National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Acute Myeloid Leukemia

Version 2.2014

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NCCN Guidelines Version 2.2014 Panel Members
Acute Myeloid Leukemia

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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus.

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Summary of the changes in the 2.2014 version of the NCCN Guidelines for Acute Myeloid Leukemia from the 1.2014 version include:

AML-4 - The following regimen changed from a category 2A to a category 1: ATRA 45 mg/m^2 in divided doses until clinical remission daily + arsenic trioxide 0.15 mg/kg IV daily until bone marrow remission.
MS-1 - The discussion section was updated to reflect the changes in the algorithm.

Summary of the changes in the 1.2014 version of the NCCN Guidelines for Acute Myeloid Leukemia from the 2.2013 version include:

AML-1
Evaluation for Acute Leukemia
- Footnote "a" modified with the addition of the following sentence: "Multiplex gene panels and sequencing assays are available for the assessment of other molecular abnormalities that may have prognostic impact in AML (see Discussion)."

AML-2
- Footnote "k" modified with the addition of the following sentence: "These risk groups are combined into one category in most treatment protocols."

AML-3
- A new regimen was added:
  - Induction: ATRA 45 mg/m^2 (days 1–36, divided) + age-adjusted idarubicin 6–12 mg/m^2 on days 2, 4, 6, 8 + arsenic trioxide 0.15 mg/kg (days 9–26 as 2-h IV infusion)
  - Consolidation: ATRA 45 mg/m^2 x 28 days + arsenic trioxide 0.15 mg/kg/day x 28 days for 5 wks x 1 cycle, then ATRA 45 mg/m^2 x 7 d every 2 wks x 3 + arsenic trioxide 0.15 mg/kg/day x 5 d for 5 wks x 1 cycle
  - The regimen is based on the following reference in footnote "u": Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-1580. A statement was added to this reference: Prophylaxis *with prednisone 1mg/kg/d for at least 10 d* is needed for differentiation syndrome *regardless of WBC at presentation*.
- Footnote "n" modified: 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. *A marrow for assessment of morphologic remission should not be performed before day 28 or until count recovery.* The first assessment of molecular remission should be made after consolidation.
- Footnote "x" added: "Consider 4-6 doses of IT chemotherapy (eg, 2 doses for each consolidation cycle) as an option for CNS prophylaxis."

AML-4
- Footnote "aa" modified: "Lo-Coco F, Avvisati G, Vignetti G, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369:111-121. ***Prophylaxis with prednisone 0.5mg/kg day 1 through completion of induction. If patient develops differentiation syndrome, change prednisone to dexamethasone 10 mg every 12 h until acute differentiation resolves, then return to previous prednisone dose."***

AML-6
- Post-remission therapy
  - Decision points added for "No prior exposure to arsenic trioxide or late relapse (≥6 mo) after arsenic trioxide-containing regimen" and "early relapse (<6 mo) after ATRA or arsenic trioxide only (no anthracycline)" and "early relapse (<6 mo) after arsenic trioxide/anthracycline-containing regimen."
  - For "early relapse (<6 mo) after ATRA or arsenic trioxide only (no anthracycline)," the following treatment recommendation was added: "Consider ATRA 45 mg/m^2 PO daily + idarubicin 12 mg/m^2 on days 2, 4, 6, 8 + arsenic trioxide 0.15 mg/kg IV daily until count recovery with marrow confirmation of remission."
  - Content as previously written for "No prior exposure to arsenic trioxide or late relapse (≥6 mo) after arsenic trioxide-containing regimen" and "Early relapse (<6 mo) after arsenic trioxide/anthracycline-containing regimen."
- Second remission: "Strongly consider" removed before "CNS prophylaxis"
- Footnote "jj" added: "Dose adjustment for patients >60 years: 9 mg/m^2/day IV (ages 61-70) or 6 mg/m^2/day IV (ages >70). Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-1580.

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Summary of the changes in the 1.2014 version of the NCCN Guidelines for Acute Myeloid Leukemia from the 2.2013 version include:

- **AML-8**
- **Footnote "oo" deleted: "ECOG reported a significant increase in complete response rates and overall survival using daunorubicin 90 mg/m^2 x 3 days versus 45 mg/m^2 x 3 days in patients <60 years of age. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 2009;361:1249-1259. If there is residual disease on days 12-14, the additional daunorubicin dose is 45 mg/m^2 x 3 days."**

AML-10

- **Intermediate risk**
  - **HiDAC dosing changed from 1.5-3g to 1-3g.**
  - **1-2 cycles of HiDAC consolidation followed by HSCT removed as a treatment option.**

AML-11

- **"Favorable cytogenetic/molecular markers" changed to "Non-adverse cytogenetic/molecular markers."**
  - **"preferred" added to idarubicin.**
  - **Mitoxantrone schedule clarified as "x 3 days"**
  - **Clofarabine removed as a treatment option.**
  - **Low-intensity therapy clarified with "may be more appropriate for elderly patients or relatively unfit patients with comorbidities"**
- **Therapy-related AML/prior MDS or unfavorable cytogenetics/molecular markers**
  - **"preferred" added to idarubicin.**
  - **Mitoxantrone schedule clarified as "x 3 days"**
  - **Clofarabine removed as a treatment option.**
  - **Low-intensity therapy clarified with "may be more appropriate for fit patients who are candidates for subsequent HSCT"**
- **Footnote "mmm" modified with the addition of "Consider continuing hypomethylating agents until progression."**

AML-12

- **Residual blasts: "HiDAC 1-2 g/m^2" added as a treatment option.**
- **Footnote "nnn" is new to the page: "Reduced-intensity HSCT may be appropriate for patients with a low level of residual disease post-induction (eg, patients with prior MDS who reverted back to MDS with 5%-7% blasts). It is preferred that this approach be given in the context of a clinical trial."**

AML-14

- **Footnote "sss" is new to the page: "Studies are ongoing to evaluate the role of molecular monitoring in the surveillance of early relapse in patients with AML (see Discussion)."**

AML-C 2 of 2

- **APL differentiation syndrome: The following sentence was added, "For ATRA + arsenic trioxide regimens, prophylaxis with prednisone 0.5mg/kg day 1 through completion of induction. If patient develops differentiation syndrome, change prednisone to dexamethasone 10 mg every 12 h until acute differentiation resolves, then return to previous prednisone dose. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369:111-121."**

AML-E

- **Induction, bullet 2: "LFTs" added to chemistry profile.**

AML-F

- **Clofarabine + cytarabine + GCSF changed to Clofarabine ± cytarabine + GCSF ± *idarubicin.***
- **Reference added: Faderl S, Ferrajoli A, Wierda W, et al. Clofarabine combination as acute myeloid leukemia salvage therapy. Cancer 2008;113:2090-2096.**

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[a]
- 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[b]
- Lumbar puncture (LP), if symptomatic[b] (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

DIAGNOSTIC STUDIES (WHO 2008)

Multidisciplinary diagnostic studies[c,d]

DIAGNOSIS[c,d,e,f]

- Acute promyelocytic leukemia (APL) → See Treatment Induction (AML-2)
- Acute myeloid leukemia (AML) → See Treatment Induction (AML-7)
- Myelodysplastic syndromes (MDS) → See NCCN Guidelines for Myelodysplastic Syndromes
- B or T lymphoblastic leukemia/lymphoma[d] → See NCCN Guidelines for Acute Lymphoblastic Leukemia

[a] 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). Multiplex gene panels and sequencing assays are available for the assessment of other molecular abnormalities that may have prognostic impact in AML (see Discussion). 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.

[b] 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).

[c] 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.

[d] 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.

[e] 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.

[f] 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.

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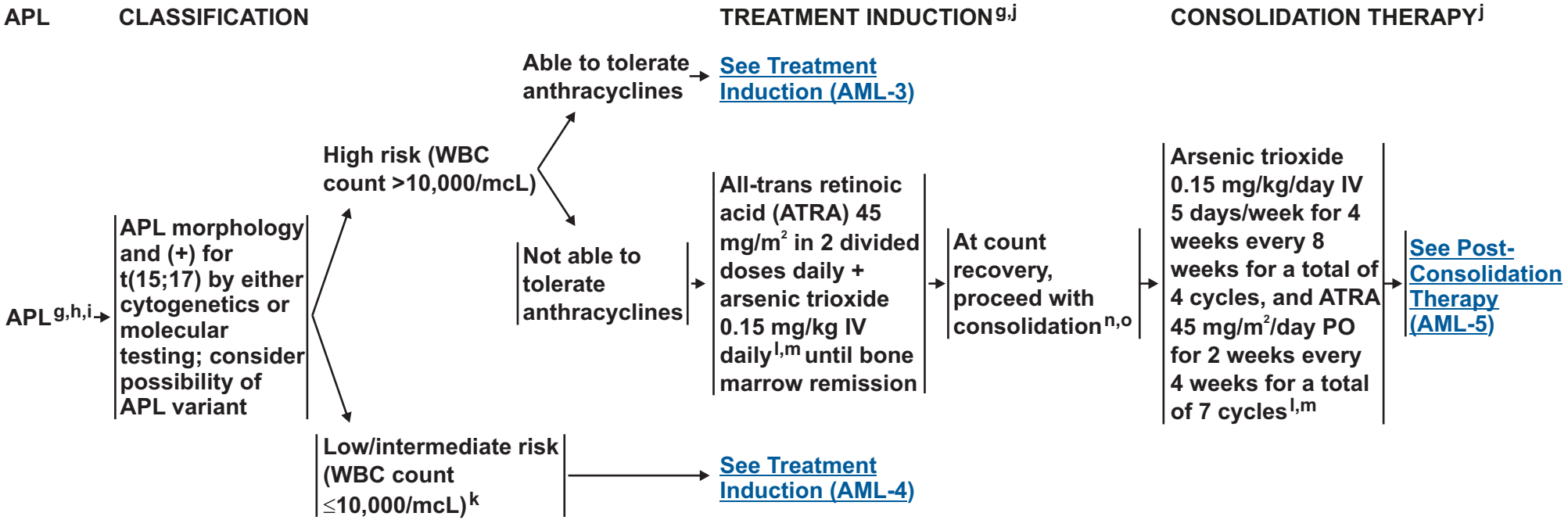
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[g] 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.

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

[i] 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.

[j] Monitor for APL differentiation syndrome and coagulopathy; see Supportive Care (AML-C 2 of 2).

[k] New data suggest similar outcomes in patients with low or intermediate risk. These risk groups are combined into one category in most treatment protocols.

[l] Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As_2O_3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci USA 2004;101(15):5328-35.
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.

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

[n] 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.

[o] Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare. See first relapse on AML-6.

