if not received previously in treatment) ± anthracycline
- Fludarabine + cytarabine + G-CSF ± idarubicin<sup>3,4</sup>
- Etoposide + cytarabine ± mitoxantrone<sup>5</sup>
- Clofarabine + cytarabine + G-CSF<sup>6</sup>

**These are aggressive regimens for appropriate patients who can tolerate such therapies; for other patients, less aggressive treatment options include low-dose cytarabine or hypomethylating agents (5-azacytidine or decitabine).**

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>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.

<sup>4</sup>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;99(4):939-944.

<sup>5</sup>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;9(7):1210-1214.

<sup>6</sup>Becker PS, Kantarjian HM, Appelbaum FR, et al. Clofarabine with high dose cytarabine and granulocyte colony-stimulating factor (G-CSF) priming for relapsed and refractory acute myeloid leukaemia. *Br J Haematol* 2011;155:182-189.

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# NCCN Guidelines Version 2.2013 Acute Myeloid Leukemia

[NCCN Guidelines Index](#)  
[AML Table of Contents](#)  
[Discussion](#)

## Discussion

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**

## Table of Contents

[Overview](#)..... **MS-2**

[Initial Evaluation](#) ..... **MS-3**

Workup..... MS-3

Diagnosis ..... MS-4

Cytogenetics and Risk Stratification ..... MS-5

Molecular Markers and Risk Stratification..... MS-6

[Principles of AML Treatment](#) ..... **MS-10**

[Management of Acute Promyelocytic Leukemia \(APL\)](#) ..... **MS-11**

Induction Therapy for Patients with APL .....MS-11

Consolidation Therapy for Patients with APL .....MS-14

Post-Consolidation or Maintenance Therapy for Patients with APL  
.....MS-17

Management of Relapsed APL .....MS-18

Supportive Care for Patients with APL .....MS-19

[Management of AML](#) .....**MS-21**

Management of AML in Patients Younger Than 60 Years.....MS-21

Management of AML in Patients Older Than 60 Years .....MS-28

Postremission Surveillance and Salvage Therapy for AML .....MS-34

Supportive Care for Patients with AML .....MS-35

Evaluation and Treatment of CNS Leukemia .....MS-36

[References](#).....**MS-38**



# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

### Overview

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. It is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths from leukemias in the United States. An estimated 13,780 people will be diagnosed with AML in 2012, and 10,200 patients will die of the disease.<sup>1</sup> The median age of diagnosis is 66 years, with 54% of patients diagnosed at 65 years or older (and approximately a third diagnosed at  $\geq 75$  years of age).<sup>2</sup> Thus, as the population ages, the incidence of AML, along with myelodysplasia, seems to be rising. Environmental factors that have long been established to increase the risks of myelodysplastic syndromes (MDS) and AML include prolonged exposure to petrochemicals; solvents such as benzene; pesticides; and ionizing radiation.<sup>3</sup> Equally disturbing is the increasing incidence of treatment-related myelodysplasia and acute leukemia in survivors of tumors of childhood and young adulthood. Therapy-related myeloid leukemia (secondary MDS/AML) is a well-recognized consequence of cancer treatment in a proportion of patients receiving cytotoxic therapy for solid tumors or hematologic malignancies. Although the exact incidence of therapy-related MDS/AML is unknown, and varies depending on the types of treatment modalities used for a given primary tumor, recent reports suggest that therapy-related MDS/AML may account for 5% to 20% of patients with MDS/AML.<sup>4-6</sup> The rate of therapy-related MDS/AML is higher among patients with certain primary tumors, including breast cancer, gynecologic cancers, and lymphomas (both non-Hodgkin's lymphoma and Hodgkin lymphoma), largely owing to the more leukemogenic cytotoxic agents that are commonly used in the treatment of these tumors.<sup>6-9</sup> The 2 well-documented categories of cytotoxic agents associated with the development of therapy-related MDS/AML are

alkylating agents (eg, cyclophosphamide, melphalan) and topoisomerase inhibitors/agents that interact with topoisomerase (eg, etoposide, doxorubicin, mitoxantrone).<sup>4,7,8</sup> Treatment with antimetabolites, such as the purine analog fludarabine, has also been associated with therapy-related MDS/AML in patients with lymphoproliferative disorders, particularly when administered in combination with alkylating agents.<sup>10,11</sup> Radiotherapy, especially in the context of myeloablative therapy (eg, total-body irradiation or radioimmunotherapy) given before autologous stem cell transplantation, may also increase the risk of therapy-related MDS/AML.<sup>12,13</sup> The disease course of therapy-related MDS/AML is generally progressive and may be more resistant to conventional cytotoxic therapies than de novo cases of MDS/AML.<sup>8</sup> Importantly, clinical outcomes in patients with therapy-related AML have been shown to be significantly inferior (both in terms of relapse-free and overall survivals) compared with patients with de novo cases,<sup>7,14</sup> except those with the therapy-related acute promyelocytic leukemia (APL) subtype<sup>6,15</sup> or the favorable-risk core binding factor (CBF) translocations. The proportion of patients with unfavorable cytogenetics tends to be higher in the population with therapy-related AML. Even among the subgroup with favorable karyotypes, those with therapy-related AML tend to do less well.

The AML panel for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) convenes annually to update recommendations for the diagnosis and treatment of AML in adults. These recommendations are based on a review of recently published clinical trials that have led to significant improvements in treatment or have yielded new information regarding biologic factors that may have prognostic importance. Most improvements in recent years have been in the treatment of patients with APL, which serves as a paradigm for understanding how the biology of the disease can inform treatment.



## Initial Evaluation

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

## Workup

The evaluation and initial workup for suspected acute leukemias include a comprehensive medical history and physical examination. Laboratory evaluations include blood chemistry and complete blood count including platelets and differentials. Bone marrow analysis with cytogenetics (karyotype, with or without FISH) is necessary to establish the diagnosis of AML. Bone marrow samples should also be obtained and cryopreserved at the time of diagnosis for potential future evaluation of molecular markers (eg, *FLT3-ITD*, mutations in *NPM1*, *CEBPA*, *c-KIT*) that may have prognostic implications (see Discussion section below, "Molecular Markers and Risk Stratification").

Extramedullary presentation, including central nervous system (CNS) disease, is uncommon in patients with AML. Patients with significant CNS signs or symptoms at presentation should be evaluated using appropriate imaging techniques, such as radiography, CT, or MRI for detection of intracranial bleeding, leptomeningeal disease, or mass lesions in either the brain or spinal cord. However, 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 LPs are not warranted at the time of diagnosis in patients with AML. However, for patients at high risk for CNS disease, such as those with monocytic differentiation (M4 or M5 morphology) or high WBC count (> 100,000/mcL) at presentation, a diagnostic LP should be considered as part of the documentation of remission status. For patients who present with solitary extramedullary disease (often referred to as myeloid sarcoma, 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 with systemic chemotherapy in emergent situations; however, these modalities, if needed at all, should be optimally deferred until count recovery to avoid excess toxicity.

Coagulopathy is fairly common at presentation in many leukemias; it is therefore standard clinical practice to screen for coagulopathy by evaluating prothrombin time, partial thromboplastin time, and fibrinogen as part of the initial evaluation/workup and before performing any invasive procedure. The need for a cardiac evaluation (eg, echocardiogram or MUGA) should be determined by individual risk factors, such as in patients with a history or symptoms of cardiac disease or those with prior exposure to cardiotoxic drugs or thoracic radiation. HLA typing should be performed in all patients with newly diagnosed AML for whom allogeneic hematopoietic stem cell transplantation (HSCT) would be considered. HLA typing of family members is recommended for patients younger than 60 years who do not have favorable-risk cytogenetics. Tissue typing should be broadened to include unrelated donor searches in patients younger than 60 years with karyotypes or molecular abnormalities deemed high-risk. 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 HSCT.

### Diagnosis

Over the past 3 decades, the classification system for AML has evolved from the French American British (FAB) system, which relied on cytochemical stains and morphology to separate AML from acute lymphoblastic leukemia (ALL) and to categorize the disease based on degree of myeloid and monocytic differentiation, to the system developed by the WHO.

In 1999, the WHO developed a newer classification system, which incorporates information from cytogenetics and evidence of dysplasia to refine prognostic subgroups that may define treatment strategies.<sup>16</sup> During this transition from the FAB system to the WHO classification, the percent blasts threshold for defining high-grade MDS and AML was lowered. The FAB classification (1976) had set the threshold between high-grade MDS and AML at 30% blasts, whereas the WHO classification lowered the threshold for diagnosing AML to 20% or more blasts; this was based on the finding that the biologic behavior (and survival outcomes) of the FAB MDS subgroup of “refractory anemia with excess blasts in transformation (RAEB-T)” with 20% to 30% blasts was equally grim compared with that of patients with greater than 30% blasts. In addition, the WHO classification system allows AML to be diagnosed regardless of the percentage of marrow blasts in patients with abnormal hematopoiesis and characteristic clonal structural cytogenetic abnormalities 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 diagnosing AML, including the reporting of dysplasia according to morphology.<sup>17</sup>

However, no evidence shows that dysplasia represents an independent risk factor, because it is frequently linked to poor-risk cytogenetics.

In 2008, the WHO revised the diagnostic and response criteria for AML to include additional recurrent genetic abnormalities created by reciprocal translocations/inversions, and a new provisional category for some of the molecular markers that have been found to have prognostic impact.<sup>18</sup> In the 2008 WHO classification, the category of AML with recurrent genetic abnormalities was expanded to include the following: t(9;11)(p22;q23), t(6;9)(p23;q34) (provisional entity), inv(3)(q21 q26.2) or inv(3;3)(q21;q26.2) (provisional entity), and t(1;22)(p13;q13) (provisional entity), in addition to the previously recognized t(8;21)(q22;q22); inv(16)(p13;1q22) or t(16;16)(p13.1;q22); and t(15;17)(q22;q12) [APL subtype]. In addition, AML with molecular lesions such as mutated *NPM1* or *CEBPA* genes are considered provisional entities (further information on these genetic lesions is provided later).<sup>18</sup>

The accurate classification of AML requires multidisciplinary diagnostic studies (using immunohistochemistry, cytochemistry, or both, in addition to molecular genetics analysis) in accordance with the 2008 WHO classification. The NCCN AML Panel suggests that complementary diagnostic 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. When presented with rare cases such as acute leukemias of ambiguous lineage (including mixed phenotype acute leukemias, as defined by the 2008 WHO classification), consultation with an experienced hematopathologist should be sought. Aberrant expression of differentiation antigens present at diagnosis may allow tracking of residual blasts through flow cytometry in follow-up

samples that may appear normal according to conventional morphology. The use of immunophenotyping and molecular markers to monitor minimal residual disease (MRD) in adult AML has not yet been incorporated into postremission monitoring strategies, except in patients with APL.

### Cytogenetics and Risk Stratification

Although cytogenetic information is often unknown when treatment is initiated in patients with de novo AML, karyotype represents the single most important prognostic factor for predicting remission rate, relapse risks, and overall survival (OS) outcomes. The cytogenetic risk categories adopted by these guidelines are primarily based on analyses of large datasets from major cooperative group trials (see “Risk Status Based on Validated Cytogenetics and Molecular Abnormalities” on page AML-A).<sup>19-21</sup> In an analysis of data from pediatric and adult patients with AML (N = 1612) enrolled on the United Kingdom Medical Research Council (UK MRC) AML 10 trial, the 5-year survival rates for those with favorable, intermediate-risk, and poor-risk cytogenetics were 65%, 41%, and 14%, respectively.<sup>20</sup> In a review of data from adult patients treated on a phase III SWOG/ECOG intergroup study (N = 609), the 5-year survival rates for those with favorable, intermediate-risk, and unfavorable cytogenetics were 55%, 38%, and 11%, respectively.<sup>21</sup> Similarly, in a retrospective review of adult patients with AML treated on CALGB protocols (N = 1213), the 5-year survival rates for those with favorable, intermediate-risk, and poor-risk cytogenetics were 55%, 24%, and 5%, respectively.<sup>19</sup>

The importance of obtaining adequate samples of marrow or peripheral blood at diagnosis for full karyotyping and fluorescence in situ hybridization (FISH) cytogenetic analysis for the most common abnormalities cannot be overemphasized. Although FISH studies for common cytogenetic abnormalities may provide a rapid screening to

identify either favorable or unfavorable risk groups, they do not provide a full picture of the genetic factors, which contribute to risk (see Discussion section below, “Molecular Markers and Risk Stratification”).

In the past 5 years, the presence of autosomal chromosome monosomies in AML has emerged as an important prognostic factor associated with extremely poor prognosis.<sup>22-24</sup> Data from 3 large studies have identified monosomal karyotypes (defined as having  $\geq 2$  autosomal monosomies, or a single monosomy with additional structural abnormalities) as a subset of unfavorable cytogenetic prognosticators. Although complex karyotype (having  $\geq 3$  clonal cytogenetic abnormalities) and  $-5$  or  $-7$  monosomies are categorized in the high-risk/unfavorable cytogenetics group, the presence of a monosomal karyotype was found to confer further negative prognostic influence within the high-risk group. The first study to identify this high-risk subgroup was HOVON. In a joint study conducted by the Dutch-Belgian and Swiss cooperative groups (HOVON/SAKK) evaluating the correlation between cytogenetics and OS outcomes in patients aged 60 years or younger with AML (N = 1,975), the 4-year OS rate in patients with monosomal karyotype was 4% compared with 26% in those with complex karyotype (but without monosomal karyotype).<sup>22</sup>

These findings were confirmed in subsequent analyses from other large cooperative group studies. In an analysis of data from patients treated on SWOG protocols (N = 1,344; age 16–88 years), 13% of patients were found to have monosomal karyotype; nearly all of these cases (98%) occurred within the unfavorable cytogenetics category.<sup>23</sup> The incidence of monosomal karyotype increased with age, from 4% in patients aged 30 years or younger to 20% in those older than 60 years. Among patients with unfavorable cytogenetics, the 4-year OS rate in the subgroup of patients with monosomal karyotype was 3% compared with 13% in the subgroup without monosomal karyotype. In patients



with monosomy 7, monosomal karyotype did not appear to influence outcomes (4-year OS, 0%–3%); the 4-year OS rates for patients with *inv(3)/t(3;3)* and *t(6;9)* and those without monosomal karyotype, were 0% and 9%, respectively.<sup>23</sup> In a recent retrospective study that evaluated the prognostic impact of monosomal karyotype in older patients (age > 60 years; N = 186) with unfavorable cytogenetics treated on a GOELAMS trial, the 2-year OS rate was significantly decreased among patients with monosomal karyotype compared with those without this abnormality (7% vs. 22%; *P* < .0001); similar outcomes were observed within the subgroup of patients with complex karyotype.<sup>24</sup>

These studies show that monosomal karyotype, independent of other unfavorable cytogenetic factors, confers very poor prognosis in both young and older patients with AML. In the NCCN Guidelines, the presence of monosomal karyotype is included in the unfavorable risk category of AML based on cytogenetics (see “Risk Status Based on Validated Cytogenetics and Molecular Abnormalities” on page AML-A).