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TREATMENT INDUCTION (HIGH RISK)[g,j,p]

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 50 mg/m² x 4 days + cytarabine 200 mg/m² x 7 days[r]
→ **At count recovery,[n,v] LP and proceed with consolidation[o]**

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[s]
→ **At count recovery,[n,v] LP and proceed with consolidation[o]**

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + idarubicin 12 mg/m² on days 2, 4, 6, 8[t]
→ **At count recovery,[n,v] LP and proceed with consolidation[o]**

or

ATRA 45 mg/m² (days 1-36, divided) + age-adjusted idarubicin 6-12 mg/m² on days 2, 4, 6, 8 + arsenic trioxide 0.15 mg/kg (days 9-26 as 2 h IV infusion)[u]
→ **At count recovery,[n,v] LP and proceed with consolidation[o]**

or

Clinical trial

CONSOLIDATION THERAPY[w]

Arsenic trioxide[m] 0.15 mg/kg/day x 5 days for 5 wks x 2 cycles, then ATRA 45 mg/m² x 7 days + daunorubicin 50 mg/m² x 3 days for 2 cycles[r,x]
→ **See Post-Consolidation Therapy (AML-5)**

Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine 2 g/m² (age <50) or 1.5 g/m² (age 50-60) every 12 h x 5 days[y,z] + daunorubicin 45 mg/m² x 3 days x 1 cycle 5 doses of IT chemotherapy[s] (category 1)
→ **See Post-Consolidation Therapy (AML-5)**

ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² and cytarabine 1 g/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/day x 5 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 dose + cytarabine 150 mg/m²/8 h x 4 days x 1 cycle[t,x]
→ **See Post-Consolidation Therapy (AML-5)**

ATRA 45 mg/m² x 28 days + arsenic trioxide[m] 0.15 mg/kg/day x 28 days for 5 wks x 1 cycle, then ATRA 45 mg/m² x 7 d every 2 wks x 3 + arsenic trioxide 0.15 mg/kg/day x 5 d for 5 wks x 1 cycle[u]
→ **See Post-Consolidation Therapy (AML-5)**

[g] 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.

[j] Monitor for APL differentiation syndrome and coagulopathy; see AML-C 2 of 2.

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

[n] 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. A marrow for assessment of morphologic remission should not be performed before day 28 or until count recovery. The first assessment of molecular remission should be made after consolidation.

[o] Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare. See first relapse on AML-6.

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

[q] Data suggest that lower doses of ATRA (25 mg/m²) in divided doses until clinical remission may be used in children and adolescents.

[r] Powell BL, 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.

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

[t] Sanz MA, 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.

[u] Iland HJ, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-1580. Prophylaxis with prednisone 1mg/kg/d for at least 10 d is needed for differentiation syndrome regardless of WBC at presentation.

[v] Breccia M, et al. Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count. Br J Haematol 2003;120:266-270.

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

[x] Consider 4-6 doses of IT chemotherapy (eg, 2 doses for each consolidation cycle) as an option for CNS prophylaxis.

[y] 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.

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

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TREATMENT INDUCTION (LOW/INTERMEDIATE RISK)[g,j,p]

ATRA 45 mg/m² in divided doses until clinical remission daily + arsenic trioxide[m] 0.15 mg/kg IV daily until bone marrow remission[aa] (category 1)

→ **At count recovery,[n,o] proceed with consolidation**

→ **Arsenic trioxide[m] 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/m²/day for 2 weeks every 4 weeks for a total of 7 cycles[aa] (category 1)**

→ **See Post-Consolidation Therapy (AML-5)**

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 50 mg/m² x 4 days + cytarabine 200 mg/m² x 7 days[r,bb]

→ **At count recovery,[n,o] proceed with consolidation**

→ **Arsenic trioxide[m] 0.15 mg/kg/day x 5 days for 5 wks x 2 cycles, then ATRA 45 mg/m² x 7 days + daunorubicin 50 mg/m² x 3 days for 2 cycles[r]**

→ **See Post-Consolidation Therapy (AML-5)**

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[s,bb] (category 1)

→ **At count recovery,[n,o] proceed with consolidation**

→ **Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine 1 g/m² every 12 h x 4 days + daunorubicin 45 mg/m² x 3 days x 1 cycle[s] (category 1)**

→ **See Post-Consolidation Therapy (AML-5)**

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + idarubicin 12 mg/m² on days 2, 4, 6, 8[t,bb] (category 1)

→ **At count recovery,[n,o] proceed with consolidation**

→ **ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/day x 5 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 dose x 1 cycle (category 1)[cc]**

→ **See Post-Consolidation Therapy (AML-5)**

or

Clinical trial

CONSOLIDATION THERAPY[w]

[g] 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.

[j] Monitor for APL differentiation syndrome and coagulopathy; see Supportive Care (AML-C 2 of 2).

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

[n] 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.

[o] Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare. See first relapse on AML-6.

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

[q] Data suggest that lower doses of ATRA (25 mg/m²) in divided doses until clinical remission may be used in adolescents.

[r] 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.

[s] 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.

[t] 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.

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

[aa] Lo-Coco F, Avvisati G, Vignetti G, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369:111-121. Prophylaxis with prednisone 0.5mg/kg day 1 through completion of induction. If patient develops differentiation syndrome, change prednisone to dexamethasone 10 mg every 12 h until acute differentiation resolves, then return to previous prednisone dose.

[bb] For patients who have rapidly escalating WBC counts or other high-risk features during course of induction therapy, see Consolidation Therapy on AML-3.

[cc] 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.

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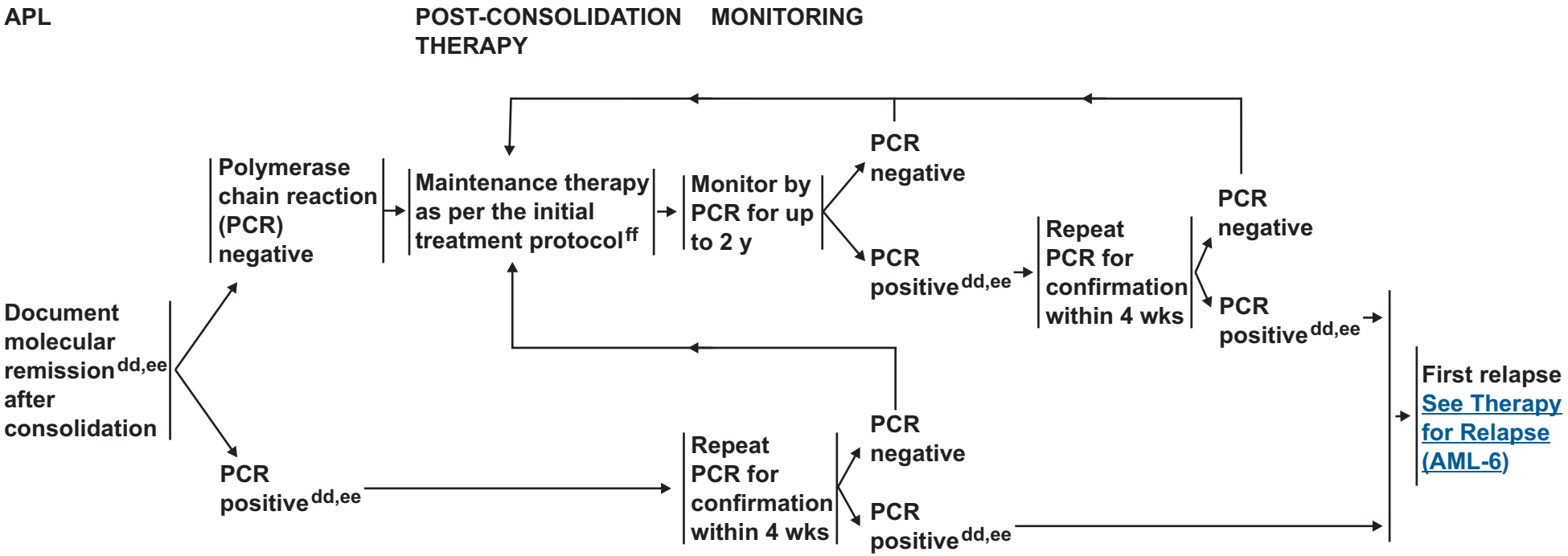

[dd] PCR should be performed on a marrow sample at completion of consolidation to document molecular remission. Subsequent monitoring by PCR can be done with peripheral blood, although marrow is a more sensitive monitoring technique and may give earlier signs of relapse. Prior practice guidelines have 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.

[ee] 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.

[ff] The majority of studies showing benefit with maintenance occurred prior to the use of ATRA and/or arsenic trioxide and/or cytarabine for consolidation. 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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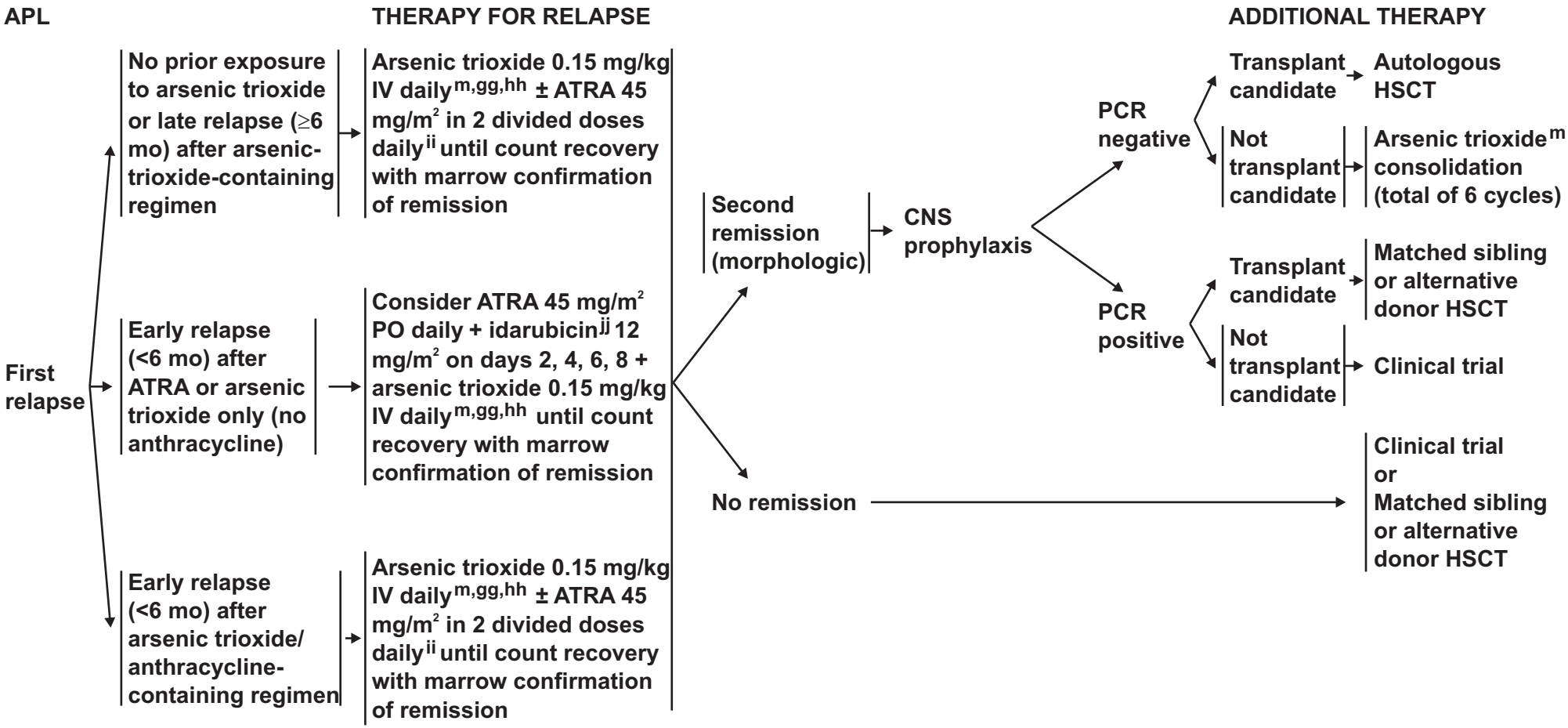


m See Arsenic trioxide monitoring, Supportive Care (AML-C 2 of 2).