### **Molecular Markers and Risk Stratification**

The intermediate-risk cytogenetic category is the most heterogeneous group in AML, because it encompasses both normal karyotype without gross structural abnormalities and those with structural changes that are considered neither poor-risk or favorable. Based on retrospective analysis of data from large cooperative group studies, 40% to 50% of patients with de novo AML have normal karyotype, which is associated with an intermediate risk in terms of survival outcomes.<sup>19,20</sup> However, clinical outcome, even in patients with normal karyotype AML (NK-AML), is heterogeneous.

Molecular profiling is increasing the ability to identify mutations at the molecular level, which carry prognostic impact. Thus, in addition to

basic cytogenetic analysis, new molecular markers help to refine prognostics groups, particularly in patients with a normal karyotype. These markers include FMS-like tyrosine kinase 3 (*FLT3*), c-KIT, nucleophosmin (*NPM1*), and *CEBPA* gene mutations.<sup>25-36</sup> Tests for these molecular markers are becoming more common in commercial reference laboratories and in referral centers. Therefore, it is important for physicians to submit sufficient samples to reserve aliquots of cryopreserved marrow from the time of diagnosis to allow for subsequent molecular diagnostic tests, particularly in patients with normal karyotype.

The 2 most frequent molecular lesions with prognostic impact in patients with AML are mutations of the *FLT3* gene (37%–46% of patients) encoding a receptor tyrosine kinase involved in hematopoiesis,<sup>29,37,38</sup> and mutations of the *NPM1* gene (28%–35%)<sup>35,37,39</sup> encoding a shuttle protein within the nucleolus. The *NPM1* mutation has been shown to be associated with normal karyotype AML (NK-AML) with a reported frequency of 48% to 53%.<sup>27,33,38</sup> Isolated *NPM1* mutation, which localizes to the cytoplasm, confers a higher complete response (CR) rate and improved event-free survival (EFS) and OS compared with patients with NK-AML with wild-type *NPM1*, resulting in outcomes similar to patients with favorable cytogenetics (eg, CBF AML).<sup>27,28,33,35,36</sup> Two major classes of activating *FLT3* mutations have been identified in patients with AML, which include the internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations.<sup>40-45</sup> *FLT3*-ITD occurs in approximately 30% of cases and is more common than *FLT3*-TKD mutations, which occur in approximately 10% of patients.<sup>25,29,38,44-48</sup> Numerous studies have shown the negative prognostic influence of *FLT3*-ITD in patients with AML, resulting in shorter remission durations (eg, decreased disease-free survival [DFS] in patients with a CR) and poorer survival outcomes compared with



patients with wild-type *FLT3*.<sup>25,29,41,42,44,46,47,49</sup> Among patients with *FLT3*-ITD and NK-AML, median OS from the time of diagnosis ranged from 6 to 12 months.<sup>25,29,44,47</sup>

Interestingly, a study in patients with NK-AML showed that prognosis was worse among patients with *FLT3*-ITD without a wild-type *FLT3*, compared with those with *FLT3*-ITD but having a wild-type *FLT3* in the second allele. The median OS among patients with *FLT3*-ITD in the absence of a wild-type *FLT3* was only 7 months compared with 46 months among both the patient subgroups with wild-type *FLT3* with or without *FLT3*-ITD.<sup>44</sup> The *FLT3*-TKD mutations predominantly occur independently of *FLT3*-ITD, and most frequently involve mutations in the D835 residue of a tyrosine kinase domain. Although the presence of *FLT3*-TKD mutations has been shown to be associated with shorter remission durations (eg, decreased DFS) and decreased OS outcomes in some studies,<sup>29,41,45,48</sup> other studies have reported no impact of *FLT3*-TKD on prognosis<sup>38,49,50</sup> or even a favorable outcome on OS with *FLT3*-TKD mutations.<sup>51</sup> In the latter study from the UK MRC, the 5-year OS rate among patients with and without *FLT3*-TKD mutations was 53% versus 37%, respectively. Patients with a higher level of *FLT3*-TKD mutations (> 25%) had a significantly higher 5-year OS rate compared with those with lower levels of mutations, which showed an OS rate similar to that of patients without *FLT3*-TKD mutations (71% vs. 37%; adjusted  $P = .004$ ).<sup>51</sup>

The discrepant findings from these studies may be a result of important differences between the studies in factors such as patient baseline characteristics, presence of concurrent genetic lesions (eg, *NPM1*, *CEBPA* mutations), or inclusion of the APL subtypes. Studies have shown that *FLT3*-TKD mutations can occur in a subgroup of patients with the prognostically favorable *NPM1* or *CEBPA* mutations.<sup>38,50</sup> Moreover, *FLT3*-TKD mutation as the sole genetic aberration or

occurring concurrently with t(15;17)/PML-RARA (underlying lesion in the APL subtype) or with *FLT3*-ITD (*FLT3* double mutation) has been associated with poorer outcomes.<sup>38,50</sup>

The *CEBPA* gene encodes for CCAAT/enhancer binding protein alpha (C/EBPα), a transcription factor that plays a key role in the differentiation of granulocytes.<sup>31</sup> Mutations in *CEBPA* have been reported in 7% to 11% of patients with AML (or 13%–15% of those with NK-AML) and has been associated with a favorable outcome (similar to patients with CBF translocations) with regard to increased remission duration and OS outcomes compared with wild-type *CEBPA*.<sup>30,37,38,52-54</sup> However, as a caveat, a recent study indicated that the OS benefit with *CEBPA* was observed for patients with double mutations of *CEBPA* but not for those with a single mutation of the gene; the 8-year OS rates reported in this study for patients with double-mutated *CEBPA*, single mutation of *CEBPA*, and wild-type gene were 54%, 31%, and 34%, respectively.<sup>53</sup>

Recently, other common molecular lesions with prognostic impact have been identified in patients with AML. The most common of these include mutations in *IDH1* and *IDH2* genes, which encode for isocitrate dehydrogenase 1 and 2, respectively, and mutations in *DNMT3A*, which encode for DNA methyltransferase 3A. Mutations in *IDH1* have been reported in 6% to 9% of AML cases, with a higher frequency reported among patients with NK-AML (8%–16%).<sup>37,55-60</sup> *IDH1* mutation was found to occur concurrently with NK-AML and *NPM1* mutations.<sup>55-58,60</sup> This mutation has also been found to be associated with wild-type *CEBPA* and the absence of *FLT3* abnormalities (eg, *FLT3*-ITD or *FLT3*-TKD mutations).<sup>58</sup>

Findings from published reports on the prognostic effects of *IDH1* mutations have been inconsistent. Although some studies showed no

prognostic effect of *IDH1* mutations on OS when considering all *IDH* mutations (*IDH1* and *IDH2* combined) or in the overall patient population,<sup>55-58</sup> *IDH1* mutations seemed to be associated with significantly worse outcomes in the subgroup of patients with NK-AML with favorable- or intermediate-risk disease.<sup>55,58,60</sup> In the subgroup of patients younger than 60 years with favorable-risk AML (*NPM1* mutation without *FLT3*-ITD) in a study of patients with NK-AML, *IDH1* mutation was associated with a significantly decreased 5-year DFS rate (42% vs. 59%;  $P = .046$ ) and trend for decreased OS rate (50% vs. 63%) compared with patients who had wild-type *IDH*.<sup>58</sup> In another study, *IDH* mutations (*IDH1* and *IDH2* combined) were associated with significantly inferior 5-year relapse-free survival rates (37% vs. 67%;  $P = .02$ ) and OS rates (41% vs. 65%;  $P = .03$ ) in the subgroup of patients with favorable-risk AML (normal karyotype with *NPM1* mutation without *FLT3*-ITD).<sup>60</sup> This prognostic significance was observed when *IDH1* and *IDH2* mutations were separately analyzed, although patient numbers were small for each subgroup and statistical significance was reached only for the relapse-free survival analysis.<sup>60</sup> *IDH1* mutation was also associated with worse EFS and OS outcomes among the subgroup of patients with intermediate-risk NK-AML (wild-type *NPM1* without *FLT3*-ITD).<sup>55</sup> Mutations in *IDH2* have been reported in 8% to 12% of patients with AML,<sup>37,55,56,60,61</sup> with a frequency of 19% reported among those with normal karyotype.<sup>58</sup> The presence of *IDH2* mutations was mutually exclusive with *IDH1* mutation in nearly all cases.<sup>55,56,58</sup> Mutations have been identified in R172 and R140 of the *IDH2* gene, with R140 mutation occurring more frequently.<sup>58,60,61</sup> Interestingly, the *IDH2*-R172 mutation seemed to be mutually exclusive with *NPM1* mutations and *FLT3*-ITD.<sup>58,60,61</sup>

Similar to findings with *IDH1* mutations, reports on the prognostic effect of *IDH2* mutations have also been inconsistent. Some studies have

reported the lack of prognostic value of *IDH2* mutations,<sup>55,56,60</sup> whereas others have reported favorable outcomes with *IDH2* mutations.<sup>37,61</sup> In one study, an association was found between *IDH2* mutations and poorer prognosis in the subgroup of patients with NK-AML with otherwise favorable risk (*NPM1* mutation without *FLT3*-ITD).<sup>60</sup> However, in another recent study, *IDH2* mutation (restricted to *IDH2*-R140) was associated with improved survival among the overall study population, and among the subgroup of patients with favorable risk (intermediate-risk AML with *NPM1* mutation without *FLT3*-ITD).<sup>37</sup> In this latter subgroup, presence of *IDH1* or *IDH2* mutations was associated with significantly increased 3-year OS rate compared with patients with *NPM1* mutation without *FLT3*-ITD and without *IDH1* or *IDH2* mutations (89% vs. 31%;  $P < .0001$ ). These results seem to suggest that in patients with NK-AML without *FLT3*-ITD, *NPM1* mutations confer a survival benefit only in the presence of concurrent *IDH* mutations.<sup>37</sup> The conflicting findings from the above studies require further investigation.

The *DNMT3A* mutations have been reported in 18% to 22% of patients with AML,<sup>37,62,63</sup> with a frequency of 29% to 34% in those with NK-AML.<sup>64-66</sup> R882 is the most commonly mutated residue. This mutation has also been observed in conjunction with *NPM1* mutations and *FLT3* mutations.<sup>63,65,66</sup> Data concerning the prognostic significance of *DNMT3A* mutations have thus far been conflicting. Some studies in the overall AML population and in patients with intermediate risk reported no significant effect of *DNMT3A* mutations on survival outcomes,<sup>37,65</sup> whereas other studies have shown a negative prognostic effect in the overall population or specific subgroups.<sup>62-64,66</sup> Studies have shown significantly decreased OS outcomes among patients with *DNMT3A* mutations compared with those with the wild-type gene (median OS. 12–21 vs. 40–41 months).<sup>62,63</sup> Significantly decreased OS with *DNMT3A* mutations has also been reported in the subgroup of patients with NK-



# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

AML with wild-type *NPM1* with or without *FLT3*-ITD or *NPM1* mutation in the presence of *FLT3*-ITD, but not in the favorable subgroup with *NPM1* mutation without *FLT3*-ITD.<sup>63</sup> A recent study reported that in younger patients (age < 60 years) with NK-AML, presence of *DNMT3A* mutations was associated with significantly decreased OS compared with the wild-type gene (5-year OS rate, 23% vs. 45%; *P* = .02).<sup>66</sup> Another recent study also showed that in younger patients (age < 60 years) with NK-AML, *DNMT3A* mutation was associated with significantly decreased DFS (3-year rate, 20% vs. 49%; *P* = .007) and a trend toward decreased OS.<sup>64</sup> Interestingly, in this latter study, non-R882 *DNMT3A* mutations were significantly associated with poorer outcomes in patients younger than 60 years (but not R882 mutations); in contrast, in patients aged 60 years and older, *DNMT3A*-R882 mutations (but not non-R882 mutations) were associated with significantly decreased DFS (3-year rate, 3% vs. 21%; *P* = .006) and OS (3-year rate, 4% vs. 24%; *P* = .01).<sup>64</sup> The authors concluded that the prognostic relevance of *DNMT3A* mutations may depend on age and mutation type. Currently, the interactions of both *IDH1* or *IDH2* and *DNMT3* mutations with other molecular changes require further investigation to determine the prognostic value in patients with NK-AML. Neither of these genetic mutations is available for testing outside of the research setting. Other candidate genes currently being evaluated for prognostic importance include *TET2* and *RUNX1*.<sup>67,68</sup>

As seen from the earlier discussions, patients with NK-AML may present with multiple molecular lesions. *NPM1* mutations can occur concurrently with *FLT3*-ITD, and patients who have both genetic lesions have an outcome more similar to those with isolated *FLT3*-ITD mutations.<sup>27,33</sup> Thus, *NPM1* mutation confers favorable prognosis only in the absence of *FLT3*-ITD.<sup>38</sup> Similarly, the benefit in OS outcomes seen with *CEBPA* mutations seems to be lost in the presence of concurrent

*FLT3*-ITD.<sup>53</sup> As previously mentioned, *FLT3*-TKD in the presence of *FLT3*-ITD or occurring with t(15;17)/PML-RARA seems to be associated with poorer prognosis. In contrast, *FLT3*-TKD may be associated with an additional favorable prognosis in the presence of *NPM1* or *CEBPA* mutations.<sup>50</sup>

Both the NCCN and the European LeukemiaNet (ELN) classify patients with NK-AML and mutated *NPM1* or *CEBPA* (without *FLT3*-ITD) as having favorable risk.<sup>69,70</sup> Specifically, within the NCCN Guidelines, patients with NK-AML with mutated *NPM1* (without *FLT3*-ITD) or with isolated biallelic *CEBPA* mutation are categorized as having favorable risk (see “Risk Status Based on Validated Cytogenetics and Molecular Abnormalities” on page AML-A). In the ELN guidelines, patients with NK-AML with both mutated *NPM1* and *FLT3*, and those with wild-type *NPM1* and mutated *FLT3* or wild-type *NPM1* and *FLT3* are categorized as having intermediate-risk AML (“Intermediate I” group).<sup>69,70</sup> ELN classifies patients with t(9;11)(p22;q23), *MLL3-MLL* and other cytogenetic abnormalities that fall into neither the favorable or adverse category into the “Intermediate II” group. A recent analysis that evaluated the prognostic value of the ELN risk classification (based on data from the German AML96 study) showed that for patients aged 60 years and younger, median relapse-free survival was shorter for the Intermediate I than for the Intermediate II group (7.9 vs. 39.1 months, respectively). In patients older than 60 years, no major difference was observed (9.6 vs. 11.6 months, respectively).<sup>70</sup> In this analysis, median OS between the Intermediate I and Intermediate II groups were not as widely separated among patients aged 60 years and younger (13.6 vs. 18.7 months, respectively); in patients older than 60 years, median OS was similar between the 2 intermediate groups (9.5 vs. 9.2 months, respectively).<sup>70</sup> However, based on the substantial difference in relapse-free survival data between the Intermediate I and Intermediate

II groups defined by ELN, the NCCN has continued to place NK-AML with *FLT3*-ITD mutations in the unfavorable risk group rather than the intermediate risk group (see “Risk Status Based on Validated Cytogenetics and Molecular Abnormalities” on page AML-A). Although data are emerging on the prognostic relevance of mutations in the *IDH* and *DNMT3A* genes (see earlier discussions), the role of these molecular lesions on the risk stratification of patients with AML remains to be defined. Therefore, these molecular markers have not been incorporated into the risk categorization schema in the current guidelines.