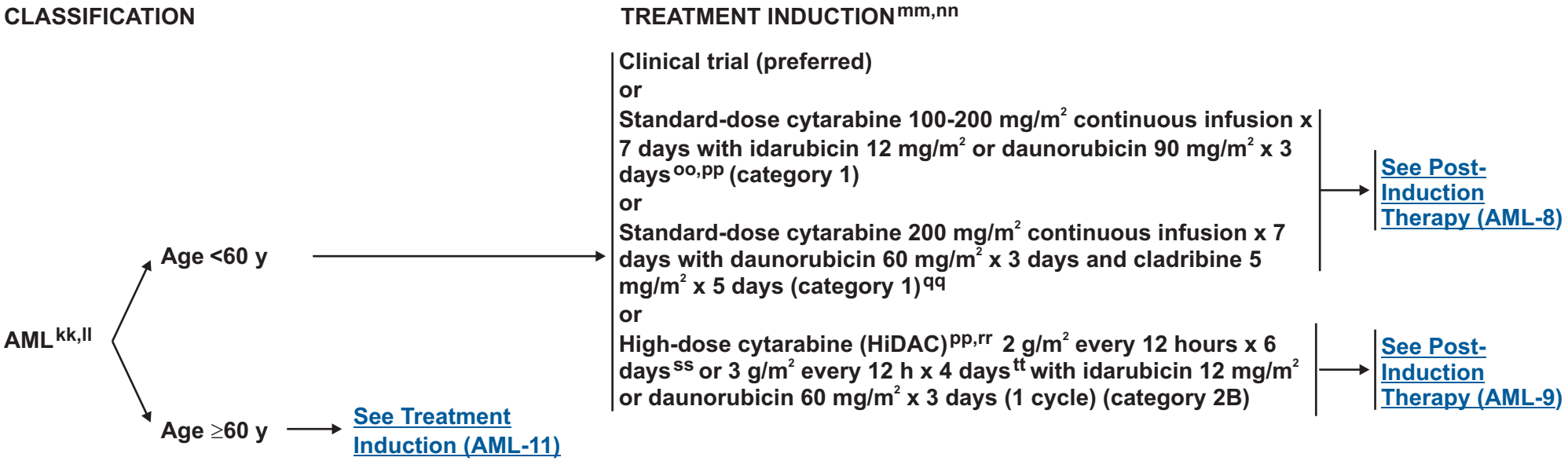
gg At the end of 2 cycles, if the patient is not in molecular remission, consider matched sibling or alternative donor HSCT or clinical trial. Testing is recommended at least 2-3 weeks after the completion of arsenic to avoid false positives.

hh Outcomes are uncertain in patients who received arsenic trioxide during initial induction/consolidation therapy.

ii 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.

jj Dose adjustment for patients >60: 9 mg/m²/day IV (ages 61-70) or 6 mg/m²/day IV (ages >70). Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-1580.

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.



kk 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.

ll Poor performance status and comorbid medical condition, in addition to age, are factors that influence ability to tolerate standard induction therapy.

mm See Supportive Care (AML-C 1 of 2).

nn See Monitoring During Therapy (AML-E).

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

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

qq 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.

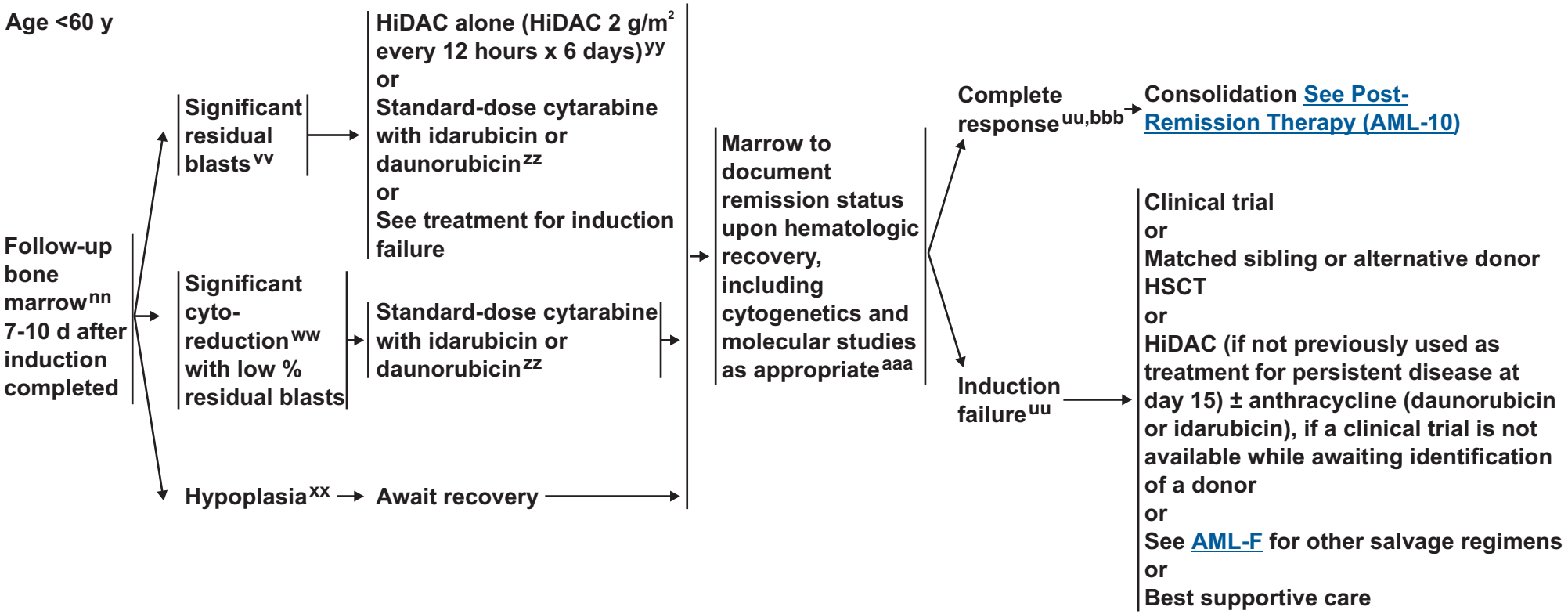
rr The use of high-dose cytarabine for induction outside the setting of a clinical trial is still controversial. While the remission rates are the same for standard- and high-dose cytarabine, two studies have shown more rapid marrow blast clearance after one cycle of high-dose therapy and a disease-free 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.

ss 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.

tt 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.

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.

AML POST-INDUCTION THERAPY AFTER STANDARD-DOSE CYTARABINE



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

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

[vv] 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.

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

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

[yy] For re-induction, no data are available to show superiority with intermediate or high-dose cytarabine.

[zz] 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.

[aaa] The role of immunophenotyping in detecting minimal residual disease is being evaluated.

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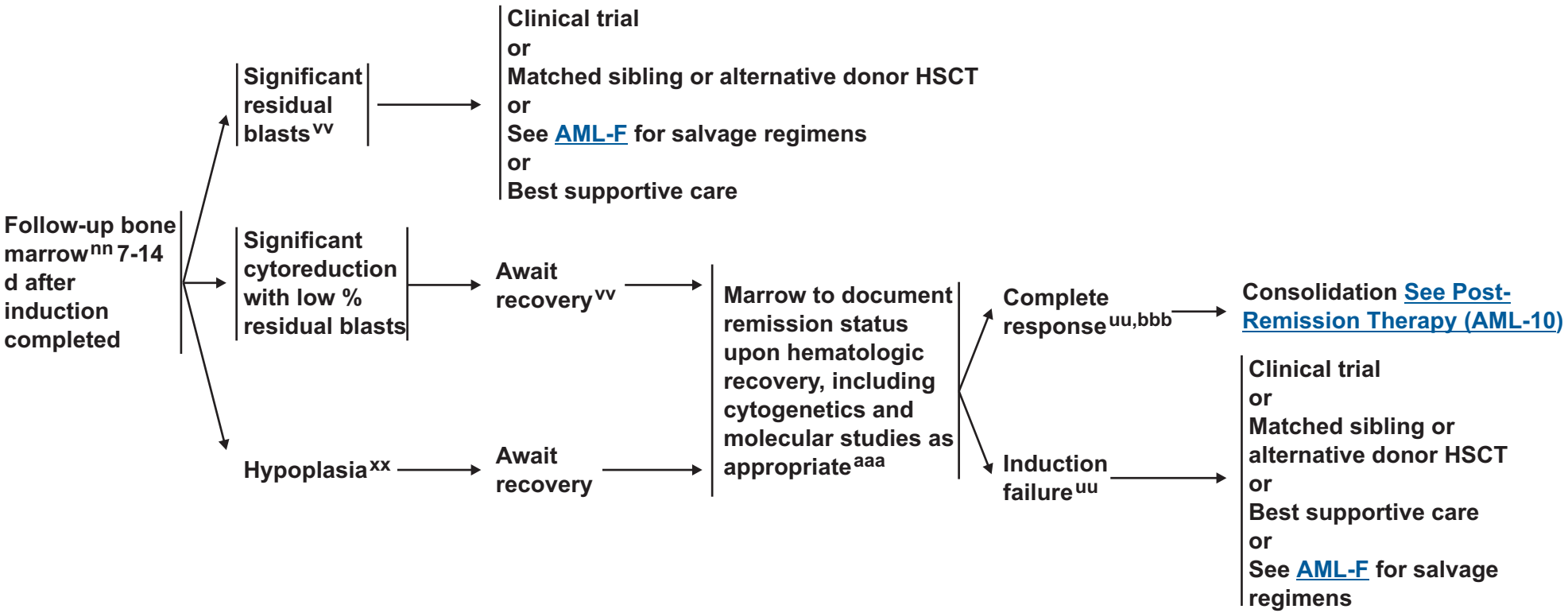
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

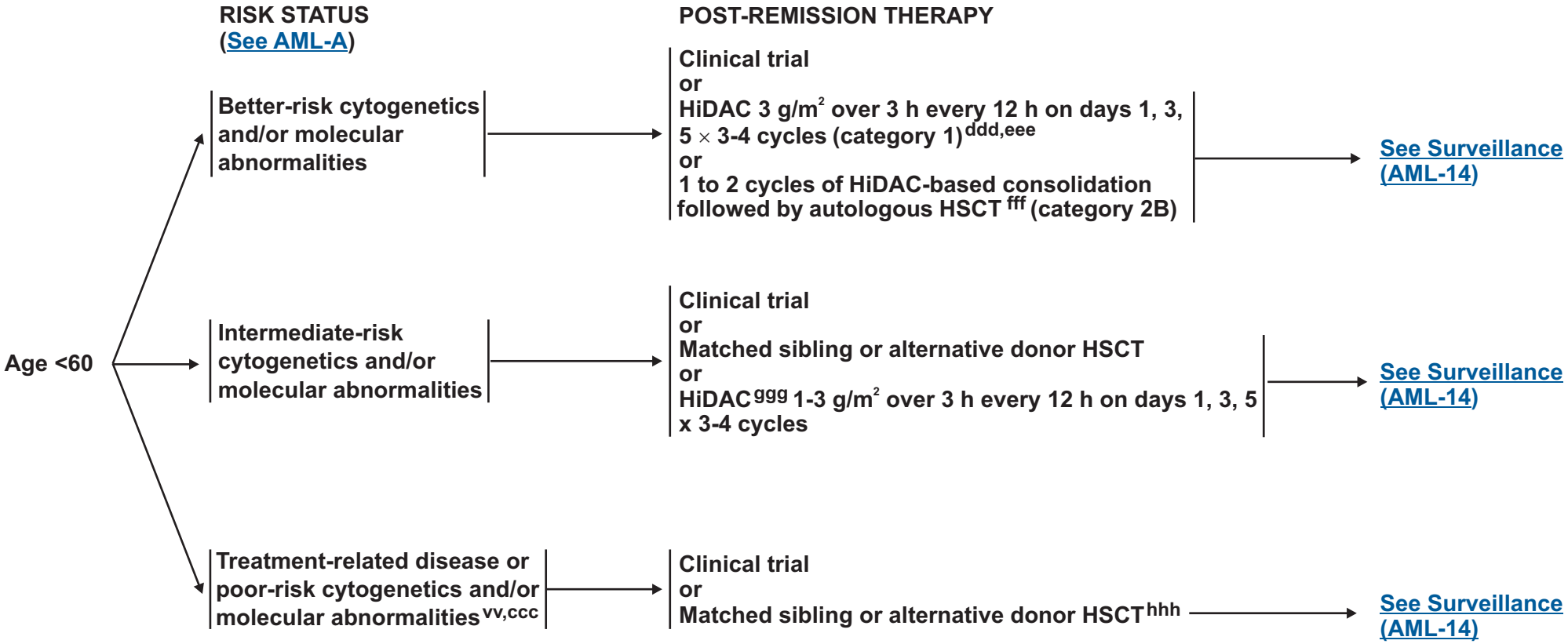
AML POST-INDUCTION THERAPY AFTER HIGH-DOSE CYTARABINE

Age <60 y



[nn] See Monitoring During Therapy (AML-E).
[uu] See Response Criteria for Acute Myeloid Leukemia (AML-D).
[vv] 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.
[xx] Hypoplasia is defined as cellularity <10%-20% and residual blasts <5%-10%.
[aaa] The role of immunophenotyping in detecting minimal residual disease is being evaluated.
[bbb] 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).

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.



[vv] 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.

[ccc] 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.

[ddd] 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.

[eee] 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.

[fff] 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.

[ggg] There is no evidence that HiDAC is superior to lower doses of cytarabine in intermediate-risk patient subgroup.

[hhh] 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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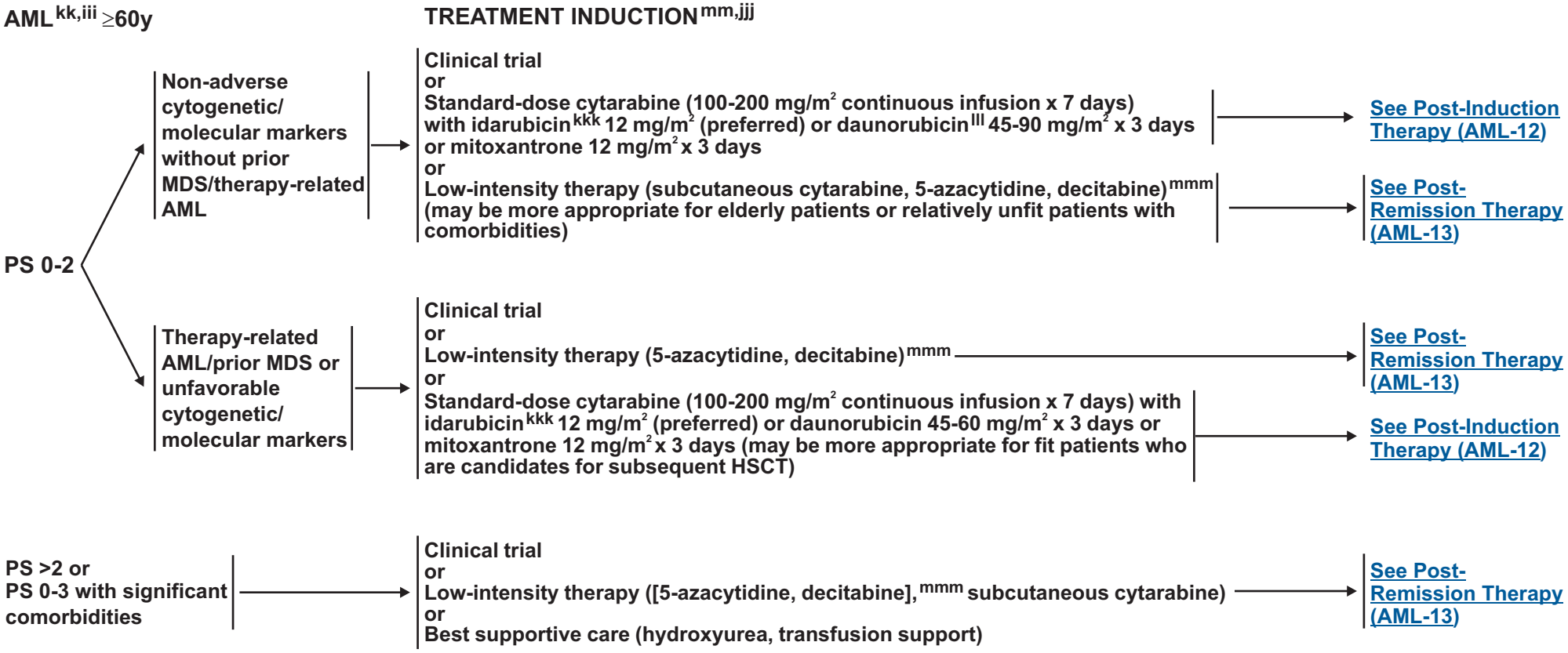

kk Patients with blast counts >50,000/mcL are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include apheresis or hydroxyurea. Prompt institution of definitive therapy is essential.

mm See Supportive Care (AML-C 1 of 2).

iii 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.

jjj 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.

kkk Idarubicin treatment compared to high doses of daunorubicin up to 80 mg/m² 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).

lll The complete response rates and 2-yr overall survival in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m² is also comparable to the outcome for idarubicin 12 mg/m²; the higher dose daunorubicin did not benefit patients > 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).

mmm 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. Consider continuing hypomethylating agents until progression.

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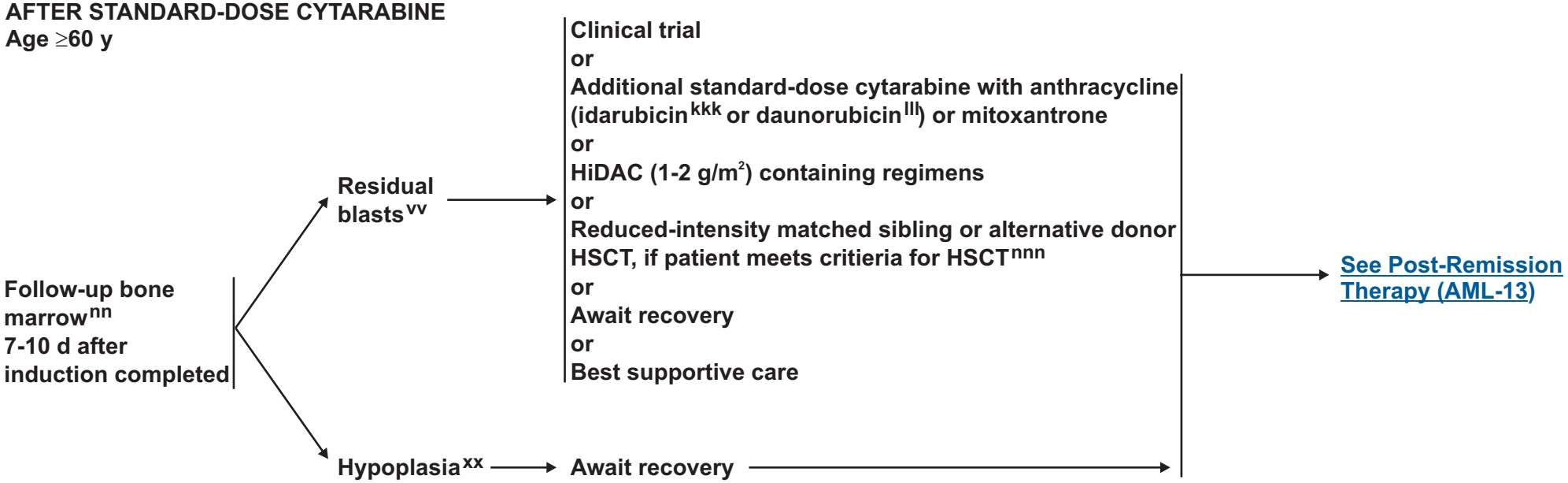
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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



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

[vv] 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.

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

[kkk] Idarubicin treatment compared to high doses of daunorubicin up to 80 mg/m² yields higher complete response rate and more complete responses after one course. (Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol 2010;28:808-814).

[lll] The complete response rates and 2-yr overall survival in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m² is also comparable to the outcome for idarubicin 12 mg/m²; the higher dose daunorubicin did not benefit patients > 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).

[nnn] Reduced-intensity HSCT may be appropriate for patients with a low level of residual disease post-induction (eg, patients with prior MDS who reverted back to MDS with 5%-7% blasts). It is preferred that this approach be given in the context of a clinical trial.