In patients with the favorable-risk CBF AML [eg, t(8;21) or inv(16)], the presence of a mutation in *c-KIT* significantly increased the risk of relapse.<sup>26,32,34</sup> *c-KIT* mutations have been reported in approximately 20% of patients with CBF AML.<sup>32,71</sup> Studies have shown that *c-KIT* mutations are associated with decreased remission duration (eg, EFS and relapse-free survival) and decreased OS in both groups of patients with t(8;21) or inv(16).<sup>26,32,34,71</sup> In a recent analysis from the German-Austrian AML Study Group, the frequency and prognostic impact of secondary genetic lesions were evaluated in patients with CBF AML who were treated on prospective trials (N=176).<sup>72</sup> Secondary chromosomal abnormalities were found in 39% of patients, with the most common abnormalities being trisomy 22 (18%), trisomy 8 (16%) and 7q deletion (5%). Secondary genetic lesions were found in 84% of patients, including mutations in *RAS* (53%; *NRAS* in 45%; *KRAS* in 13%), *KIT* (37%), and *FLT3* (17%; *FLT3*-TKD in 14%; *FLT3*-ITD in 5%; both mutations present in 2%). In addition, 25% of patients had more than one of these mutations. Mutations in *KIT* and *RAS* were less likely to occur concurrently whereas mutations in *KIT* and *FLT3* occurred concurrently in 6% of patients.<sup>72</sup> Of these secondary genetic lesions, *KIT* mutation and trisomy 22 were significant independent factors

predictive of relapse-free survival in multivariable analysis; *FLT3* mutations, trisomy 22 and trisomy 8 were significant independent predictors for OS.<sup>72</sup> These studies demonstrate the importance of secondary genetic mutations in the prognostic classification of patients with otherwise favorable-risk CBF AML. Patients with t(8;21) or inv(16)/t(16;16) with *c-KIT* mutation are categorized as having intermediate risk AML (see “Risk Status Based on Validated Cytogenetics and Molecular Abnormalities” on page AML-A).

Although none of the genetic abnormalities discussed earlier affect the initial course of AML treatment, they provide prognostic information that 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 incorporating molecular data along with cytogenetics is summarized in the guidelines (see “Risk Status Based on Validated Cytogenetics and Molecular Abnormalities” on page AML-A). The NCCN AML Panel recognizes that molecular genetics is a rapidly evolving field in AML; therefore, risk stratification should be modified based on continuous evaluation of evolving research data. Again, it is important that sufficient bone marrow samples are submitted at the time of diagnosis to allow aliquots of cryopreserved marrow to be reserved for future molecular diagnostics for patients who have NK-AML or in other situations where molecular analysis may refine the prognostic category.

### Principles of AML Treatment

Treatment of acute leukemia has been divided into induction chemotherapy and postremission (or consolidation) therapy. Although obtaining a remission is the first step in controlling the disease, it is also important for patients to emerge from the induction phase in a condition



to tolerate subsequent, more intensive treatments during consolidation to achieve durable disease control. Patients who do not receive postremission therapy will experience 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 preexisting myelodysplasia. This is particularly true of elderly patients with AML. Patients whose performance status would make them poor candidates for the standard antineoplastic 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 younger patients, strategies for consolidation are based on the potential risk of relapse, with higher-risk patients receiving more aggressive therapy. Cytogenetic and molecular lesions are the most significant prognostic indicators, with failure to achieve remission after 1 cycle of induction therapy and tumor burden (WBC  $\geq$  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 and cytogenetic and molecular responses (see “Monitoring During Therapy” and “Response Criteria for Acute Myeloid Leukemia” on pages AML-D and AML-E for definitions of complete and partial response and disease relapse).

Finally, all patients require attentive supportive care related both to the underlying leukemia (ie, tumor lysis syndrome) and the adverse effects of chemotherapy (see “Supportive Care” on page AML-C).

### **Management of Acute Promyelocytic Leukemia (APL)**

Acute promyelocytic leukemia (APL) is a particularly aggressive subtype of AML, with a distinct morphology and clinical presentation

that may be associated with potentially fatal coagulopathy. The incorporation of all-trans retinoic acid (ATRA) and the use of risk-stratification (based on WBC counts) in the management of APL has largely improved outcomes for patients with this aggressive subtype. The translocation of the promyelocytic leukemia (PML) gene on chromosome 15 adjacent to the retinoic acid receptor alpha (RAR $\alpha$ ) gene on chromosome 17 [ie, t;(15;17)(q22;q12)] produces a *PML-RAR $\alpha$*  fusion gene, which can be quantitatively monitored using polymerase chain reaction (PCR) to document disease burden and to ultimately confirm “molecular remission”. The unique ability of 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 represents 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.<sup>73</sup> 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 and daunorubicin.<sup>74,75</sup>

The French APL 93 trial compared ATRA followed by chemotherapy (cytarabine 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.<sup>76,77</sup>

Induction regimens were pared down to ATRA and idarubicin (the AIDA schedule) in both the Italian GIMEMA 93 trial and the Spanish PETHEMA LPA 94 trial, which produced CR rates of 89-95% and thereby raised the question of whether there was a need for cytarabine in APL induction.<sup>78,79</sup> In these trials, 51% to 61% of evaluable patients achieved PCR-negative status for *PML-RARA* following induction therapy; 93% to 98% were PCR-negative after consolidation. The estimated 2-year EFS rate was 79% in both trials.<sup>78,79</sup> In the PETHEMA trial, the 2-year OS rate was 82%.<sup>79</sup> It had been commonly observed that patients with elevated WBC have high-risk disease based on both higher number of 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 study based solely on WBC and platelet count at presentation. In this study, the induction regimen remained the same (ATRA and idarubicin) but ATRA was added to consolidation cycles 1-3 for all but low risk patients (ie, those with WBC ( $\leq 10,000/\text{mCL}$ ) and platelets  $>40,000/\text{mCL}$ ). The CR rate in this trial was 90% with almost all the failure attributed to hemorrhage, infection, or differentiation syndrome. Factors predictive of death during induction were WBC count greater than  $10,000/\text{mCL}$ , age older than 60 years, creatinine 1.4 or greater, and male sex.<sup>80,81</sup> In 2006, ADES et al reported the outcome of the French APL 2000 trial (N = 340) in which patients under age 60 years with WBC counts less than  $10,000/\text{mCL}$  were randomized to receive ATRA ( $45 \text{ mg}/\text{m}^2$ ) and daunorubicin ( $60 \text{ mg}/\text{m}^2$  per day for 3 days) as induction therapy with or without cytarabine ( $200 \text{ mg}/\text{m}^2$  per day for 7 days). Those randomized to cytarabine in induction also received cytarabine during consolidation.<sup>82</sup> Patients with WBC

greater than  $10,000/\text{mCL}$  or over age 60 years all received cytarabine. While the CR rates were similar between the randomized groups (99% with and 94% without cytarabine), those receiving cytarabine had a lower 2-year cumulative incidence of relapse (5% with cytarabine and 16% without cytarabine) that translated into an improved EFS rate (93% with cytarabine and 77% with no cytarabine, at 2 years). The 2-year OS rate was 98% with cytarabine and 90% without cytarabine. Among patients with WBC count greater than  $10,000/\text{mCL}$ , the CR rate was 97% and the 2-year EFS rate was 89% for those under 60 years and 79% for those over 60 years of age.<sup>82</sup> A report of a joint analysis of the outcomes in the PETHEMA 99 and the French APL 2000 trial in patients less than 65 years of age showed that in patients with WBC count less than  $10,000/\text{mCL}$ , CR rates were similar but the relapse rates at 3 years were lower in the PETHEMA trial, which used ATRA plus idarubicin and no cytarabine during induction (with ATRA during consolidation), than in the APL 2000 cytarabine containing regimen (4% vs. 14%;  $P = .03$ ).<sup>83</sup> However, for patients with WBC count greater than  $10,000/\text{mCL}$ , the cytarabine containing protocol resulted in higher CR rate (95% vs. 84%;  $P = .018$ ) and improved 3-year OS rate (91.5% vs. 81%;  $P = .026$ ).<sup>83</sup> The second North American Intergroup trial also used ATRA ( $45 \text{ mg}/\text{m}^2$ ), daunorubicin ( $50 \text{ mg}/\text{m}^2$  per day for 4 days) and cytarabine ( $200 \text{ mg}/\text{m}^2$  per day for 7 days) with similar initial CR rates (90%).<sup>84</sup> Consolidation in this trial differed in that 2 cycles of a novel agent, arsenic trioxide (ATO) were given following induction and prior to the final 2 cycles of anthracycline.

Arsenic trioxide (ATO) has also been found to be a potent promoter of apoptosis in APL cells.<sup>85,86</sup> In 2004, Shen et al first published outcomes using single-agent ATRA; single-agent ATO; or the combination of both drugs.<sup>87</sup> While CR rates exceeded 90% in all three treatment arms, the decline in quantity of *PML/RARA* fusion transcripts (as measured by

quantitative PCR) was significantly higher with the combination. Time to hematologic response was more rapid and relapse-free survival (after a median follow up of 18 months) was improved with the combination regimen compared with the monotherapy regimens.<sup>87</sup> Subsequently, Estey et al used a similar combination of ATRA and ATO to treat patients with low-/intermediate-risk APL.<sup>88</sup> High-risk patients in the same study were treated using the ATRA and ATO combined with gemtuzumab ozogamicin 9 mg/m<sup>2</sup> on day 1 of induction therapy. In the final report from this study (N = 82), the CR rate in all patients was 92% (95% for low-risk and 81% for high-risk patients) and the estimated 3-year OS rate was 85%.<sup>89</sup> The authors suggested that ATRA combined with ATO, with or without gemtuzumab ozogamicin may be an alternative to conventional chemotherapy in patients with untreated APL. 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 AML.

A phase II study (APML4) from Australia/New Zealand evaluated an induction regimen with ATO added to a backbone of ATRA and idarubicin in patients with previously untreated APL (N = 124; median age 44 years).<sup>90</sup> Patients received 1 cycle of induction therapy with ATRA (45 mg/m<sup>2</sup> days 1–36 in divided doses), age-adjusted idarubicin (6–12 mg/m<sup>2</sup> days 2, 4, 6, 8) and ATO (0.15 mg/kg days 9–36 as a 2-hour IV infusion). Patients with a CR to induction received consolidation with 2 cycles of ATRA and ATO. Maintenance therapy was administered for 2 years and consisted of eight 3-month cycles of treatment with ATRA, oral methotrexate and 6-mercaptopurine. The hematologic CR rate after induction was 95%. The 2-year OS rate was 93%.<sup>90</sup>

In a recent phase III randomized trial of the Italian-German Cooperative Group, induction with ATRA combined with ATO was compared with

the AIDA regimen in patients with newly diagnosed, low- or intermediate-risk APL (N = 162; APL0406 study).<sup>91</sup> Patients in Arm A received ATRA (45 mg/m<sup>2</sup>) plus ATO (0.15 mg/kg) daily until CR, then ATO 5 days per week for 4 weeks every 8 weeks for a total of 4 courses, and ATRA daily for 2 weeks every 4 weeks for a total of 7 courses. Patients in Arm B received the standard AIDA induction followed by consolidation with 3 cycles of anthracycline-based consolidation combined with ATRA and then maintenance comprising low-dose chemotherapy and ATRA.<sup>92</sup> The primary endpoint of this study was the 2-year EFS rate. Among evaluable patients (n = 154), CR rates were not different between Arm A and Arm B (100% vs. 95%). After a median follow-up period of 31 months, the 2-year EFS rate was significantly longer in Arm A compared with Arm B (97% vs. 87%; *P*=0.03).<sup>91</sup> This randomized study showed non-inferiority of an ATRA / ATO regimen compared with AIDA, which may allow for elimination of chemotherapy agents in the initial treatment of patients with non-high-risk APL.

All 4 induction regimens discussed above offer excellent outcomes. These regimens are ATRA + ATO; ATRA + daunorubicin [50 mg/m<sup>2</sup> × 4 days] + cytarabine; or ATRA + daunorubicin [60 mg/m<sup>2</sup> × 3 days] + cytarabine; or ATRA + idarubicin (AIDA). Choices of regimen will be influenced by risk group, age and cardiovascular risks. The NCCN AML Panel recommends that patients with APL be treated according to one of the regimens established from the clinical trials; importantly, one should use a regimen consistently through all components of the protocol and not mix induction regimens from one trial with consolidation regimens from another trial. The recommendations within the Guidelines are broken down by: 1) risk classification using WBC count (cut off of 10,000/mcL) at diagnosis; and 2) patient's ability to tolerate anthracyclines. For low- or intermediate-risk patients (WBC



counts  $\leq 10,000/\text{mcL}$ ), the panel recommends initial induction with ATRA plus ATO<sup>91</sup>; ATRA plus idarubicin alone<sup>93</sup> (category 1); or ATRA plus daunorubicin and cytarabine<sup>75,83,84</sup> (category 1 for those on French APL 2000 protocol<sup>83</sup>); or enrollment in a clinical trial. For high-risk patients (WBC counts  $>10,000/\text{mcL}$ ), the AML panel had a preference for regimens that include cytarabine along with ATRA plus daunorubicin over ATRA plus idarubicin because of a higher CR and 3-year OS rates.<sup>83,93</sup> In addition, the panel recommends the administration of prophylactic corticosteroids (eg, dexamethasone) in patients with WBC count greater than 10,000/mcL to prevent differentiation syndrome (also see Guidelines section on “Supportive Care” on page AML-C 2 of 2). For patients with high-risk APL who cannot tolerate anthracyclines, the Guidelines list induction and consolidation regimen using ATRA plus ATO as an alternative (see Guidelines section on “Treatment Induction and Consolidation Therapy on page AML-2).

### 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 to 6 weeks after induction. Cytogenetic analysis is usually normal by this point, but molecular remission often requires at least 2 cycles of consolidation. Thus, the first assessment of molecular remission should only be made after completion of consolidation therapy. At count recovery following induction therapy, patients should proceed with consolidation; for patients with high-risk disease, lumbar puncture should be considered at count recovery following induction therapy, before proceeding with consolidation.<sup>94</sup> All consolidation regimens involve high cumulative doses of cardiotoxic agents. It is therefore

important to assess the cardiac function of patients prior to initiating each anthracycline- or mitoxantrone-containing consolidation cycle.

The goal of consolidation therapy for APL is a durable molecular remission. Data from the two sequential PETHEMA trials,<sup>79-81</sup> which produced the current risk model, were used to construct subsequent trials that intensify therapy for the high-risk groups. In the second PETHEMA trial (LPA 99), 15 days of ATRA (45 mg/m<sup>2</sup>) were added to each of three cycles of anthracycline-based consolidation therapy. Overall, relapse rates were reduced from 20% to 9% with the incorporation of ATRA in the consolidation phase.<sup>81</sup> For the low-risk group, there was no difference in relapse rate (3–6%) or in 3-year DFS rate (93–97%) with the ATRA group compared with a similar consolidation without ATRA in trial LPA 94.<sup>81</sup> Among patients with intermediate risk, the relapse rate was reduced from 14% to 2.5% with the incorporation of ATRA; the 3-year DFS rate was 97% with ATRA consolidation versus 82% in historical controls.<sup>81</sup> Although the addition of ATRA to the high-risk group did improve relapse and DFS rates, there was room for improvement given a relapse rate of 21% and a 3-year DFS rate of 77%. In the more recent PETHEMA LPA 2005 study, both ATRA and cytarabine were included in the anthracycline-containing consolidation regimen for the high-risk patients.<sup>93</sup> In this high-risk group, the 3-year relapse rate was reduced to 11% (compared with 26% from the LPA 99 study; data updated from original publication above) and the 3-year DFS and OS rates were 82% and 79%, respectively. 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 dose reduction of mitoxantrone (from 10 mg/m<sup>2</sup>/day for 5 days to 10 mg/m<sup>2</sup>/day for 3 days in cycle 2) and a small reduction of idarubicin dose between low- and intermediate-risk groups (from 7 mg/m<sup>2</sup>/day for 4 days to 5 mg/m<sup>2</sup>/day for 4 days in cycle



1; from 2 doses of 12 mg/m<sup>2</sup>/day to 1 dose of 12 mg/m<sup>2</sup>/day in cycle 3). Based on 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 (compared with results in low- and intermediate-risk groups from LPA 99 study). With the consolidation regimens evaluated in the LPA 2005 study, outcomes were similar between low-risk and intermediate-risk groups with regards to 3-year cumulative incidence of relapse (6% vs. 6%), 3-year DFS (93% vs. 94%) and 3-year OS rate (96% vs. 93%).<sup>93</sup> The recent AIDA-2000 trial of the Italian GIMEMA group has confirmed that inclusion of ATRA in consolidation significantly improved outcome, most notably for high-risk patients; the high-risk group received a consolidation regimen containing ATRA and cytarabine along with anthracyclines.<sup>92</sup> In this study, the 6-year cumulative incidence of relapse was 9% for patients in the high-risk group; the 6-year DFS and OS rates in this group were 84.5% and 83%, respectively. In the AIDA-2000 study, the low- and intermediate-risk groups were collapsed into a single category, and received the same consolidation regimen with ATRA, mitoxantrone and idarubicin (ATRA 45 mg/m<sup>2</sup> for 15 days + idarubicin 5 mg/m<sup>2</sup> for 4 days in cycle 1; ATRA for 15 days and mitoxantrone 10 mg/m<sup>2</sup>/day for 5 days in cycle 2; and ATRA for 15 days and idarubicin 12 mg/m<sup>2</sup> for 1 dose in cycle 3). For patients in the low- and intermediate-risk group, the 6-year cumulative incidence of relapse was 11%; the 6-year DFS and OS rates in this group were 86% and 89%, respectively.<sup>92</sup>

In the French APL 2000, which randomized daunorubicin with or without cytarabine for the consolidation phase (no ATRA during consolidation) for the low- and intermediate-risk (ie, 'standard risk') groups, the 2-year EFS rate was higher with the addition of cytarabine.<sup>82</sup> Long-term follow up from this study showed that in

patients with standard risk, the addition of cytarabine substantially reduced cumulative relapse rates (5-year relapse rate 13% vs. 29%;  $P = .013$ ) and increased 5-year EFS rates (82% vs. 65%;  $P = .01$ ) compared with the regimen without cytarabine.<sup>95</sup> Thus, the outcomes using consolidation regimens with anthracycline plus ATRA or with anthracycline plus cytarabine appeared to be similar for patients with non-high-risk APL. In the French APL 2000 study where all high-risk patients received cytarabine during induction and consolidation, the 5-year relapse rate, EFS rate, and OS rate was 7.5%, 82.5%, and 90%, respectively.<sup>95</sup>

The North American Intergroup trial also approached the topic of decreasing toxicity during consolidation by incorporating ATO into the consolidation schema directly after achieving remission.<sup>84,96</sup> In this trial, patients who were randomized to receive 2 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 2 more courses of ATRA plus daunorubicin had significantly higher 3-year EFS rate (80% vs. 63%;  $P < .0001$ ) and improved OS outcomes (3-year OS rate 86% vs. 81%;  $P = .06$ ) compared with those who received only the 2 courses of ATRA plus chemotherapy. The 3-year DFS rate was also significantly improved with the addition of ATO (90% vs. 70%;  $P < .0001$ ). The favorable outcomes with the incorporation of ATO were observed in both the subgroups of patients with low-/intermediate-risk and high-risk disease.<sup>84,96</sup> Notably, in the high-risk group, DFS outcomes with the addition of ATO were similar to the DFS rate observed for the low-/intermediate-risk group, suggesting that ATO may help to overcome the negative prognostic influence of high-risk disease. The overall outcomes do not appear to be superior to the less complex consolidation schedules used in either of the two most recent European trials for patients in the low- and intermediate-risk groups, but did



# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

appear to offer improved survival for patients with high-risk disease. However, the consolidation phase in the North American Intergroup protocol is longer and may be difficult for some patients to complete. The ongoing French APL 2006 randomized trial is evaluating the role of ATO in consolidation therapy for previously untreated APL, both for standard-risk patients (WBC count <10,000/mcL; ATO vs. cytarabine vs. ATRA, all in combination with idarubicin during consolidation) and high-risk patients (WBC>10,000/mcL; cytarabine vs. ATO + cytarabine, both in combination with idarubicin during consolidation).<sup>97</sup> Based on results from the interim analysis (median follow-up period 22–24 months), all regimens resulted in CR rates exceeding 95% with low rates of relapse. However, the use of ATO in the consolidation phase was associated with longer durations of myelosuppression, which necessitated a protocol amendment to further reduce the chemotherapy dose in patients receiving ATO.<sup>97</sup> 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. In the recent phase II APML4 study from Australia/New Zealand, 2 cycles of ATO and ATRA were used as consolidation in patients who achieved a CR after a 3-drug induction with ATRA, idarubicin and ATO.<sup>90</sup> Among the patients who proceeded to consolidation (n = 112), all achieved molecular remission, and the 2-year DFS rate was 97.5%. The 2-year OS rate in all evaluable patients in this study (N = 124) was 93%.<sup>90</sup> As discussed earlier, in the phase III randomized trial of ATRA combined with ATO versus AIDA regimen (APL0406 study) in patients with newly diagnosed, low- or intermediate-risk APL (N = 162), patients in the ATRA plus ATO arm received consolidation with ATO 5 days per week for 4 weeks every 8 weeks for a total of 4 courses, and ATRA daily for 2 weeks every 4 weeks for a total of 7 courses (Arm A).<sup>91</sup> Patients in the AIDA arm received 3 cycles of anthracycline-based consolidation combined with ATRA and then

maintenance with low-dose chemotherapy and ATRA.<sup>92</sup> After a median follow-up period of 31 months, the 2-year EFS rate was significantly longer in Arm A compared with Arm B (97% vs. 87%;  $P=0.03$ ). In addition, the 2-year OS was also longer in Arm A (99% vs. 91%;  $P=0.03$ ), with no differences in 2-year DFS (97% vs. 92%) or cumulative incidence of relapse (2% vs.4%) between treatment arms.<sup>91</sup>

For patients with high-risk disease, the NCCN AML Panel suggests the inclusion of cytarabine with daunorubicin as used in the French APL 2000 trial<sup>82</sup> or cytarabine with ATRA and idarubicin as used in the PETHEMA LPA 2005 trial<sup>93</sup> and GIMEMA AIDA-2000 trial<sup>92</sup> or 2 cycles of ATO followed by 2 additional cycles of standard chemotherapy as used in the US Intergroup trial for consolidation.<sup>84,96</sup> When using a cytarabine containing regimen, dose adjustments of cytarabine may be needed for older patients or for patients with renal dysfunction.<sup>83,84</sup> In patients who could not tolerate anthracyclines and who received ATRA and ATO for induction therapy, the reported trials continued with repeated cycles of these two agents following induction.<sup>88,89</sup> For patients with high-risk disease who cannot receive anthracycline-containing therapy, the NCCN Guidelines panel recommends ATO (0.15 mg/kg IV daily for 5 days/week for 2 weeks every 8 weeks for 4 cycles) with ATRA (45 mg/m<sup>2</sup> daily PO for 2 weeks every 4 weeks for a total of 7 cycles) for consolidation.

For low- and intermediate-risk patients, the NCCN Guidelines panel has positioned the ATRA plus ATO regimen first, based on results from the APL0406 phase III randomized trial in comparison with the AIDA regimen.<sup>91</sup> The GIMEMA AIDA-2000 regimen may be positioned slightly higher than either the French APL 2000 or the US Intergroup regimens because of the ease of administration and potentially decreased toxicity. However, all four of these regimens will yield excellent results. Again, it is important to note that clinicians should use



a regimen consistently through all components of the treatment protocol and not mix induction regimens from one trial with consolidation regimens from another trial.

### **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 patients who are PCR negative, a 1-2 year course of ATRA maintenance therapy, which may be combined with 6-mercaptopurine and methotrexate, may be a reasonable approach. 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 therapy. The French APL 93 trial randomized eligible patients (n = 289) to four different maintenance regimens: no maintenance, continuous chemotherapy with 6-mercaptopurine and methotrexate, intermittent ATRA, and the combination of ATRA with 6-mercaptopurine and methotrexate.<sup>76</sup> Results showed decreased 2-year relapse rates with continuous chemotherapy (11.5% vs. 27% with no chemotherapy) and with ATRA (13.5% vs. 25% with no ATRA). The estimated 2-year relapse rate for patients who received maintenance with ATRA in combination with chemotherapy was 7.4%, suggesting an additive benefit with the combined use of these regimens. The 2-year EFS rate was also improved with continuous chemotherapy (92% vs. 77% without chemotherapy) and with ATRA (87% vs. 82% without ATRA); the 2-year EFS rate among patients who received ATRA in combination with chemotherapy was 93%.<sup>76</sup> Results from long-term follow-up of the APL 93 study showed a beneficial effect of maintenance treatment with intermittent ATRA and continuous chemotherapy, with an additive effect of the 2 modalities; the 10-year cumulative relapse rate with no

maintenance, ATRA alone, continuous chemotherapy, and ATRA combined with chemotherapy, was 43%, 33%, 23%, and 13%, respectively ( $P < .001$ ).<sup>98</sup> Patients considered to be a high risk (WBC count  $>5000/\text{mcL}$ ) appeared to derive the most benefit from maintenance therapy; the 10-year cumulative relapse rate among high-risk patients with no maintenance, ATRA alone, continuous chemotherapy, and ATRA combined with chemotherapy, was 68%, 53%, 33%, and 21%, respectively ( $P < .001$ ). No statistically significant difference in 10-year relapse rates was observed among patients with lower risk disease, although the relapse rate dropped from 29% without maintenance to 11.5% with ATRA combined with chemotherapy. Overall, the 10-year OS rate with no maintenance, ATRA alone, continuous chemotherapy, and ATRA combined with chemotherapy, was 74%, 88%, 93%, and 94%, respectively ( $P < .001$ ).<sup>98</sup>

The first US Intergroup trial showed superior DFS outcomes for patients receiving maintenance ATRA compared with no maintenance.<sup>75</sup> In this trial, patients were randomized to induction therapy with daunorubicin plus cytarabine or with ATRA, and subsequently underwent a second randomization to maintenance therapy with ATRA or no maintenance (observation only). Consolidation therapy comprised the initial induction therapy regimen for course 1, and then daunorubicin and high-dose cytarabine for course 2. The 5-year DFS rates for the four randomization groups, chemotherapy induction plus observation, chemotherapy induction plus ATRA maintenance, ATRA induction plus observation, and ATRA induction plus ATRA maintenance, were 16%, 47%, 55%, and 74%, respectively.<sup>75</sup> Thus, the incorporation of ATRA during induction and maintenance appeared to improve long-term remission durations. However, as treatment strategies have evolved to incorporate ATRA or ATO into consolidation regimens, the role of maintenance therapy is less clear, particularly for patients with low-risk



disease who achieve a molecular remission at the end of consolidation. It should be noted that in the above US Intergroup trial, molecular remission status was not assessed prior to randomization to maintenance treatment. Data from the AIDA 0493 trial suggested that there was no long-term benefit to maintenance therapy (either with combination chemotherapy with 6-mercaptopurine and methotrexate, ATRA alone, or ATRA in combination with chemotherapy) in patients who were in molecular remission (PCR negative) at the end of consolidation therapy.<sup>99,100</sup> In this trial, ATRA was not given during consolidation. A phase III cooperative group trial (SWOG 0521) is designed to examine the need for maintenance therapy (using the combination of ATRA, 6-mercaptopurine and methotrexate) in patients with low-/intermediate-risk APL. In this trial, patients receive induction therapy with ATRA, daunorubicin, and cytarabine, followed by consolidation therapy with ATO, ATRA and daunorubicin. Patients are then randomized to receive maintenance therapy or no further treatment (observation only). The benefit of maintenance therapy likely depends upon the regimens used during induction and consolidation therapies. Therefore, it is important to use maintenance therapy in conjunction with treatment protocols in which it has been shown to confer benefit.

RT-PCR should be performed on a marrow sample at completion of consolidation to document molecular remission. It is at the discretion of the treating physician to determine the appropriate frequency of monitoring for individual patients. Subsequent monitoring of patients by PCR can be performed on peripheral blood samples, although using marrow samples is a more sensitive monitoring technique and may give earlier signs of relapse. Periodic monitoring is recommended for up to 2 years during maintenance therapy 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 test sensitivity/specificity, a change from PCR negative to positive status should be confirmed by bone marrow samples in a reliable laboratory within 4 weeks. If molecular relapse is confirmed by a second positive test, patients should be treated for relapsed disease (see Guidelines section on “Post-remission Therapy: First Relapse” on page AML-6). If the second test was negative, maintenance therapy and frequent monitoring (eg, every 2–3 months) for up to an additional 2 years may be considered to ensure that the patient remains PCR negative. Testing should be done in the same laboratory to maintain a consistent level of sensitivity. For patients who develop cytopenias and who have a negative RT-PCR, a marrow is recommended to assess for new cytogenetics abnormalities, as secondary MDS and AML can occur following APL therapy.