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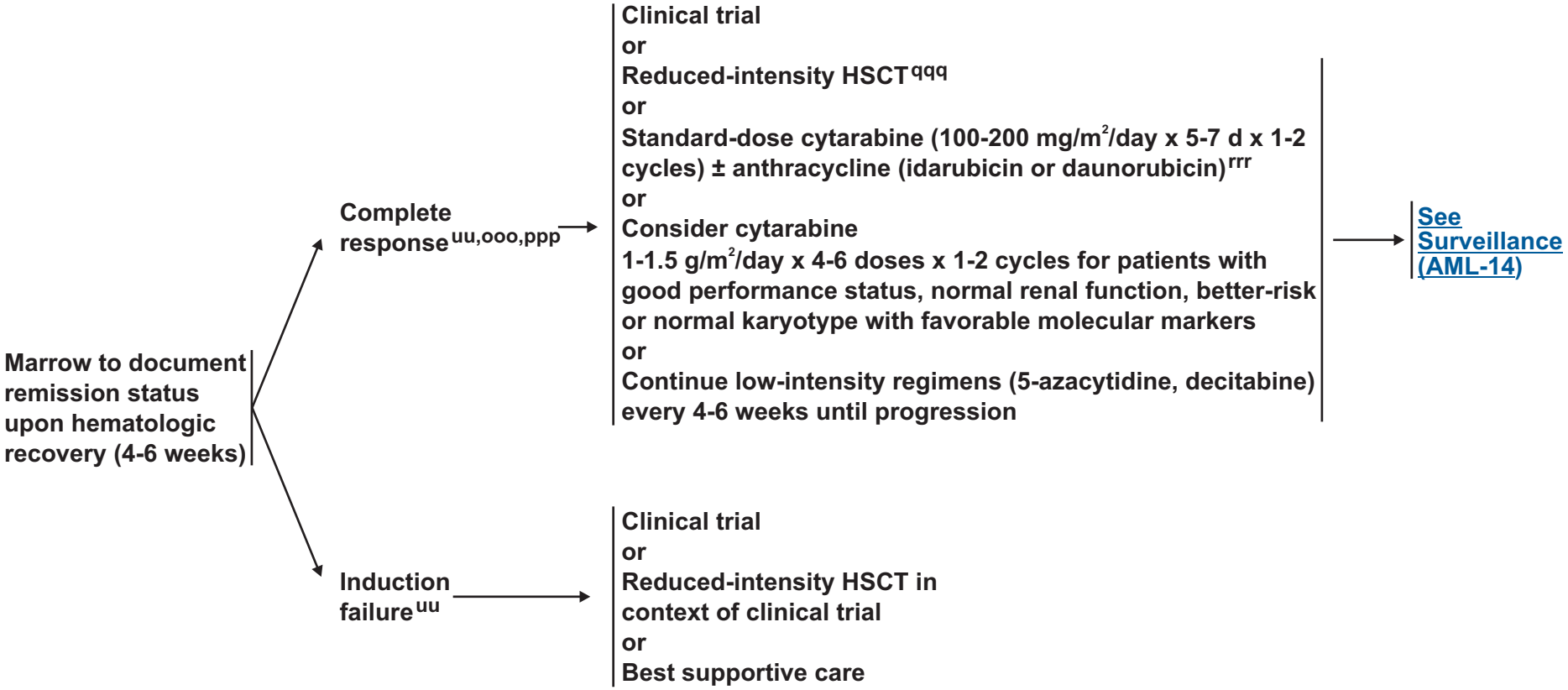
AML POST-REMISSION THERAPY
Age ≥60 y



uu See Response Criteria for Acute Myeloid Leukemia (AML-D).

ooo 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).

ppp HLA-typing for patients considered strong candidates for allogeneic transplantation.

qqq Patients who are deemed as strong candidates for stem cell transplant and who have an available donor should be transplanted in first remission.

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

SURVEILLANCE[sss]
(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

→ **Relapse[uu]**

SALVAGE THERAPY

Age <60

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

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

Age ≥60

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

Late (>12 mo) →
Clinical trial (strongly preferred)
or
Repeat initial successful induction regimen[uuu]
or
Salvage chemotherapy[ttt] followed by matched sibling or alternative donor HSCT[vvv]
or
Best supportive care

[uu] See Response Criteria for Acute Myeloid Leukemia (AML-D).
[sss] Studies are ongoing to evaluate the role of molecular monitoring in the surveillance for early relapse in patients with AML (see Discussion).
[ttt] See Salvage Chemotherapy Regimen Options (AML-F).
[uuu] 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.
[vvv] 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[1]

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

[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.

[2] Other cytogenetic abnormalities in addition to these findings do not alter better risk status.

[3] 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 (AMLSG). Blood 2013;121:170-177.

[4] For Philadelphia+ AML t(9;22), manage as myeloid blast crisis in CML, with addition of tyrosine kinase inhibitors.

[5] 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.

[6] 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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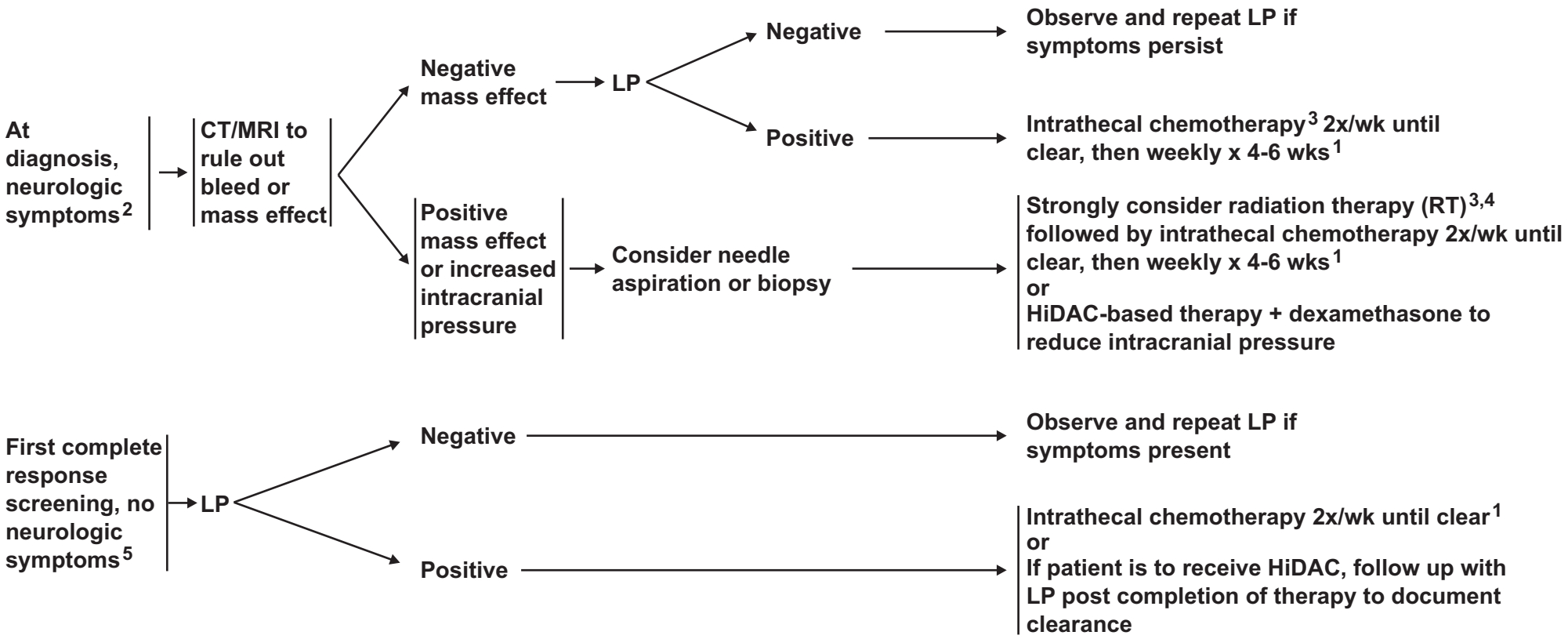
EVALUATION AND TREATMENT OF CNS LEUKEMIA[1]



[1] Further CNS surveillance per institutional practice.
[2] For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or CNS bleeding. LP should be performed if no mass, lesion, or hemorrhage was detected on the imaging study.
[3] Induction chemotherapy should be started concurrently. However, for patients receiving high-dose cytarabine, since this agent crosses the blood brain barrier, IT therapy can be deferred until induction is completed.
[4] Concurrent use of CNS RT with high-dose cytarabine, IT methotrexate, or IT liposomal cytarabine may increase risk of neurotoxicity.
[5] Screening LP should be considered at first remission for patients with M4 or M5 morphology, 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 ≤8 g/dL or per institutional guidelines or symptoms of anemia; platelets for patients with platelets <10,000/mcL or with any signs of bleeding.[1]**
  - **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.[2] Outcomes with other azoles, such as voriconazole, echinocandins, or amphotericin B, may produce equivalent results.**

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

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

See 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 ≥50,000/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/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.**
  - **For ATRA + arsenic trioxide regimens, prophylaxis with prednisone 0.5 mg/kg day 1 through completion of induction. If patient develops differentiation syndrome, change prednisone to dexamethasone 10 mg every 12 h until acute differentiation resolves, then return to previous prednisone dose. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369:111-121.**
- **Arsenic trioxide monitoring[1]**
  - **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.**

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

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RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA[1]

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

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

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

[3] 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, LFTs, blood urea nitrogen (BUN), creatinine, uric acid, and PO_4, 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.**

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.

SALVAGE CHEMOTHERAPY REGIMEN OPTIONS[1]

- **Cladribine + cytarabine + granulocyte colony-stimulating factor (GCSF) ± mitoxantrone or idarubicin[1,2]**
- **High-dose cytarabine (if not received previously in treatment) ± anthracycline**
- **Fludarabine + cytarabine + GCSF ± idarubicin[3,4]**
- **Etoposide + cytarabine ± mitoxantrone[5]**
- **Clofarabine ± cytarabine + GCSF ± idarubicin[6,7]**

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).

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

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

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

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

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

[6]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.

[7]Faderl S, Ferrajoli A, Wierda W, et al. Clofarabine combinations as acute myeloid leukemia salvage therapy. Cancer 2008;113:2090-2096.

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.

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.

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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 18,860 people will be diagnosed with AML in 2014, and 10,460 patients will die of the disease.[1] The projected incidence of new cases is increased by more than 5,000 compared to the 2013 statistics, though the number of estimated deaths is modestly increased by 260 cases.[2] The median age of diagnosis is 66 years, with 54% of patients diagnosed at 65 years or older (and approximately a third diagnosed at ≥75 years of age).[3] 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.[4] 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.[5-7] 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.[7-10] 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 (eg, etoposide, doxorubicin, mitoxantrone).[5,8,9] 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.[11,12] 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.[13,14] 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.[9] Importantly, clinical outcomes in patients with therapy-related AML have been shown to be significantly inferior (both in terms of relapse-free survival (RFS) and overall survival [OS]) compared with patients with de novo cases,[8,15] except those with the therapy-related acute promyelocytic leukemia (APL) subtype[7,16] 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 can 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 a complete blood count including platelets and differentials. Bone marrow analysis with cytogenetics (karyotype, with or without fluorescence in situ hybridization [FISH]) is necessary to establish the diagnosis of AML. Evaluation of several molecular markers (eg, *FLT3*, *NPM1, CEBPA,* and *c-KIT*) may be important for risk assessment and prognostication, and may also guide treatment decisions. Recent studies have reported on the prognostic impact of a number of molecular abnormalities in patients with AML (see *Molecular Markers and Risk Stratification*). If molecular testing is not available at the patient's treatment center, bone marrow samples should be cryopreserved at the time of diagnosis for potential future evaluation at an outside reference laboratory.