### **Management of Relapsed APL**

Arsenic trioxide (ATO) is the recommended therapy for patients who do not achieve molecular remission at completion of consolidation or who subsequently demonstrate molecular relapse. As a single agent, ATO produced CR rates of 80% to 90% in patients with hematologic relapse and achieved molecular remissions in 70% to 80% of those patients.<sup>86,101,102</sup> ATRA and ATO appear to be synergistic and one could consider using the combination in patients who had not received ATRA during consolidation.<sup>85-87</sup> However, a small randomized study of patients with relapsed APL (N = 20), all previously treated with ATRA-containing chemotherapy, showed no improvement in response by adding ATRA to ATO compared with ATO alone.<sup>103</sup> The role of retreatment with ATO for patients who relapse following therapy with ATO-containing regimens during initial induction and/or consolidation therapy remains



unknown. A retrospective analysis in a small number of patients reported a second CR rate of 93% among patients who were retreated with ATO combined with ATRA (with or without anthracyclines) after a relapse following first-line therapy with ATO-containing regimens (n = 14).<sup>104</sup>

A small percentage of relapsed APL has a CNS component.<sup>105,106</sup> Therefore, for patients who are in second morphologic remission, the NCCN Guidelines panel strongly recommends the use of intrathecal therapy for 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. A retrospective analysis conducted by the European APL Group showed that in patients who received HSCT following a second hematologic remission (primarily with ATRA-containing regimens), outcomes were more favorable with autologous HSCT (n = 50) compared with allogeneic HSCT (n = 23); the 7-year relapse-free survival (79% vs. 92%) and EFS (61% vs. 52%) rates were not statistically significantly different between patients who received autologous HSCT versus allogeneic HSCT, however, 7-year OS rates were significantly improved with autologous compared with allogeneic HSCT (60% vs. 52%;  $P = .04$ ).<sup>107</sup> Among patients who received a PCR-negative autograft, the 7-year relapse-free survival and OS rates were 87% and 75%, respectively. Although the relapse rates were low with allogeneic HSCT, the reduced OS with this procedure was accounted for by the higher treatment-related mortality observed in the allogeneic HSCT group compared with the autologous HSCT group (39% vs. 6%).<sup>107</sup> Given the data from this study, the NCCN Guidelines include recommendations for autologous HSCT in patients who achieve second molecular remission, and to reserve allogeneic transplant for those patients who have persistent disease despite salvage therapy.

It should be noted that only limited evidence from retrospective studies exist with regards to the role of autologous and allogeneic HSCT following relapse of APL in the era of ATO therapy. The optimal consolidation strategy following salvage therapy with ATO-containing regimens remains to be defined.<sup>108</sup> In a small retrospective study in patients with relapsed APL treated with ATO-containing induction and consolidation therapy, outcome of further consolidation with autologous HSCT was compared with maintenance (without autologous HSCT) with ATO with or without ATRA.<sup>104</sup> In this analysis, all patients had achieved second molecular remission following induction and consolidation therapy with ATO-containing regimens; subsequently, 14 patients underwent autologous HSCT and 19 patients opted for ATO-containing maintenance regimen. Consolidation with autologous HSCT was associated with significantly higher 5-year EFS rate (83% vs. 34.5%;  $P = .001$ ) and OS rate (100% vs. 38.5%;  $P = .001$ ) compared with ATO-containing maintenance therapy.<sup>104</sup> The authors concluded that consolidation with autologous HSCT was superior to ATO-containing maintenance alone in patients who achieved molecular remission after relapse.

For patients in second CR who have contraindications to HSCT, continued therapy with ATO for six cycles is recommended in the absence of a suitable 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”. Approximately 15% to 25% of previously untreated patients



# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

receiving ATRA-containing therapy develop this syndrome.<sup>109,110</sup> Early in the treatment with either ATRA or ATO as single agents or in combination, patients may begin to develop evidence of “differentiation syndrome”. These patients develop fever, often accompanied by rapidly rising WBC counts (>10,000/mcL). Patients should be closely monitored for hypoxia and the development of pulmonary infiltrates or pleural effusion. Differentiation syndrome, along with hemorrhage, is the leading causes of death during induction therapy. Early recognition and prompt initiation of corticosteroids are key to managing this complication. In some studies, low mortality and morbidity rates were reported when corticosteroids were administered prophylactically in patients presenting with high WBC counts.<sup>81,111</sup> Kelaidi et al assessed the outcomes of patients with high WBC (>10,000/mcL) enrolled in APL 93 and APL 2000.<sup>112</sup> The supportive care factor that had an effect on the rate of early induction deaths was the use of dexamethasone (10 mg every 12 hours beginning on day 1) for patients on APL 2000. The early death rate from differentiation syndrome dropped from 8 in 139 patients (6%) in the APL 93 trial to 2 in 133 patients (1.5%) in the APL 2000 trial. For patient with WBC count greater than 10,000/mcL or first signs or symptoms of differentiation syndrome, the AML Panel recommends treating with dexamethasone 10 mg twice a day for 3 to 5 days, then tapering the dose over 2 weeks (see Guidelines section for “Supportive Care” on page AML-C 2 of 2). ATRA may need to be held during the initial acute symptomatic period, but may be resumed when symptoms resolve. Other factors that have been reported to increase the risk of differentiation syndrome include a high body mass index and age over 40 years.

Leukapheresis is not routinely recommended in the management of patients with high WBC counts in APL because of the difference in leukemia biology. However, in cases of potentially life-threatening

leukostasis not responsive to other modalities, leukapheresis can be considered with caution.

Because coagulopathy is common in patients with APL, it is important to screen for this problem with evaluation of prothrombin time, partial thromboplastin time and fibrinogen as part of the initial work-up and before any invasive procedure. Clinical coagulopathy is managed by aggressive transfusion support to maintain platelet counts 50,000/mcL or greater, by fibrinogen replacement with cryoprecipitate and frozen plasma to maintain a level of 150 mg/dL, and maintaining levels of prothrombin time and partial thromboplastin time close to normal. Patients with clinical coagulopathy need to be monitored daily until resolution.

ATO therapy may prolong the QT interval, making patients susceptible to ventricular arrhythmias. Therefore, prior to initiation of therapy, an electrocardiogram (ECG or EKG) is recommended to assess the QT interval. Routine monitoring (eg, weekly) during therapy is also suggested for older patients. Serum electrolytes should also be monitored prior to and during therapy to maintain electrolytes (Ca  $\geq$ 9.0, K  $\geq$ 4.0, Mg  $\geq$ 1.8) in the upper normal range. Other drugs that prolong the QT interval should be avoided during ATO therapy to minimize the risk of cardiac arrhythmias. Patients with an absolute QT interval greater than 500 milliseconds should be reassessed on a weekly basis during induction therapy, and prior to each course of post-remission therapy.

In the French APL 93 trial, a 4% incidence of CNS relapse was reported in patients with WBC count greater than 10,000/mcL. In the APL 2000 trial, that high-risk population received five doses of intrathecal chemotherapy using a combination of methotrexate, cytarabine, and steroids, upon count recovery following induction

therapy. The patients also received a higher dose of cytarabine ( $2 \text{ g/m}^2$ ) during consolidation (in cycle 2) as compared with  $1 \text{ g/m}^2$  in the APL 93 trial. There were no cases of CNS relapses in APL 2000, compared with 5 cases in APL 93. While the original treatment protocol on APL 2000 used high-dose cytarabine in the second cycle of consolidation, some investigators suggest the use of high-dose cytarabine earlier, particularly in those patients who are not receiving intrathecal therapy for CNS prophylaxis.

### Management of AML

Most initial treatment decisions for AML are based on age, history of prior myelodysplasia or cytotoxic therapy, and performance status. Although karyotype and molecular markers are powerful predictors of DFS outcomes, induction chemotherapy will be initiated before this information is available in most instances. 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 in patients with AML consider age 60 years 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 older than 60 years, and an increased frequency of comorbid medical conditions that affect the patient's ability to tolerate intensive treatment.<sup>113</sup> Because complete remission rates rarely exceed 70% in younger patients and 50% in older patients, substantial opportunity exists for innovative clinical trials involving both patient populations. The guidelines consider recommendations for patients older or younger than 60 years of age separately.

### Management of AML in Patients Younger Than 60 Years

#### Induction Therapy

Standard induction regimens are appropriate for patients younger than age 60 years. These regimens are based on a backbone of cytarabine and an anthracycline, and have changed little in the past 25 years. Historically, in most large cooperative group trials, daunorubicin has been the most commonly used anthracycline at doses of 45 to 60  $\text{mg/m}^2 \times 3$  days. Idarubicin, which has a longer intracellular retention time, used at doses of  $12 \text{ mg/m}^2 \times 3$  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 range of 60% to 70% in most large cooperative group trials of infusional cytarabine and anthracycline. A large randomized phase III ECOG study reported a significant increase in CR rate (71% vs. 57%;  $P < .001$ ) and median OS (24 vs. 16 months;  $P = .003$ ) using daunorubicin  $90 \text{ mg/m}^2 \times 3$  days ( $n=327$ ) versus  $45 \text{ mg/m}^2 \times 3$  days ( $n = 330$ ) in patients with previously untreated AML younger than 60 years.<sup>114</sup> Based on subgroup analyses, however, the survival benefit with high-dose daunorubicin was shown to be restricted to patients with favorable- and intermediate-risk cytogenetic profiles (median OS, 34 vs. 21 months;  $P = .004$ ) and those younger than 50 years (median OS, 34 vs. 19 months;  $P = .004$ ). The survival outcome for patients with unfavorable cytogenetics was poor, with a median OS of only 10 months in both treatment arms.<sup>114</sup> In a European trial that compared idarubicin  $12 \text{ mg/m}^2 \times 3$  or 4 days versus daunorubicin  $80 \text{ mg/m}^2 \times 3$  days in patients between ages 50 and 70 years, CR rates were 83% and 70%, respectively ( $P = .024$ ).<sup>115</sup> No difference was seen in relapse rate, EFS, or OS outcomes between the treatment arms. According to the NCCN AML Panel, infusional cytarabine at the standard doses ( $100\text{-}200 \text{ mg/m}^2$  continuous infusion)  $\times 7$  days combined with either idarubicin ( $12 \text{ mg/m}^2$  for 3 days) or



# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

escalated daunorubicin (90 mg/m<sup>2</sup> for 3 days) is a category 1 recommendation.

Recently, a phase III randomized trial from the Polish Adult Leukemia Group evaluated the efficacy and safety of adding a purine analog to an induction regimen comprising daunorubicin and cytarabine in patients 60 years or younger with previously untreated AML (N=652).<sup>116</sup> In this study, patients were randomized to the following treatment arms: daunorubicin and cytarabine (daunorubicin 60 mg/m<sup>2</sup> × 3 days and cytarabine 200 mg/m<sup>2</sup> continuous infusion × 7 days; DA arm); DA with addition of cladribine (5 mg/m<sup>2</sup> × 5 days; DAC arm); and DA with addition of fludarabine (25 mg/m<sup>2</sup> × 5 days; DAF arm). Patients with a PR after induction could receive a second cycle of the assigned induction regimen. Post-remission treatment was the same in the 3 arms. Patients with a CR after induction received consolidation with a course of intermediate-dose cytarabine (1.5 g/m<sup>2</sup> days 1–3) and mitoxantrone (10 mg/m<sup>2</sup> days 3–5), followed by a course of high-dose cytarabine (2 g/m<sup>2</sup> every 12 hours on days 1, 3, 5).<sup>116</sup> A similar proportion of patients in the 3 arms proceeded with allogeneic HSCT. The DAC regimen resulted in significantly higher CR rate after induction (67.5% vs. 56%; *P* = .01) and improved OS outcomes (median 24 vs. 14 months; 3-year OS 45% vs. 33%; *P* = .02) compared with the DA arm. Based on subgroup analysis, significant improvements in OS rate with DAC compared with DA were observed for patients 50 years and older, those with initial WBC count 50 × 10<sup>9</sup>/L or greater, and patients with high-risk karyotype.<sup>116</sup> No significant improvements in efficacy were observed in the overall DAF arm with regards to CR rate (59%) or OS (median 16 months; 3-year OS rate 35%); however, in subgroup analysis, significant improvements with DAF compared with DA was observed among patients with high-risk karyotype. The incidence of hematologic toxicities and other adverse events were similar between

treatment arms.<sup>116</sup> This randomized trial showed that the addition of cladribine to a standard induction regimen improved CR rate and OS for patients 60 years or younger with AML. The NCCN AML panel has included this regimen as another category 1 treatment option.

For patients with impaired cardiac function, other regimens that combine nonanthracycline agents (such as fludarabine<sup>117</sup> or topotecan<sup>118</sup>) with cytarabine have been published.

High-dose cytarabine therapy during induction was explored previously in 2 large cooperative group trials. In an Australian Leukemia Study Group trial,<sup>119,120</sup> patients younger than 60 years were randomized (N = 301) to receive either high-dose cytarabine (3 g/m<sup>2</sup> every 12 hours on days 1, 3, 5, and 7 for a total of 24 g/m<sup>2</sup>) or standard cytarabine therapy (100 mg/m<sup>2</sup>/d × 7 days via continuous infusion); patients in both arms received daunorubicin (50 mg/m<sup>2</sup> on days 1–3) and etoposide (75 mg/m<sup>2</sup>/day × 7 days). The CR rates were equivalent in both arms (71% and 74%, respectively), with significantly higher 5-year relapse-free survival rates with high-dose cytarabine (48% vs. 25%; *P* = .007).<sup>120</sup> Patients in both treatment arms received only 2 cycles of standard-dose cytarabine, daunorubicin, and etoposide for consolidation therapy. Median remission duration was 45 months for the high-dose arm, compared with 12 months for the standard treatment arm.<sup>119</sup> However, treatment-related morbidity and mortality were higher in the high-dose cytarabine arm; the 5-year OS rates were 33% in the high-dose arm compared with 25% with the standard dose.<sup>120</sup>

In a large SWOG study,<sup>121</sup> patients younger than 65 years (N = 665) were randomized to receive high-dose cytarabine (2 g/m<sup>2</sup> every 12 hours × 6 days for a total of 24 g/m<sup>2</sup>; patients aged < 50 years were initially randomized to receive 3 g/m<sup>2</sup> at the above schedule before the high-dose arm was redefined to 2 g/m<sup>2</sup> because of toxicity concerns) or



# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

standard-dose cytarabine (200 mg/m<sup>2</sup>/d × 7 days); patients in both treatment arms also received daunorubicin (45 mg/m<sup>2</sup>/d × 3 days). Patients treated in the high-dose cytarabine arm received a second high-dose cycle for consolidation, whereas patients in the standard-dose arm were randomized to receive consolidation therapy with either 2 cycles of standard-dose cytarabine or 1 cycle of high-dose cytarabine plus daunorubicin. The CR rates were similar, with 55% for the high-dose 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. DFS rate (for patients with a CR) and OS rate (for all patients) at 4 years was not significantly different between treatment arms. Induction therapy with high-dose cytarabine was associated with significantly higher rates of treatment-related mortality (14% vs. 5% for patients age < 50 years; 20% vs. 12% for patients age 50–64 years; *P* = .003) and grade 3 or higher neurologic toxicity (8% vs. 2% for patients < 50 years; 5% vs. 0.5% for patients age 50–64 years; *P* < .0001).<sup>121</sup> For patients younger than 50 years, consolidation with high-dose cytarabine was associated with similar rates of treatment-related mortality (2% vs. 0%) and grade 3 or higher neurologic toxicity (2% vs. 0%) compared with standard dose. For patients younger than 50 years who received high-dose cytarabine at the 3-g/m<sup>2</sup> dose schedule for induction, the rates of treatment-related deaths (10% vs. 5%) and grade 3 or greater neurologic toxicity (16% vs. 2%) were higher than for those who received the standard dose. Similarly, for patients younger than 50 years who received high-dose cytarabine at the 3-g/m<sup>2</sup> dose schedule for consolidation, the rates of treatment-related deaths (4% vs. 0%) and grade 3 or greater neurologic toxicity (16% vs. 0%) were higher than for those who received the standard dose.<sup>121</sup>

Younger patients (age < 50 years) who received high-dose cytarabine induction and consolidation in the SWOG trial had the best OS and DFS rates at 4 years (52% and 34%, respectively) compared with those who received standard-dose induction and consolidation (34% and 24%, respectively) or standard induction with high-dose consolidation (23% and 14%, respectively).<sup>121</sup> 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.<sup>121</sup> The risks for neurotoxicity and renal insufficiency are increased with high-dose cytarabine; therefore, both renal and neurologic function should be closely monitored in patients receiving this treatment. In a CALGB trial,<sup>122</sup> the subgroup of patients aged 60 years or younger (n = 156) who received standard-dose cytarabine-daunorubicin induction therapy and 4 courses of high-dose cytarabine consolidation (3 g/m<sup>2</sup> every 12 hours on days 1, 3, and 5, per course) experienced a 4-year DFS rate of 44%. Among all patients who received consolidation with high-dose cytarabine, the rates of treatment-related deaths and serious neurotoxicity were 5% and 12%, respectively.<sup>122</sup>

Because the OS outcomes for the high-dose arm in the SWOG trial (high-dose cytarabine induction and 2 cycles of high-dose cytarabine consolidation; 4-year OS rate of 52% for patients age < 50 years) is comparable to those of the CALGB trial with standard-dose infusional cytarabine induction and 4 cycles of high-dose cytarabine consolidation (4-year OS rate of 52% for patients age ≤ 60 years), the use of high-dose cytarabine in the induction phase outside of a clinical trial remains controversial. The decision to use high- 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 those who will undergo early autologous HSCT. Although the remission rates are similar for high-

and standard-dose cytarabine, 2 studies have shown more rapid marrow blast clearance after 1 cycle of high-dose therapy and a DFS advantage for patients aged 50 years or younger who received the high-dose therapy.<sup>123</sup> No data are available using more than 60 mg/m<sup>2</sup> of daunorubicin or 12 mg/m<sup>2</sup> 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 CR rates of 87%, 79%, and 62% for favorable-, intermediate-, and poor-risk groups, respectively.<sup>124</sup>

Patients with antecedent hematologic disease or treatment-related secondary leukemia are considered poor-risk, 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. Although all patients with AML are best managed within the context of an appropriate clinical trial, this poor-risk group of patients, in particular, should be entered into a clinical trial (incorporating either chemotherapy or low-intensity therapy), if available, because only 40% to 50% of these patients experience a CR with standard induction therapy. In addition, HLA testing should be performed promptly in those who may be candidates for either fully ablative or reduced-intensity allogeneic HSCT from a matched sibling or an unrelated donor, which constitutes the best option for long-term disease control.<sup>125</sup>

### ***Postinduction Therapy***

To judge the efficacy of the induction therapy, a bone marrow aspirate and biopsy should be performed 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 patients with residual blasts after induction with standard-dose cytarabine combined with daunorubicin and cytarabine, a second cycle of the same induction regimen may be administered.<sup>116</sup> For those with significant residual blasts, escalation to high-dose cytarabine (2 g/m<sup>2</sup> every 12 hours for 6 days) or standard-dose cytarabine with anthracyclines may be considered; for re-induction, no data are available to determine superiority of intermediate- or high-dose cytarabine. For clear cut induction failure, high-dose cytarabine (if not previously used as treatment for persistent disease at day 15) with or without an anthracycline is a salvage strategy. Other options include an allogeneic HSCT if a matched sibling or alternative donor has been identified, participation in a clinical trial or salvage regimens (see Discussion below for Salvage Therapy for AML). For 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 to 10 days after completion of induction chemotherapy are considered to have experienced induction failure. These patients should be considered for a clinical trial, allogeneic HSCT with matched sibling or matched unrelated donor, salvage regimens (see Discussion below for Salvage Therapy for AML), or best



supportive care. Additional high-dose cytarabine at this time is unlikely to induce remission in these cases. If an HLA-matched sibling or 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. Again, if the patient's clinical condition has deteriorated to a point at which active therapy would be detrimental, best supportive care may be the most appropriate option.

Occasionally, patients with both myeloid and lymphoid markers at diagnosis (biphenotypic leukemia) may experience response to ALL therapy if an AML induction regimen failed.<sup>3</sup> 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.

#### ***Postremission or Consolidation Therapy***

Although successful induction therapy clears the visible signs of leukemia in the marrow and restores normal hematopoiesis in patients with de novo AML, additional postremission therapy (ie, consolidation) is needed to 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 standard consolidation regimen for patients younger than 60 years with either good- or intermediate-risk cytogenetics. This consolidation therapy is based on a CALGB trial comparing 100 mg/m<sup>2</sup>, 400 mg/m<sup>2</sup>, and 3 g/m<sup>2</sup> doses of cytarabine.<sup>122</sup> The 4-year DFS rate for patients receiving consolidation with 3 g/m<sup>2</sup> of high-dose cytarabine 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 remission duration by cytogenetic groups, subsequent analysis showed a 5-year relapse-free survival (continuous CR measured from time of randomization) rate of 50% for CBF AML, 32% for patients with normal karyotype, and 15% for patients in other cytogenetic categories, overall ( $P < .001$ ). Among the patients who received high-dose cytarabine consolidation, the 5-year relapse-free survival rate was 78% for CBF AML, 40% for normal karyotype, and 21% for other cytogenetic categories.<sup>124</sup> Notably, however, in patients with CBF AML who were treated with postremission therapy with high-dose cytarabine, the presence of *c-KIT* mutations resulted in poorer outcomes.<sup>32</sup> In an analysis of patients with CBF AML treated on CALGB trials ( $n = 110$ ), *c-KIT* mutations among patients with *inv(16)* were associated with a higher cumulative incidence of relapse at 5 years (56% vs. 29%;  $P = .05$ ) and decreased 5-year OS rate (48% vs. 68%) compared with wild-type *c-KIT*; in multivariate analysis, the presence of *c-KIT* mutations remained a significant predictor of decreased OS in the subgroup with *inv(16)*. In patients with *t(8;21)*, *c-KIT* mutations were also associated with a higher incidence of relapse at 5 years (70% vs. 36%;  $P = .017$ ), but no differences were observed in 5-year OS (42% vs. 48%).<sup>32</sup> The CALGB trial also included maintenance chemotherapy following the consolidation phase; however, not all patients in remission received maintenance (55% of patients in CR) following high-dose cytarabine consolidation.<sup>122</sup> Subsequent clinical trials have not included maintenance as postremission therapy.

The recent shortages of several chemotherapy agents have raised the question of how best to use cytarabine. The HOVON/SAKK study compared a double-induction concept using intermediate- or high-dose cytarabine as part of an induction/consolidation regimen in a phase III randomized study in patients (age 18–60 years) with newly diagnosed AML ( $N = 860$ ).<sup>126</sup> Patients were randomized to treatment with an

“intermediate-dose” cytarabine regimen (cycle 1: cytarabine, 200 mg/m<sup>2</sup> × 7 days + idarubicin, 12 mg/m<sup>2</sup> × 3 days; cycle 2: cytarabine, 1 g/m<sup>2</sup> every 12 hours × 6 days + amsacrine, 120 mg/m<sup>2</sup> × 3 days)[12 g/m<sup>2</sup> cytarabine] or a “high-dose” cytarabine regimen (cycle 1: cytarabine, 1 g/m<sup>2</sup> every 12 hours × 5 days + idarubicin, 12 mg/m<sup>2</sup> × 3 days; cycle 2: cytarabine, 2 g/m<sup>2</sup> every 12 hours × 4 days + amsacrine, 120 mg/m<sup>2</sup> × 3 days) [26 g/m<sup>2</sup> cytarabine]. Patients who experienced a CR after both treatment cycles were eligible to receive consolidation with a third cycle of chemotherapy or autologous or allogeneic HSCT.<sup>126</sup> A similar proportion of patients in each treatment arm received consolidation with a third chemotherapy cycle (26%–27%), autologous HSCT (10%–11%), and allogeneic HSCT (27%–29%). No significant differences were observed between the intermediate- and high-dose arms in rates of CR (80% vs. 82%), 5-year EFS (34% vs. 35%), or 5-year OS (40% vs. 42%),<sup>126</sup> results that seem comparable to those from the CALGB study with high-dose cytarabine.<sup>122</sup> More than 50% of patients in each arm had already experienced a CR when they received cycle 2. The 5-year cumulative rate of relapse risk was also similar between treatment arms (39% vs. 27%, respectively).<sup>126</sup> Outcomes were poor for patients with monosomal karyotype at baseline (n = 83), although the high-dose regimen was associated with significantly improved rates of 5-year EFS (13% vs. 0%; *P* = .02) and OS (16% vs. 0%; *P* = .02) compared with those of the intermediate-dose in this subgroup. The incidence of grade 3 or 4 toxicities after cycle 1 was higher in the high-dose arm than in the intermediate-dose arm (61% vs. 51%; *P* = .005), but the incidence of 30-day mortality was the same in both arms (10%).<sup>126</sup> This study suggests that 2 cycles of intermediate-dose cytarabine (1 g/m<sup>2</sup> every 12 hours × 6 days; total dose 12 g/m<sup>2</sup> per cycle) for each consolidation cycle may be a feasible alternative to the current NCCN recommendations of 3 cycles of high-dose cytarabine (3 g/m<sup>2</sup> for 6 doses; total dose of 18 g/m<sup>2</sup> per cycle). However, what importance

amsacrine may have served in the outcomes of the HOVON/SAKK study is currently not known.

Other options for consolidation strategies include one or more cycles of high-dose cytarabine followed by autologous HSCT or allogeneic HSCT from matched sibling or unrelated donors. When choosing among these options, decisions are influenced by: 1) the expected relapse rate with high-dose cytarabine consolidation chemotherapy (which in turn is strongly influenced by cytogenetic and molecular abnormalities); 2) the additional morbidity and mortality associated with the transplant procedure, which in turn are strongly influenced by patient-specific comorbidity; and 3) salvage therapy 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 2 cycles of chemotherapy to achieve a remission are likely to have more resistant disease and should be considered for a more intensive approach as initial consolidation whenever possible.

Previous versions of these guidelines have used cytogenetics as the major defining criteria for risk of relapse. In the latest versions of these guidelines, the panel has endeavored 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 (see “Risk Status Based on Validated Cytogenetics and Molecular Abnormalities” on page AML-A).

In the EORTC/GIMEMA trial comparing outcomes between patients aged 45 or younger in no-donor (patients in CR planned for autologous HSCT) versus donor groups (patients in CR with matched sibling donor

planned for allogeneic HSCT) on an intent-to-treat basis, the 4-year DFS rate for the subgroup with good-risk cytogenetics [eg, t(8;21) or inv(16)] was 66% for the no-donor group (n = 73; 63% underwent HSCT) and 62% for the donor group (n = 50; 72% underwent HSCT).<sup>127</sup> Treatment-related mortality rates were 6% and 17%, respectively.

Outcomes from the earlier phase III SWOG/ECOG study in younger patients (age ≤ 55 years) also suggested similar outcomes in those with favorable cytogenetics undergoing HSCT; based on intent-to-treat analysis, the 5-year survival rate (from time of CR) was 71% for the autologous HSCT group (n = 26; 65% underwent HSCT) and 63% for the allogeneic HSCT group (n = 19; 84% underwent HSCT).<sup>21</sup> The UK MRC study (AML 10) also reported no DFS or OS advantage with allogeneic HSCT among patients (age < 55 years) with favorable-risk cytogenetics.<sup>128</sup> These data suggest that in the favorable-risk subgroup of patients with AML, the potential advantage with allogeneic HSCT in preventing relapse may be offset by high rates of transplant-related deaths. Outcomes from multiple cycles of high-dose cytarabine consolidation are comparable to results with autologous HSCT. Thus, for this subgroup of patients, high-dose cytarabine followed by autologous HSCT should be the preferred HSCT option, and allogeneic HSCT may be better reserved as salvage therapy or for those with *c-KIT* mutations.

The panel has provided the following options for consolidation therapy for patients with better risk cytogenetics (those with CBF leukemia, without *c-KIT* mutations): 1) participation in a clinical trial; 2) 3 to 4 cycles of high-dose cytarabine (category 1); or 3) 1 to 2 cycles of high-dose cytarabine followed by autologous HSCT (category 2B). However, outcomes in favorable-risk patients who have *c-KIT* mutations are more similar to those of patients with intermediate-risk karyotype, and these patients should be considered for either clinical trials targeted toward

the molecular abnormality or consolidation strategies similar to those used in the intermediate-risk group. A well-thought-out plan for salvage therapy with either a matched sibling or unrelated donor HSCT should be an important part of the treatment decision for these patients.

The panel members agreed that transplant-based options (either matched sibling or alternate donor allogeneic HSCT, or 1–2 cycles of dose-intensive cytarabine followed by autologous HSCT) afforded a lower risk of relapse and a somewhat higher DFS as consolidation for most patients with intermediate-risk cytogenetics. Clinical trial participation is also encouraged. In the previously discussed SWOG/ECOG trial, the 5-year survival rates (from time of CR) for patients with intermediate-risk cytogenetics were 36% for the autologous HSCT group (n = 37; 59% underwent HSCT) and 52% for the allogeneic HSCT group (n = 47; 66% underwent HSCT).<sup>21</sup> In the UK MRC AML 10 trial, significant benefit with allogeneic HSCT was observed for the subgroup of patients with intermediate-risk cytogenetics (but not for those with favorable or high-risk cytogenetics); in this subgroup, the DFS (50% vs. 39%; *P* = .004) and OS rates (55% vs. 44%; *P* = .02) were significantly higher among the donor groups than the no-donor groups.<sup>128</sup> In the aforementioned EORTC/GIMEMA trial, the 4-year DFS rate among patients with intermediate-risk AML was 48.5% for the no-donor group (n = 104; 62.5% underwent HSCT) and 45% for the donor group (n = 61; 75% underwent HSCT).<sup>127</sup> The incidence of relapse was 47% and 35%, respectively, and the incidence of deaths in CRs was 5% and 20%, respectively. The 4-year OS rate among intermediate-risk patients was 54% for the no-donor group and 53% for the donor group.<sup>127</sup> Other options for this group include clinical trials or multiple courses (3–4) of high-dose cytarabine consolidation.<sup>129</sup> Alternative regimens incorporating intermediate doses of cytarabine (1.5–2 g/m<sup>2</sup>) may also be reasonable in patients with intermediate-risk

disease. Comparable 5-year DFS rates were reported in patients younger than 60 years with normal karyotype after either 4 cycles of intermediate- or high-dose cytarabine (41%) or autologous HSCT (45%).<sup>129</sup> At this time, there is no evidence that high-dose cytarabine is superior to lower doses of cytarabine in patients with intermediate-risk AML.