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 white blood cell (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 after 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 activity as part of the initial evaluation/workup and before performing any invasive procedure. The need for a cardiac evaluation (eg, echocardiogram or multiple gated acquisition [MUGA] scan) 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. Human leukocyte antigen (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

Originally, the classification system for AML was defined by 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. In 1999, WHO developed a newer classification system, which incorporates information from cytogenetics and evidence of dysplasia, to refine prognostic subgroups that may define treatment strategies.[17] 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 change 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)”, defined as patients with 20% to 30% blasts, was similar compared with that of patients with greater than 30% blasts.

The WHO classification system further 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.[18] However, no evidence shows that dysplasia represents an independent risk factor, because it is frequently linked to poor-risk cytogenetics.

In 2008, 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.[19] Additionally, 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]. Other provisional entities include AML with molecular lesions such as mutated *NPM1* or *CEBPA* genes (further information on these genetic lesions is provided later).[19]

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. However, ongoing research is moving MRD monitoring to the forefront for all patients with AML (see *Role of MRD Monitoring*).

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 rates, relapse risks, and 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).[20-22] In an analysis of data from pediatric and adult patients with AML (N = 1612) enrolled in the United Kingdom Medical Research Council (UK MRC) AML 10 trial, the 5-year survival rates for those with favorable, intermediate, and unfavorable risk cytogenetics were 65%, 41%, and 14%, respectively.[21] 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, and adverse risk cytogenetics were 55%, 38%, and 11%, respectively.[22] 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.[20] The AML 11 trial had similar results with 5-year survival of the favorable, intermediate-risk, and poor-risk cytogenetics of 34%, 13% and 2%, respectively. This last study included an older population of patients which is believed to attribute to the overall lower percent survivals in all groups.

The importance of obtaining adequate samples of marrow or peripheral blood at diagnosis for full karyotyping and 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, additional tests are needed to provide a full picture of the genetic factors that contribute to risk (see *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.[23-25] Data from 3 large studies have identified monosomal karyotypes (defined as having ≥2 autosomal monosomies, or a single monosomy with additional structural abnormalities) as a subset of unfavorable cytogenetic prognosticators. Although complex karyotype (having ≥3 clonal cytogenetic abnormalities) and either monosomy 5 or monosomy 7 are categorized as high-risk/unfavorable cytogenetics, 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-Swiss cooperative groups (HOVON/SAKK), the correlation between cytogenetics and OS outcomes in patients aged 60 years or younger with AML (N = 1,975) was evaluated. The 4-year OS rate in

patients with monosomal karyotype was 4% compared with 26% in those with complex karyotype (but without monosomal karyotype).[23]

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.[24] 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.[24] 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 in 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.[25]

These studies show that monosomal karyotype, independent of other unfavorable cytogenetic factors, confers very poor prognosis. 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 nor 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.[20,21] However, even in patients with normal karyotype AML (NK-AML), clinical outcome is heterogeneous.

Molecular profiling is increasing the ability to identify mutations that 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.[26-37] Tests for these molecular markers are becoming more common in commercial reference laboratories and in referral centers. Therefore, it is important for physicians to obtain reserve aliquots of cryopreserved marrow from the time of diagnosis 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 *NPM1* gene (28%–35%)[36,38,39] encoding a shuttle protein within the nucleolus and mutations of the *FLT3* gene (37%–46% of patients) encoding a receptor tyrosine kinase involved in hematopoiesis[30,39,40]. The *NPM1* mutation has been shown to be associated with NK-AML with a reported frequency of 48% to 53%.[28,34,40] 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 that are NK-AML and wild-type *NPM1*, resulting in outcomes similar to patients with favorable cytogenetics (eg, CBF AML).[28,29,34,36,37] 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.[41-46] *FLT3*-ITD occurs in approximately 30% of cases and is more common than *FLT3*-TKD mutations, which occur in approximately 10% of patients.[26,30,40,45-49] 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 who have wild-type *FLT3*.[26,30,42,43,45,47,48,50] Among patients with *FLT3*-ITD and NK-AML, median OS from the time of diagnosis ranged from 6 to 12 months.[26,30,45,48]

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 wild-type *FLT3* patients with or without *FLT3*-ITD.[45] The *FLT3*-TKD mutations predominantly occur independently of *FLT3*-ITD, and most frequently involve mutations in the D835 residue of a TKD. 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,[30,42,46,49] other studies have reported no impact of *FLT3*-TKD on prognosis[40,50,51] or even a favorable outcome on OS with *FLT3*-TKD mutations.[52] In the latter study from the UKMRC, 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).[52]

The discrepant findings from these studies may be a result of important differences 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.[40,51] Moreover, *FLT3*-TKD mutation as the sole genetic aberration or occurring concurrently with t(15;17)/promyelocytic leukemia (PML)-retinoic acid receptor alpha (RARA) (underlying lesion in the APL subtype) or with *FLT3*-ITD (*FLT3* double mutation) has been associated with poorer outcomes. [40,51]

Another mutation associated with prognosis is the *CEBPA* gene that encodes for CCAAT/enhancer binding protein alpha (C/EBPα), a transcription factor that plays a key role in the differentiation of granulocytes.[32] 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*.[31,39,40,53-55] One caveat identified in a recent study is 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-mutant-positive, single mutation, and wild-type CEBPA genes were 54%, 31%, and 34%, respectively.[54]

Recently, other common molecular lesions with prognostic impact have been identified in patients with AML. The most common of these

include mutations in the *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%).[39,56-61] *IDH1* mutation was found to occur concurrently with NK-AML and *NPM1* mutations.[56-59,61] 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).[59]

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,[56-59] *IDH1* mutations seemed to be associated with significantly worse outcomes in the subgroup of patients with NK-AML with favorable- or intermediate-risk disease.[56,59,61] In the subgroup of patients younger than 60 years with favorable-risk AML (*NPM1* mutation without *FLT3*-ITD), *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*.[59] In another study, *IDH* mutations (*IDH1* and *IDH2* combined) were associated with significantly inferior 5-year RFS 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).[61] 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 RFS analysis.[61] *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).[56] Mutations in *IDH2* have been reported in 8% to 12% of patients with AML,[39,56,57,61,62] with a frequency of 19% reported among those with normal karyotype.[59] The presence of *IDH2* mutations was mutually exclusive with *IDH1* mutation in nearly all cases.[56,57,59] Mutations have been identified in R172 and R140 of the *IDH2* gene, with R140 mutation occurring more frequently.[59,61,62] Interestingly, the *IDH2*-R172 mutation seemed to be mutually exclusive with *NPM1* mutations and *FLT3*-ITD.[59,61,62]

Reports on the prognostic effect of *IDH2* mutations have also been inconsistent. Some studies have reported the lack of prognostic value of *IDH2* mutations,[56,57,61] whereas others have reported favorable outcomes with *IDH2* mutations.[39,62] In one study, an association was found between *IDH2* mutations and poorer prognosis in the subgroup of patients with NK-AML and otherwise favorable risk (*NPM1* mutation without *FLT3*-ITD).[61] 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).[39] 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.[39] The conflicting findings from the above studies require further investigation.

The *DNMT3A* mutations have been reported in 18% to 22% of patients with AML,[39,63,64] with a frequency of 29% to 34% in those with NK-AML.[65-67] R882 is the most commonly mutated residue. This mutation has also been observed in conjunction with *NPM1* mutations and *FLT3*

mutations.[64,66,67] 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,[39,66] whereas other studies have shown a negative prognostic effect in the overall population or specific subgroups.[63-65,67] Studies have shown significantly decreased OS outcomes among patients with *DNMT3A* mutations compared with patients who have the wild-type gene (median OS, 12–21 vs. 40–41 months).[63,64] Significantly decreased OS with *DNMT3A* mutations has also been reported in the subgroup of patients with NK-AML who have 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.[64] 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%; $P = .02$).[67] 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.[65] 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%; $P = .01$).[65] The authors concluded that the prognostic relevance of *DNMT3A* mutations may depend on age and mutation type. Currently, the interactions of *IDH1* or *IDH2* and *DNMT3* mutations with other molecular changes require further investigation to determine the prognostic value in patients with NK-AML. None 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*.[68,69]

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.[28,34] Thus, *NPM1* mutation confers favorable prognosis only in the absence of *FLT3*-ITD.[40] Similarly, the benefit in OS outcomes seen with *CEBPA* mutations seems to be lost in the presence of concurrent *FLT3*-ITD.[54] 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.[51]

Both NCCN and the European LeukemiaNet (ELN) classify patients with NK-AML and mutated *NPM1* or *CEBPA* (without *FLT3*-ITD) as having favorable risk.[70,71] 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).[70,71] ELN classifies patients with t(9;11)(p22;q23), *MLLT3-MLL*, and other cytogenetic abnormalities that fall into neither the favorable nor 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 RFS 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).[71] In this analysis, median OS between the Intermediate I and Intermediate II groups was 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).[71] However, based on the substantial difference in RFS data between the Intermediate I and Intermediate II groups defined by ELN, 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).

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.[27,33,35] *c-KIT* mutations have been reported in approximately 20% of patients with CBF AML.[33,72] Studies have shown that *c-KIT* mutations are associated with decreased remission duration (eg, EFS and RFS) and decreased OS in both groups of patients with t(8;21) or inv(16).[27,33,35,72] 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 in prospective trials (n=176).[73] 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.[73] Of these secondary genetic lesions, *KIT* mutation and trisomy 22 were significant independent factors predictive of RFS in multivariable analysis; *FLT3* mutations, trisomy 22, and trisomy 8 were significant independent predictors for OS.[73] These studies demonstrate the importance of secondary genetic mutations in the prognostic classification of patients with otherwise favorable-risk CBF AML as evidenced by the classification of patients with t(8;21) or inv(16)/t(16;16) with *c-KIT* mutation as intermediate-risk AML (see *Risk Status Based on Validated Cytogenetics and Molecular Abnormalities* on page AML-A).

Despite emerging data 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 has yet to be defined. Therefore, these molecular markers have not been incorporated into the current risk categorization schema. Although none of the genetic abnormalities discussed earlier affects the initial course of AML treatment, each provides 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 (eg, 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; however, failure to achieve remission after 1 cycle of induction therapy or high tumor burden, defined as a WBC ≥100,000/mcL, are included as poor-risk factors for long-term remission. Therefore, response is assessed based on bone marrow morphology and cytogenetic and molecular responses taken at several points during the course of treatment (see *Response Criteria for Acute Myeloid Leukemia* and *Monitoring During Therapy* 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 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 is a particularly aggressive subtype of AML, comprising approximately 10% of AML cases. APL has a distinct morphology and clinical presentation that may be associated with high early death rate due to potentially fatal coagulopathy.[74-76] In a recent analysis of data (from 1992 to 2007) from the National Cancer Institute SEER registry, the age-adjusted annual incidence rate of APL was 0.23 per 100,000 persons.[77] The median age of APL diagnosis was 44 years, which is younger than that of patients with AML (median age 67 years).[77,78] APL is cytogenetically distinguished by the t(15;17) chromosomal translocation. The translocation of the *PML* gene on chromosome 15 to the *RARA* gene on chromosome 17 [ie, t;(15;17)(q24.1;q21.1)] produces a *PML-RARA* fusion gene that can be quantitatively monitored using polymerase chain reaction (PCR) to document disease burden and to ultimately confirm molecular remission. 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 subtype. 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 screen should promptly start ATRA 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 will be continued.

Induction Therapy for Patients with APL

The evolution of treatment strategies for APL built on clinical observation and well-constructed clinical trials represent 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.[79] 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.[80,81] Induction regimens with ATRA combined with anthracyclines (with or without cytarabine) are associated with CR rates exceeding 90%, as demonstrated in several large cooperative group trials.[82-85] Using ATRA-based induction regimens followed by consolidation with regimens containing either ATRA with anthracyclines, or cytarabine with anthracyclines, more than 80% of patients with APL can be cured of their disease.[82,84-86] Risk stratification is a major consideration in the treatment of APL (see *APL Classification* on page AML-2).[85] Patients with low- or intermediate-risk disease (WBC count ≤10,000/mcL) are typically treated with less intensive consolidation regimens compared with regimens used for high-risk patients (WBC count >10,000/mcL) depending upon the treatment protocol used.

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.[87,88]

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% to 95% and thereby raised the question of whether there was a need for cytarabine in APL induction.[89,90] 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. [89,90] In the PETHEMA trial, the 2-year OS rate was 82%.[90] It had been commonly observed that patients with elevated WBC had high-risk disease based on both the higher number of deaths during induction and the 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 (≤10,000/mcL and platelets >40,000/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 than10,000/mcL, age older than 60 years, creatinine 1.4 or greater, and male sex.[91,92] In 2006, Ades et al reported the outcome of the French APL 2000 trial (N = 340) in which patients younger than 60 years of age with WBC counts less than 10,000/mcL were randomized to receive ATRA (45 mg/m^2) and daunorubicin (60 mg/m^2 per day for 3 days) as induction therapy with or without cytarabine (200 mg/m^2 per day for 7 days). Those randomized to cytarabine in induction also received cytarabine during consolidation.[93] Patients with WBC greater than 10,000/mcL or older than 60 years of age all received cytarabine. While the CR rates were similar between the randomized groups (99% with cytarabine 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/mcL, the CR rate was 97% and the 2-year EFS rate was 89% for those younger than 60 years of age and 79% for those older than 60 years of age.[93] A report of a joint analysis of the outcomes in the PETHEMA 99 and the French APL 2000 trials in patients younger than 65 years of age showed that in patients with WBC count less than 10,000/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).[83] However, for patients with WBC count greater than 10,000/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).[83] The second North American Intergroup trial also used ATRA (45 mg/m^2), daunorubicin (50 mg/m^2 per day for 4 days,) and cytarabine (200 mg/m^2 per day for 7 days) with a similar initial CR rate (90%).[84] 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.

ATO has been found to be a potent promoter of apoptosis in APL cells.[94,95] In 2004, Shen et al first published outcomes using single-agent ATRA; single- agent ATO; or the combination of both drugs.[96] 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 RFS (after a median follow-up of 18 months) was improved with the combination regimen compared with the monotherapy regimens.[96] Subsequently, Estey et al used a similar combination of ATRA and ATO to treat patients with low-/intermediate-risk APL.[97] High-risk patients in the same study were treated using the ATRA and ATO combined with gemtuzumab ozogamicin 9 mg/m^2 on day 1 of induction therapy. 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%.[98] 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 United States 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).[99] Patients received 1 cycle of induction therapy with ATRA (45 mg/m^2 days 1–36 in divided doses), age-adjusted idarubicin (6–12 mg/m^2 days 2, 4, 6, and 8), and ATO (0.15 mg/kg days 9–36 as a 2-hour IV infusion). All patients received prednisone (1 mg/kg/day for at least 10 days) regardless of initial WBC count as prophylaxis for differentiation syndrome.[99] The most common grade 3 or 4 non-hematologic adverse events during induction included infections (76%; including febrile neutropenia), hepatic toxicity (44%), gastrointestinal toxicity (28%), metabolic abnormalities (16%), and prolonged QTc interval (14%); grade 3 or 4 differentiation syndrome occurred in 14% of patients. 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.[99] Grade 3 or 4 adverse

events occurred primarily during induction (as above); the most common grade 3 or 4 events during consolidation (cycle 1) included infections (19%) and hepatic toxicity (12%), and no deaths occurred during consolidation cycles. The hematologic CR rate after induction was 95%; early death (during induction) occurred in 3% of patients. The 2-year DFS and failure-free survival rates were 97.5% and 88%, respectively. The 2-year OS rate was 93%.[99]

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).[100] Patients in Arm A received ATRA (45 mg/m^2) 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.[86] In addition, all patients received prednisone (0.5 mg/kg/day from day 1 until the end of induction) as prophylaxis for differentiation syndrome. The primary endpoint of this study was the 2-year EFS rate. Among evaluable patients (n = 156), CR rates were not different between Arm A and Arm B (100% vs. 95%). After a median follow-up period of 34.4 months, the 2-year EFS rate was significantly higher in Arm A compared with Arm B (97% vs. 86%; $P < 0.001$ for non-inferiority; $P = .02$ for superiority). The 2-year OS probability was also significantly higher in Arm A compared with Arm B (99% vs. 91%; $P = .02$). Four patients in Arm B died during induction therapy (2 deaths were caused by differentiation syndrome). One patient in Arm A and 3 patients in Arm B died during consolidation. Grade 3 or 4 neutropenia and thrombocytopenia lasting more than 15 days were significantly more frequent in Arm B compared with Arm A throughout induction and consolidation cycles. Grade 3 or 4 hepatic toxicities occurred significantly more frequently in Arm A compared with Arm B (63% vs. 6%; $P < .001$).[100]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 (with the addition of idarubicin for high-risk patients only); ATRA + daunorubicin [50 mg/m^2 × 4 days] + cytarabine; or ATRA + daunorubicin [60 mg/m^2 × 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. With the advances in treatment regimens, the panel emphasizes the importance of receiving treatment from an established treatment center, regardless of risk stratification, for the monitoring and treatment of adverse events. 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 ≤10,000/mcL), the panel recommends initial induction with ATRA plus ATO[100] (category 1); ATRA plus idarubicin alone[85] (category 1); ATRA plus daunorubicin and cytarabine [81,83,84] (category 1 for those on French APL 2000 protocol[83]); or enrollment in a clinical trial.

For high-risk patients (WBC counts >10,000/mcL), the NCCN AML Panel historically has recommended a regimen that includes cytarabine along with ATRA plus daunorubicin (PETHEMA LPA99 trial) over ATRA plus idarubicin (APL2000 trial) because of higher CR and 3-year OS rates.[83,85] To improve patient outcome, the PETHEMA LPA99 trial and the GIMEMA AIDA-0493 study were modified to incorporate the combination of ATRA with cytarabine either during induction (LPA2005)[85] or during consolidation (AIDA-2000).[86] The improved outcomes in both these studies suggest a supra-additive effect with ATRA plus cytarabine, independent of the anthracycline. Recently, the APML4 trial has shown the benefit of induction that includes ATRA and ATO. Unlike the other regimens, the APML4 trial does not use cytarabine during induction. In light of these new studies, the panel recommends initial induction with ATRA plus daunorubicin and cytarabine [81,83,84]; ATRA plus idarubicin alone[85]; ATRA plus idarubicin and ATO[100]; or enrollment in a clinical trial. In addition, the panel recommends the administration of prophylactic corticosteroids (eg, dexamethasone) in patients with a WBC count greater than 10,000/mcL (or in patients receiving induction with both ATRA and ATO, regardless of WBC count) to prevent differentiation syndrome (see *Supportive Care* on page AML-C). For patients with high-risk APL who cannot tolerate anthracyclines, the Guidelines list induction and consolidation regimens using ATRA plus ATO as an alternative (see *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 days 7 to 14 post induction are misleading and may lead to overtreatment. 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, LP should be considered at count recovery following induction therapy, before proceeding with consolidation.[101] Many 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. Consolidation regimens employing ATO will require monitoring of QTc interval and optimizing electrolytes (see *Supportive Care* on page AML-C and *Supportive Care for Patients with APL*).

The goal of consolidation therapy for APL is a durable molecular remission. Data from the two sequential PETHEMA trials,[90-92] 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^2) 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.[92] 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.[92] 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.[92] 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.[85] 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^2/day for 5 days to 10 mg/m^2/day for 3 days in cycle 2) and a small reduction of idarubicin dose between low- and intermediate-risk groups (from 7 mg/m^2/day for 4 days to 5 mg/m^2/day for 4 days in cycle 1; from 2 doses of 12 mg/m^2/day to 1 dose of 12 mg/m^2/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 regard to 3-year cumulative incidence of relapse (6% vs. 6%), 3-year DFS (93% vs. 94%), and 3-year OS rate (96% vs. 93%).[85] 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.[86] 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^2 for 15 days + idarubicin 5 mg/m^2 for 4 days in cycle 1; ATRA for 15 days and mitoxantrone 10 mg/m^2/day for 5 days in cycle 2; and ATRA for 15 days and idarubicin 12 mg/m^2 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.[86]

In the European APL 2000 trial, 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.[93] Long-term follow up from this study showed that in patients with standard risk, the addition of cytarabine substantially reduced cumulative incidence of relapse (7-year relapse rate 13% vs. 29%; P = .0065) and increased 7-year EFS rates (83% vs. 65%; P = .0029) compared with the regimen without cytarabine.[102] A poorer response was seen in patients who did not receive cytarabine despite maintenance treatment of continuous 6-mercaptopurine plus methotrexate and intermittent ATRA. Furthermore, all high-risk patients received cytarabine during induction and consolidation resulting in a 7-year relapse rate, EFS rate, and OS rate of 7.1%, 82.2%, and 87.6%, respectively, an outcome that was slightly improved over standard-risk patients treated without cytarabine. Although the results of the European APL 2000 trial are limited by the use of a single anthracycline in all study arms, the data support the use of cytarabine in standard-risk APL when the anthracycline is daunorubicin.