During the past 3 to 5 years, “normal” cytogenetics have been shown to encompass several molecular lesions with divergent risk behaviors. A large German trial has revealed additional molecular prognostic markers for patients with NK AML.<sup>27</sup> The presence of an isolated *NPM1* or *CEBPA* mutation improves prognosis only slightly less than for patients with CBF translocations (see “Initial Evaluation” on page AML-1). For this subset of patients, therapy with multiple cycles of high-dose cytarabine is a category 1 option, and allogeneic HSCT should be reserved until relapse. Another option for this group is 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT (category 2B). In contrast, patients with an isolated *FLT3*-ITD mutation and normal karyotype have an outlook similar to those with poor-risk cytogenetics<sup>34</sup> and should be considered for a clinical trial or early allogeneic HSCT. In a recent report that evaluated the ELN risk classification in a large cohort of patients, those in the “Intermediate I” risk group (which includes all patients with NK AML with *FLT3* abnormalities and those lacking both *FLT3* and *NPM1* mutations), relapse-free survival was more favorable with allogeneic HSCT (94 vs. 7.9 months without allogeneic HSCT).<sup>70</sup> Preliminary trials incorporating *FLT3* inhibitors either as part of induction or postremission therapy (including post-HSCT) continue; however, the agents currently under investigation have shown only minimal impact. The panel strongly recommends clinical trials as standard therapy for patients with poor prognostic features, which include *FLT3* abnormalities in the setting of

otherwise normal karyotype, high WBC (> 50,000/mcL) at diagnosis, or 2 cycles of induction therapy needed to achieve CR.

In the aforementioned EORTC/GIMEMA trial, a 43% 4-year DFS rate was reported in the donor group of patients with poor-risk cytogenetics (n = 64; 73% underwent HSCT); this was significantly higher than the 4-year DFS rate (18%; *P* = .008) among the no-donor group (n = 94; 46% underwent HSCT), although only approximately half of the patients were able to proceed with the planned HSCT in the no-donor group.<sup>127</sup> The SWOG/ECOG trial reported a 5-year survival rate (from time of CR) of 44% with allogeneic HSCT (n = 18; 61% underwent HSCT) and 13% with autologous HSCT (n = 20; 50% underwent HSCT) among the subgroup of patients with unfavorable cytogenetics; moreover, the 5-year survival rate was similar between those allocated to autologous HSCT and those intended for chemotherapy consolidation alone (13% and 15%, respectively).<sup>21</sup>

The panel uniformly endorsed clinical trial participation or allogeneic HSCT with matched sibling or matched unrelated donor (including cord blood) as consolidation therapy options for patients with poor-risk cytogenetics or molecular abnormalities. Treatment with high-dose cytarabine-based consolidation may be required to maintain remission while searching for a potential matched donor.

### Management of AML in Patients Older Than 60 Years

#### Induction Therapy

The creation of separate guidelines for patients older than 60 years recognizes the poor outcomes in this group treated with standard cytarabine and an anthracycline. In patients older than 60 years, the proportion of those with favorable CBF translocations decreases, as does the number with isolated *NPM1* mutations, whereas the number of those with unfavorable karyotypes and mutations increases. Secondary

AML, either related to prior myelodysplasia or prior chemotherapy, also increases, along with a higher rate of multidrug resistance protein expression. Although studies in the Swedish Leukemia Registry documented improvement in outcomes for patients younger than 60 years over the past 3 decades, no similar improvement was observed for the older population.<sup>113,118</sup> Treatment-related mortality frequently exceeds any expected transient response in this group, particularly in patients older than 75 years or in those who have significant comorbid conditions or ECOG performance status greater than 2.

For older patients (age > 60 years) with AML, the panel recommends using patient performance status, in addition to adverse features (eg, unfavorable cytogenetics and therapy-related AML or prior MDS) and comorbid conditions, to select treatment options rather than relying on a patient's chronologic age alone. A treatment decision-making algorithm for previously untreated, medically fit, elderly patients (age ≥ 60 years) with AML was recently developed by the German AML cooperative group. Based on data from a large study in elderly patients (N = 1406), patient and disease factors significantly associated with CR and/or early death were identified and risk scores were developed based on multivariate regression analysis.<sup>130</sup> The predictive model was subsequently validated in an independent cohort of elderly patients (N = 801) treated with 2 courses of induction therapy with cytarabine and daunorubicin. The algorithm, with or without knowledge of cytogenetic or molecular risk factors, predicts the probability of achieving a CR and the risk for an early death for elderly patients with untreated AML, who are medically fit and therefore considered eligible for standard treatments.<sup>130</sup> The factors included in the algorithm are the following: body temperature (≤ 38°C, > 38°C), hemoglobin levels (≤ 10.3, > 10.3 g/dL), platelet counts (≤ 28K, > 28K–≤ 53K, > 53K–≤ 10K, > 10K counts/mcL), fibrinogen levels (≤ 150, > 150 mg/dL), age at diagnosis

(60–64, > 64–67, > 67–72, > 72 years), and type of leukemia (de novo, secondary). The algorithm can be access online at <http://www.aml-score.org/>.

Older adults with intact functional status (ie, ECOG score 0–2), minimal comorbidity, and favorable cytogenetic or molecular mutations, may benefit from standard therapies regardless of chronologic age. A reasonable treatment regimen for these patients includes standard-dose cytarabine (100–200 mg/m<sup>2</sup> by continuous infusion per day × 7 days) along with 3 days of anthracycline. Although patients older than 75 years with significant comorbidities generally do not benefit from conventional chemotherapy treatment, the rare patient with favorable or normal karyotype and no significant comorbidities might be the exception to this dogma. For patients with NK AML, the remission rates are 40% to 50% with cytarabine combined with idarubicin, daunorubicin or mitoxantrone. The randomized French ALFA-9801 study (N = 468) showed that idarubicin induction (the standard 12 mg/m<sup>2</sup> × 3 days or intensified with 12 mg/m<sup>2</sup> × 4 days) compared with high-dose daunorubicin (up to 80 mg/m<sup>2</sup>) yielded a significantly higher CR rate in patients aged 50 to 70 years (80% vs. 70%, respectively; *P* = .03).<sup>115</sup> The median OS for all patients was 17 months. The estimated 2-year EFS and OS rates were 23.5% and 38%, respectively, and estimated 4-year EFS and OS rates were 18% and 26.5%, respectively; no differences were observed between treatment arms with regard to EFS, OS, and cumulative relapse rates.<sup>115</sup> In the HOVON trial, which randomized patients aged 60 years and older to induction therapy with standard-dose cytarabine combined with either standard-dose daunorubicin (45 mg/m<sup>2</sup> × 3 days; n = 411) or dose-escalated daunorubicin (90 mg/m<sup>2</sup> × 3 days; n = 402), the CR rate was 54% and 64%, respectively (*P* = .002).<sup>131</sup> No significant differences were observed in EFS, DFS, or OS outcomes between treatment arms.

Among the subgroup of patients aged 60 to 65 years ( $n = 299$ ), an advantage with dose-escalated compared with standard-dose daunorubicin was observed with regard to rates of CR (73% vs. 51%), 2-year EFS (29% vs. 14%), and 2-year OS (38% vs. 23%). These outcomes with dose-escalated daunorubicin seemed similar to those with idarubicin ( $12 \text{ mg/m}^2 \times 3 \text{ days}$ ) from the ALFA-9801 study, in which the 3-year EFS and OS rates were 30% and 40%, respectively.<sup>132</sup> In the HOVON trial, the benefit in OS outcomes for the dose-escalated daunorubicin group was observed only in patients aged 65 years and younger or in those with CBF translocations.<sup>131</sup>

Two phase III randomized trials recently evaluated the efficacy and safety of adding the anti-CD33 antibody-drug conjugate gemtuzumab ozogamicin to induction therapy with daunorubicin and cytarabine in older patients with previously untreated AML.<sup>133,134</sup> In the phase III trial from the Acute Leukemia French Association (ALFA-0701 trial), patients aged 50 to 70 years with *de novo* AML ( $N = 280$ ) were randomized to receive induction with daunorubicin ( $60 \text{ mg/m}^2 \times 3 \text{ days}$ ) and cytarabine ( $200 \text{ mg/m}^2$  continuous infusion  $\times 7 \text{ days}$ ), without (control arm) or with fractionated gemtuzumab ozogamicin  $3 \text{ mg/m}^2$  given on days 1, 4 and 7.<sup>134,135</sup> Patients with persistent marrow blasts at day 15 received additional daunorubicin and cytarabine. Patients with a CR/CRp after induction received two consolidation courses with daunorubicin and cytarabine, with or without gemtuzumab ozogamicin ( $3 \text{ mg/m}^2$  on day 1). The CR/CRp after induction was similar between the gemtuzumab ozogamicin and control arms (81% vs. 75%). The gemtuzumab ozogamicin arm was associated with significantly higher estimated 2-year EFS (41% vs. 17%;  $P = .0003$ ), RFS (50% vs. 23%;  $P = .0003$ ) and OS (53% vs. 42%;  $P = .0368$ ) rates compared with control.<sup>135</sup> The gemtuzumab ozogamicin arm was associated with a higher incidence of hematological toxicity (16% vs. 3%;  $P < .0001$ ); this

was not associated with an increase in the risk of death from toxicity.<sup>135</sup> In another multicenter phase III randomized trial from the UK and Denmark (AML-16 trial), patients older than 50 years with previously untreated AML or high-risk MDS ( $N = 1,115$ ) were randomized to receive daunorubicin-based induction (daunorubicin combined with cytarabine or clofarabine) without (control) or with gemtuzumab ozogamicin ( $3 \text{ mg/m}^2$  on day 1 of course 1 of induction).<sup>133</sup> The median age was 67 years (range, 51–84 years) and 98% of patients were age 60 years or older; 31% were 70 years or older. The CR/CRi rate after induction was similar between the gemtuzumab ozogamicin and control arms (70% vs. 68%). The gemtuzumab ozogamicin arm was associated with significantly lower 3-year cumulative incidence of relapse (68% vs. 76%;  $P = .007$ ) and higher 3-year RFS (21% vs. 16%;  $P = .04$ ) and OS (25% vs. 20%;  $P = .05$ ) rates compared with the control arm. The early mortality rates were not different between treatment arms (30-day mortality rate: 9% vs. 8%); in addition, no major increases in adverse events were observed with the gemtuzumab ozogamicin arm.<sup>133</sup>

These trials suggest that the addition of gemtuzumab ozogamicin to standard induction regimens reduced the risk of relapse and improved OS outcomes in older patients with previously untreated AML. As previously mentioned, gemtuzumab ozogamicin is currently not available in the US after the FDA withdrew its prior approval of the drug for treatment of older patients in the relapsed AML setting due to concerns for early non-relapse mortality rate in clinical trials in younger patients.

Another option for patients who are medically fit is the purine nucleoside analogue clofarabine (currently FDA-approved only for the treatment of relapsed or refractory pediatric ALL). In a large phase II study from the MD Anderson Cancer Center, 112 patients (age  $> 60$  years; median age, 71 years), most of whom had additional risk factors,

received clofarabine, 30 mg/m<sup>2</sup> intravenously for 5 days.<sup>136</sup> CR/complete response with incomplete platelet recovery (CRp) was achieved in 46% of patients, with a 30-day mortality rate of 10%. Patients who experienced a remission continued to receive therapy every 4 to 6 weeks to maintain remission for up to 6 additional treatment cycles. For the entire patient cohort, the median DFS and OS were 37 and 41 weeks, respectively; patients experiencing a CR had a median OS of 72 weeks.<sup>136</sup> An ECOG-led phase III trial is currently in progress, which will compare induction therapy with single-agent clofarabine versus cytarabine/daunorubicin in patients older than 60 years. Consolidation therapy in this trial would be either continuation of clofarabine or intermediate-dose cytarabine.

For patients who are deemed unfit for standard induction or for intermediate-intensity therapy such as clofarabine, options for low-intensity therapy may include epigenetic agents such as the hypomethylating drugs 5-azacytidine and decitabine (alone or in combination with histone deacetylase inhibitors), or low-dose cytarabine.

An international randomized phase III study by Fenaux et al<sup>137</sup> compared the hypomethylating agent 5-azacytidine with conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy) in patients with MDS (N = 358). Although this study was designed for evaluation of treatment in patients with high-risk MDS (based on FAB criteria), 113 study patients (32%) fulfilled criteria for AML using the 2008 WHO classification, with marrow-blast percentage between 20% and 30%.<sup>137,138</sup> In the subgroup of these patients with AML, a significant survival benefit was found with 5-azacytidine compared with conventional care regimens, with a median OS of 24.5 versus 16 months (hazard ratio [HR], 0.47; 95% CI, 0.28–0.79; *P* = .005).<sup>138</sup> The 2-year OS rate was 50% and 16%, respectively (*P* = .001).

Another hypomethylating agent, decitabine, has also been evaluated as remission induction therapy for older patients with AML.<sup>139</sup> In a phase II study in previously untreated patients aged 60 years and older (N = 55; median age, 74 years), the CR rate with this agent (20 mg/m<sup>2</sup> for 5 days every 28 days) was 24% (including 6/24 patients [24%] with poor-risk cytogenetics), and the median EFS and OS were 6 and 8 months, respectively.<sup>139</sup> An earlier phase I study evaluated different dose schedules of decitabine in patients with relapsed/refractory leukemias (N=50; AML diagnosis, n=37).<sup>140</sup> In this study decitabine was given at 5, 10, 15, or 20 mg/m<sup>2</sup> for 5 days per week for 2 to 4 consecutive weeks (ie, 10, 15, or 20 days). Decitabine dose of 15 mg/m<sup>2</sup> for 10 days (n=17) was associated with the highest response rates, with an ORR of 65% and CR rate of 35%. Among the patients with relapsed/refractory AML (n=37), the ORR was 22% with a CR in 14%, across all dose levels.<sup>140</sup> In an open-label randomized phase III study, decitabine (20 mg/m<sup>2</sup> for 5 days every 28 days) was compared with physician's choice (either low-dose cytarabine or supportive care) in older patients (age ≥ 65 years) with newly diagnosed AML.<sup>141,142</sup> Based on the protocol-specified final analysis of the primary end point (OS), decitabine was associated with a statistically nonsignificant trend for increased median OS compared with physician's choice (7.7 vs. 5 months; HR, 0.85; 95% CI, 0.69–1.04; *P* = .108). A subsequent post hoc analysis of OS with additional follow-up time showed the same median OS with a statistically significant advantage associated with decitabine (HR, 0.82; 95% CI, 0.68–0.99; *P* = .037). The CR (including CRp) rate was significantly higher with decitabine (18% vs. 8%; *P* = .001).<sup>141,142</sup> The most common treatment-related adverse events with decitabine versus cytarabine included thrombocytopenia (27% vs. 26%), neutropenia (24% vs. 15%), febrile neutropenia (21% vs. 15%), and anemia (21% vs. 20%). The 30-day mortality rates were similar between the decitabine and cytarabine groups (9% vs. 8%).<sup>142</sup> Both azacytidine and



decitabine are approved by the FDA as treatment for patients with MDS.

The United Kingdom National Cancer Research Institute AML 14 trial randomized 217 older patients (primarily age > 60 years; de novo AML, n = 129; secondary AML, n = 58; high-risk MDS, n = 30) unfit for chemotherapy to receive either low-dose cytarabine subcutaneously (20 mg twice daily for 10 consecutive days, every 4–6 weeks) or hydroxyurea (given to maintain target WBC counts < 10,000/mcL).<sup>143</sup> Patients were also randomized to receive all-trans retinoic acid (ATRA) or no ATRA. Low-dose cytarabine resulted in a CR rate of 18% (vs. 1% with hydroxyurea) and a survival benefit compared with hydroxyurea in patients with favorable or normal karyotype. No advantage was observed with the addition of ATRA. The median DFS in patients who achieved a CR with low-dose cytarabine was 8 months.<sup>143</sup> Even with this “low-intensity” treatment approach, induction death occurred in 26% of patients, and overall prognosis remained poor for older patients who cannot tolerate intensive chemotherapy regimens. A recent phase II study evaluated a regimen with low-dose cytarabine (20 mg twice daily for 10 days) combined with clofarabine (20mg/m<sup>2</sup> daily for 5 days) in patients aged 60 years or older with previously untreated AML (N=60; median age 70 years, range 60–81 years).<sup>144</sup> Patients with a response received consolidation (up to 17 courses) with clofarabine plus low-dose cytarabine alternating with decitabine. Among evaluable patients (n=59), the CR rate was 58% and median relapse-free survival was 14 months. The median OS for all patients was 12.7 months. Induction mortality rate was 7% at 8 weeks.<sup>144</sup> Although this regimen appeared to be active in older patients with AML, the authors noted that the benefits of prolonged consolidation remain unknown.

The panel has included subcutaneous cytarabine, 5-azacytidine, and decitabine as low-intensity treatment options, and clofarabine as an

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 leukocytosis.

Older adults with newly diagnosed AML with ECOG performance status score of 0 to 2, with or without adverse features (such as therapy-related AML/prior MDS or unfavorable cytogenetic or molecular markers) may be managed with one of the following options: clinical trial, standard infusional cytarabine and anthracycline; low-intensity therapy (eg, subcutaneous cytarabine, azacitidine, or decitabine); or intermediate-intensity therapy with clofarabine (category 2B).

Patients with an ECOG performance status score of greater than 2 or those with significant comorbidities (regardless of performance status score) are more likely to experience toxicity and less likely to benefit from standard-induction chemotherapy. For these patients, the panel feels it is reasonable to offer low-intensity therapy or best supportive care. Participation in a clinical trial investigating novel agents may also be appropriate for patients with a performance status score of greater than 2 without significant comorbid conditions.

#### ***Postinduction Therapy***

Similar to younger patients, older patients who receive standard cytarabine/anthracycline induction are evaluated with a bone marrow evaluation 7 to 10 days after completion of chemotherapy and categorized according to the presence of blasts or hypoplasia. Patients with residual blasts without hypoplasia may receive additional standard-dose cytarabine with an anthracycline or mitoxantrone. A repeat bone marrow evaluation is performed in these patients and in those with hypoplasia after induction to document 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 fewer than 5% marrow blasts but mild residual cytopenia.

Many of the newer treatment strategies are designed to work more gradually using agents that may allow expression of tumor suppressor genes (eg, a methyltransferase inhibitor such as decitabine or 5-azacytidine) or increase apoptosis (eg, histone deacetylase inhibitors). Thus, success in these trials may be assessed using indirect measures, such as hematologic improvement or decreased transfusion requirements and survival, without actually achieving CR. Frequently, in these trials, marrow examination is not performed until completion of 1 to 2 cycles of therapy.

### ***Postremission Therapy***

Patients who achieve a CR (including CRi) with standard induction chemotherapy may receive further consolidation with these agents. The French ALFA 98 trial randomized patients aged 65 years and older who achieved remission (n = 164 randomized for postremission therapy), to consolidation with either 1 additional course of standard-dose cytarabine (200 mg/m<sup>2</sup> × 7 days) plus the anthracycline to which they had been randomized for induction (idarubicin, 9 mg/m<sup>2</sup> × 4 days or daunorubicin, 45 mg/m<sup>2</sup> × 4 days) or 6 monthly courses of anthracycline (1 day only) at the above doses and 60 mg/m<sup>2</sup> of cytarabine every 12 hours as a subcutaneous infusion at home for 5 days each month.<sup>145</sup> Based on intent-to-treat analysis, patients randomized to the ambulatory arm had a significantly higher 2-year DFS rate (28% vs. 17%; *P* = .04) and OS rate (from time of CR; 56% vs. 37%; *P* = .04) compared with the single course of intense chemotherapy

consolidation. In addition, the 2-year death rate in CR was significantly lower in the ambulatory arm (0% vs. 5%; *P* = .04) and no differences were observed in the cumulative relapse rate between arms.<sup>145</sup> Although 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 (1.0–1.5 g/m<sup>2</sup>/d × 4–6 doses) without an anthracycline.

The role of myeloablative allogeneic HSCT is limited in older patients because of significant comorbidities; however, ongoing interest has been shown in reduced-intensity conditioning (RIC) allogeneic HSCT as consolidation therapy.<sup>146,147</sup> Case series and analysis of registry data have reported encouraging results, with 40% to 60% 2-year OS rates and 20% nonrelapse mortality for patients who underwent transplant in remission.<sup>146,147</sup> In a retrospective analysis comparing outcomes with RIC allogeneic HSCT and autologous HSCT in patients aged 50 years and older based on large registry data, allogeneic HSCT was associated with lower risk for relapse and superior DFS and OS relative to autologous HSCT.<sup>146</sup> The authors also noted that a survival benefit was not observed in the subgroup of patients undergoing allogeneic HSCT in first CR because of an increased incidence of nonrelapse mortality.

Estey et al.<sup>148</sup> prospectively evaluated a protocol in which patients aged 50 years and older with unfavorable cytogenetics would be evaluated for a RIC allogeneic HSCT.<sup>148</sup> Of the 259 initial patients, 99 experienced a CR and were therefore eligible for HSCT evaluation; of these patients, only 14 ultimately underwent transplantation because of illness, lack of donor, refusal, or unspecified reasons. The authors compared the results of RIC allogeneic HSCT with those from matched subjects receiving conventional-dose chemotherapy. This analysis

suggested that RIC allogeneic HSCT was associated with improved relapse-free survival, and the authors concluded that this approach remains of interest.<sup>148</sup> In an analysis of outcomes between 2 different strategies for matched sibling allogeneic HSCT, outcomes in younger patients (age ≤ 50 years; n = 35) receiving conventional myeloablative allogeneic HSCT were compared with those in older patients (age > 50 years; n = 39) receiving RIC allogeneic HSCT.<sup>149</sup> This study showed similar rates of 4-year nonrelapse mortality (19% and 20%, respectively), and no difference was seen in relapse and OS rates.<sup>149</sup>

A retrospective study based on data in older patients (age 50–70 years) with AML compared outcomes in patients who underwent allogeneic HSCT (either myeloablative conditioning or RIC; n = 152) and those who did not receive HSCT in first CR (chemotherapy only; n = 884).<sup>150</sup> Allogeneic HSCT in first CR was associated with a significantly lower 3-year cumulative relapse rate (22% vs. 62%;  $P < .001$ ) and higher 3-year relapse-free survival rate (56% vs. 29%;  $P < .001$ ) compared with the non-HSCT group. Although HSCT was associated with a significantly higher rate of nonrelapse mortality (21% vs. 3%;  $P < .001$ ), the 3-year OS rate showed a survival benefit with HSCT (62% vs. 51%;  $P = .012$ ).<sup>150</sup> Among the patients who underwent allogeneic HSCT, myeloablative conditioning was used in 37% of patients, whereas RIC was used in 61%. Survival outcomes between these groups were similar, with a 3-year OS rates of 63% and 61%, respectively.<sup>150</sup>

Another recent study evaluating treatment in older patients (age 60–70 years) compared outcomes between RIC allogeneic HSCT (reported to the Center for International Blood and Marrow Transplant Research; n = 94) and standard chemotherapy induction and postremission therapy from the CALGB studies (n = 96).<sup>151</sup> Allogeneic HSCT in first CR was associated with significantly lower 3-year relapse (32% vs. 81%;  $P < .001$ ) and higher 3-year leukemia-free survival rates (32% vs. 15%;  $P <$

.001) compared with the chemotherapy-only group. As would be expected, allogeneic HSCT was associated with a significantly higher rate of nonrelapse mortality (36% vs. 4%;  $P < .001$ ) at 3 years; the 3-year OS rate was not significantly different between the groups (37% vs. 25%;  $P = .08$ ), although a trend was seen favoring allogeneic HSCT.<sup>151</sup>

Collectively, these studies suggest that RIC allogeneic HSCT is a feasible treatment option for patients aged 60 years and older, particularly those in first CR with minimal comorbidities and who have an available donor. For this strategy to be better used, potential transplant options should be considered during induction therapy, and unrelated donor options/searches explored earlier in the disease management.

The guidelines note that RIC allogeneic HSCT is considered an additional option for patients aged 60 years and older for the following situations: 1) as postremission therapy in those experiencing a CR to induction therapy, or 2) as treatment of induction failure (in the context of a clinical trial) only in patients with low-volume disease.

### Postremission Surveillance and Salvage Therapy for AML

The guidelines recommend monitoring complete blood counts, including platelets, every 1 to 3 months for the first 2 years after patients have completed consolidation therapy, then every 3 to 6 months thereafter for a total of 5 years. Bone marrow evaluation is recommended only if the hemogram becomes abnormal, rather than as routine surveillance at fixed intervals, unless this is being performed as part of a clinical 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 reinduction therapy.

Treatment strategies for relapse are categorized according to patient 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 panel. If the relapse occurs after a relatively “long” (> 12 months) period of remission, retreatment with the previously successful induction 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 entered remission or in the context of a clinical trial.

Similarly, patients 60 years or older who are physically fit and wish to pursue treatment after relapse may be offered the following options: 1) therapy on clinical trial (strongly preferred option by the panel); or 2) salvage chemotherapy followed by matched sibling or alternate donor HSCT (again, transplant should be considered only if the patient has entered remission or in the context of a clinical trial); or 3) retreatment with the initial successful induction for a patients with a long initial remission duration (ie, relapse > 12 months). Best supportive care is always an option for patients who cannot tolerate or do not wish to pursue further intensive treatment.

The guidelines provide a list of several commonly used salvage regimens (see “Salvage Chemotherapy Regimen Options” on page AML-F). The regimens represent purine analog (eg, fludarabine, cladribine, clofarabine)–containing regimens, which have shown remission rates of 30% to 45% in several clinical trials, and those that have been used as the comparator arms in US cooperative group trials

in the past decade. The representative regimens included are: 1) cladribine, cytarabine, and granulocyte colony-stimulating factor (G-CSF), with or without mitoxantrone or idarubicin<sup>152,153</sup>; 2) fludarabine, cytarabine, and G-CSF (FLAG regimen) with or without idarubicin<sup>154,155</sup>; 3) etoposide and cytarabine, with or without mitoxantrone<sup>156</sup>; or 4) clofarabine (25 mg/m<sup>2</sup> daily for 5 days), cytarabine (2 g/m<sup>2</sup> daily for 5 days) and G-CSF.<sup>157</sup> More recently, a regimen with clofarabine (40 mg/m<sup>2</sup>) combined with cytarabine (2 g/m<sup>2</sup>) was evaluated in a randomized placebo-controlled phase III trial (CLASSIC I trial) in relapsed/refractory AML, resulting in an ORR of 47% (CR rate 35%) and median OS of 6.6 months.<sup>158</sup> In addition, high-dose cytarabine, if not previously used as treatment for persistent disease at day 15, with or without anthracycline may also be considered in the salvage setting. Notably, these salvage treatment options are aggressive regimens intended for appropriate patients who can tolerate such therapies; for other patients, less aggressive treatment options may include low-dose cytarabine<sup>143,159</sup> or hypomethylating agents.<sup>138-141,160,161</sup>

### **Supportive Care for Patients with AML**

Although variations exist between institutional standards and practices, several supportive care issues are important to consider in the management of patients with AML. In general, supportive care measures may include the use of blood products or transfusion support, tumor lysis prophylaxis, neurologic assessments, antiinfective prophylaxis, and use of growth factors. These supportive care measures are tailored to address the specific needs and infection susceptibility of each individual patient.

When transfusion support is required, leukocyte-depleted blood products should be used for transfusion. Radiation of all blood products is advised in all patients receiving immunosuppressive therapy, particularly for patients receiving fludarabine-based regimens and those



# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

undergoing HSCT. Cytomegalovirus (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.

Standard tumor lysis prophylaxis includes hydration with diuresis, alkalinization of the urine, and 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 evidence of impaired renal function.

Patients who receive high-dose cytarabine should be closely monitored for changes in renal function, because renal dysfunction is highly correlated with increased risk of cerebellar toxicity. Patients should be monitored and assessed for nystagmus, dysmetria, slurred speech, 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 administered as standard dose. Patients who develop cerebellar toxicity should not be rechallenged with high-dose cytarabine in future treatment cycles.<sup>162</sup> High-dose cytarabine should also be discontinued in patients with rapidly rising creatinine caused by tumor lysis.

Decisions regarding the 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. A randomized phase III study has shown that in patients with neutropenia undergoing induction chemotherapy for AML or MDS, posaconazole was significantly more effective in preventing invasive fungal infections than fluconazole or itraconazole, and was associated with improved OS outcomes.<sup>163</sup>

Growth factors have no clear role in initial induction therapy; however, they may be considered as part of supportive care for postremission therapy. Use of growth factors may be a confounding factor in the interpretation of pathology results from bone marrow evaluations. Therefore, G-CSFs or granulocyte-macrophage colony-stimulating factors should be discontinued for a minimum of 7 days before bone marrow samples are assessed when documenting remission status.

### Evaluation and Treatment of CNS Leukemia

Leptomeningeal involvement is much less frequent (< 3%) in patients with AML than in those with ALL; therefore, the panel does not recommend lumbar punctures (LP) as part of the routine diagnostic workup. However, if neurologic symptoms (eg, headache, confusion, altered sensory input) are present at diagnosis, an initial CT/MRI should be performed to rule out the possibility of intracranial hemorrhage or presence of mass/lesion. If no mass effect is seen, cerebrospinal fluid (CSF) cytology should be sampled by 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, given concurrently with systemic induction therapy. Initially, the intrathecal therapy should be given twice weekly until the cytology shows no blasts, and then weekly for 4 to 6 weeks. High-dose cytarabine, when used as part of induction therapy, may substitute for intrathecal chemotherapy because it crosses the blood-brain barrier; the CSF must then be reassessed after completion of induction therapy, and further intrathecal therapy should be 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, then radiation therapy should be strongly considered, followed by intrathecal therapy, as described earlier. However, intrathecal therapy or high-dose cytarabine should not be administered concurrently with cranial radiation because of the increased risks of neurotoxicity. Another option for these patients includes high-dose cytarabine-containing therapy with dexamethasone to help reduce intracranial pressure.

The panel does not recommend routine screening for occult central nervous system (CNS) disease in most patients with AML in remission. The exceptions are patients with M4 or M5 morphology, biphenotypic leukemia, or WBC count greater than 100,000/mcL at diagnosis. For patients with positive cytology, the panel recommends either intrathecal chemotherapy, as outlined earlier, 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 should be followed based on institutional practice.



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# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

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# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

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# NCCN Guidelines Version 2.2013

## Acute Myeloid Leukemia

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