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.[84] 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.[84] 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 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).[103,104] 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.[103] In the second interim analysis, the only change was a decrease of idarubicin during second consolidation. Data from this analysis show a 99.4% CR across all groups encompassing a total of 347 patients.[104] While the two-year EFS and OS were above 95% for all three groups, there was a reduction of myelosuppression in the group treated with IDA-ATRA compared to IDA-AraC and IDA-ATO, which had similar durations.[104] The potential benefits of the use of ATO or ATRA 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.[99] 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%.[99] 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).[105] Patients in the AIDA arm received 3 cycles of anthracycline-based consolidation combined with ATRA and then maintenance with low-dose chemotherapy and ATRA.[86] 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.[105]

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;[93] cytarabine with ATRA and idarubicin as used in the PETHEMA LPA 2005 trial[85] and the GIMEMA AIDA-2000 trial;[86] or 2 cycles of ATO followed by 2 additional cycles of standard chemotherapy as used in the US Intergroup trial for consolidation.[84] When using a cytarabine-containing regimen, dose adjustments of cytarabine may be needed for older patients or for patients with renal dysfunction.[83,84] 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.[97,98] 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^2 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.[100] 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 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- to 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 that showed superior RFS 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. [87] 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%.[87] 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 ($P < .001$).[82] Patients considered to be at high risk (WBC count >5000/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 ($P < .001$).[82]

The first US Intergroup trial showed superior DFS outcomes for patients receiving maintenance ATRA compared with no maintenance.[81] 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.[81] Thus, the incorporation of ATRA during induction and maintenance appeared to improve long-term remission durations. It should be noted that in the above US Intergroup trial, molecular remission status was not assessed prior to randomization to maintenance treatment.

The Japanese APL97 randomized study evaluated the role of maintenance with intensified chemotherapy compared with observation in patients with APL who were in molecular remission following consolidation (n=175).[106] The estimated 6-year DFS was not significantly different between the chemotherapy maintenance and observation arms (63% vs. 80%). In fact, the estimated 6-year OS was significantly lower with maintenance (86% vs. 99%; $P= .014$), which the investigators attributed to possible effects of chemotherapy maintenance on development of secondary malignancies and responses to subsequent (second-line) therapies.[106]

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.[107,108] In this trial, ATRA was not given during consolidation. The above studies have not demonstrated long-term benefit with the use of maintenance therapy in patients who achieve molecular remission following consolidation therapy. 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. Further data from randomized trials are needed to address the question of maintenance. 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). No benefit for maintenance was observed.[109] 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 the 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 monitoring of marrow samples is a more sensitive technique and may detect 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 2 to 4 weeks. If molecular relapse is confirmed by a second positive test, patients should be treated for relapsed disease (see *Therapy for 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 bone marrow aspirate is recommended to assess for new cytogenetic abnormalities, as secondary MDS and AML can occur following APL therapy.

Management of Relapsed APL

ATO has been 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.[95,110-112] In a retrospective analysis of patients with APL who relapsed after first-line therapy with ATRA combined with chemotherapy (n=23), salvage therapy with ATO-containing regimens (ATO monotherapy, n=20; ATO combined with ATRA and anthracycline, n=2; ATO combined with mitoxantrone, n=1) resulted in hematologic CR in 95% and molecular remission in 83% of patients.[113] ATRA and ATO appear to be synergistic and one could consider using the combination in patients who had not received ATRA during consolidation.[94-96] However, in a small randomized study of patients with relapsed APL (N = 20), all patients previously treated with ATRA-containing chemotherapy showed no improvement in response by adding ATRA to ATO compared with ATO alone.[114] 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% (both for hematologic CR and molecular remission) among patients who were retreated with ATO combined with ATRA (with or without anthracyclines) after a relapse following first-line therapy with single-agent ATO (n = 14).[113] For patients with APL who relapse after an initial CR to first-line therapy with ATRA-containing regimens (no prior ATO) or who experience a late relapse (≥6 months) to ATO-containing regimens, ATO with or without ATRA is recommended as first salvage therapy. For patients who experience an early relapse (<6 months) after an initial CR to ATO-containing first-line regimens (but with no anthracyclines or only limited cycles of anthracyclines), it would be reasonable to consider salvage therapy with ATRA combined with idarubicin, with or without ATO. In the rare instance of a patient who presents with an early relapse after ATO- and anthracycline-containing regimens, it is recommended that the patient receive salvage therapy with ATO with or without ATRA until count recovery with marrow confirms remission. After 2 cycles, if the patient does not enter molecular remission, a

matched sibling or alternative donor HSCT or clinical trial is recommended.

A small percentage of relapsed APL has a CNS component.[115,116] 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 RFS (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).[117] Among patients who received a PCR-negative autograft, the 7-year RFS 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%).[117] 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 regard 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.[118] 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.[113] 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 a 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.[113] The authors concluded that consolidation with autologous HSCT was superior to ATO-containing maintenance alone in patients who achieved molecular remission after relapse. A recent abstract presented at the 2013 American Society of Hematology meeting reported results of a registry study suggesting that long-term survival is possible without transplantation (3-year OS 66%); however, transplant seems to improve outcome (3-year OS 82%)[119]

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 receiving ATRA-containing therapy develop this syndrome.[120,121] Patients may begin to develop evidence of differentiation syndrome early in the treatment with either ATRA or ATO as single agents or in combination. 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.[92,122] Kelaidi et al assessed the outcomes of patients with high WBC (>10,000/mcL) enrolled in APL 93 and APL 2000.[123] A key difference between these two trials 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 a patient with a WBC count greater than 10,000/mcL or first signs or symptoms of differentiation syndrome, the NCCN AML Panel recommends treating with dexamethasone 10 mg twice a day for 3 to 5 days, then tapering the dose over 2 weeks (see *Supportive Care* on page AML-C). ATRA may need to be withheld 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 older than 40 years. For induction regimens that include both ATRA and ATO, prophylaxis with corticosteroids (eg, dexamethasone, prednisone) should be given for (at least) the first 5 days of induction therapy (see *Supportive Care* on page AML-C). It is recommended that the prophylaxis regimen follow the specific treatment protocol used. In the Australia/New Zealand study that evaluated induction with ATO added to a backbone of ATRA and idarubicin (phase II APML4 trial), all patients received prednisone (1 mg/kg/day for at least 10 days) as prophylaxis for differentiation syndrome regardless of initial WBC count (see *Treatment Induction (High Risk)* on page AML-3).[99] In the Italian-German Cooperative Group study that evaluated ATRA combined with ATO versus the AIDA regimen (phase III APL0406 trial), patients received prophylaxis with prednisone (0.5 mg/kg/day) from day 1 until the end of induction (see *Treatment Induction (Low/Intermediate Risk)* on page AML-4).[100] If a patient develops differentiation syndrome, it is recommended that treatment be changed from prednisone to dexamethasone 10 mg every 12 hours until acute differentiation resolves. The patient may then be returned to the previous prednisone dose.[100]

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 concentration as part of the initial workup 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 by maintenance 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 ≥9.0, K ≥4.0, Mg ≥1.8) in the upper normal range. Other drugs that prolong the QT interval should be avoided during ATO 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. These patients also received a higher dose of cytarabine (2 g/m^2) during consolidation (in cycle 2) as compared with 1 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. In general, it is recommended that 4 to 6 doses of intrathecal chemotherapy be given during consolidation for high-risk patients with APL. For example, 2 doses of intrathecal chemotherapy for each consolidation cycle may be one recommended approach for CNS prophylaxis. Intrathecal chemotherapy may include agents such as methotrexate, cytarabine, liposomal cytarabine, alone or combined with corticosteroids; the choice of single drug versus combinations may vary based on clinical situation and institutional practice.

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.[124] 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 used for patients younger than age 60 years 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 mg/m^2 × 3 days. Idarubicin, which has a longer intracellular retention time, used at doses of 12 mg/m^2 × 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 mg/m^2 × 3 days (n=327) versus 45 mg/m^2 × 3 days (n = 330) in patients with previously untreated AML younger than 60 years.[125] 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.[125] In a European trial that compared idarubicin 12 mg/m^2 × 3 or 4 days versus daunorubicin 80 mg/m^2 × 3 days in patients between ages 50 and 70 years, CR rates were 83% and 70%, respectively (P = .024).[126] 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 (100–200 mg/m^2 continuous infusion) × 7 days combined with either idarubicin (12 mg/ m^2 for 3 days) or escalated daunorubicin (90 mg/m^2 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).[127] In this study, patients were randomized to the following treatment arms: daunorubicin and cytarabine (daunorubicin 60 mg/m^2 × 3 days and cytarabine 200 mg/m^2 continuous infusion × 7 days; DA arm); DA with addition of cladribine (5 mg/m^2 × 5 days; DAC arm); and DA with addition of fludarabine (25 mg/m^2 × 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^2 days 1–3) and mitoxantrone (10 mg/m^2 days 3–5), followed by a course of high-dose cytarabine (2 g/m^2 every 12 hours on days 1, 3, and 5).[127] A similar proportion of patients in the 3 arms proceeded with allogeneic HSCT. The DAC regimen resulted in a 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 × 10^9/L or greater, and patients with high-risk karyotype.[127] 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 were observed among patients with high-risk karyotype. The incidence of hematologic toxicities and other adverse events were similar between treatment arms.[127] 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[128] or topotecan[129]) 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,[130,131] patients younger than 60 years were randomized (N = 301) to receive either high-dose cytarabine (3 g/m^2 every 12 hours on days 1, 3, 5, and 7 for a total of 24 g/m^2) or standard cytarabine therapy (100 mg/m^2/d × 7 days via continuous infusion); patients in both arms received daunorubicin (50 mg/m^2 on days 1–3) and etoposide (75 mg/m^2/day × 7 days). The CR rates were equivalent in both arms (71% and 74%, respectively), with significantly higher 5-year RFS rates with high-dose cytarabine (48% vs. 25%; *P* = .007).[131] 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.[130] 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% in the standard-dose arm.[131]

In a large SWOG study,[132] patients younger than 65 years (N = 665) were randomized to receive high-dose cytarabine (2 g/m^2 every 12 hours × 6 days for a total of 24 g/m^2; patients aged <50 years were initially randomized to receive 3 g/m^2 at the above schedule before the high-dose arm was redefined to 2 g/m^2 because of toxicity concerns) or standard-dose cytarabine (200 mg/m^2/d × 7 days); patients in both treatment arms also received daunorubicin (45 mg/m^2/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).[132] 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^2 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^2 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.[132]

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).[132] 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.[132] 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,[133] 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^2 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.[133]

Because the OS outcomes for the high-dose arm in the SWOG trial consisting of 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.[134] No data are available using more than 60 mg/m^2 of daunorubicin or 12 mg/m^2 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 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.[135]

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 11q23 abnormalities, monosomy -5 or -7 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, it is particularly important that this poor-risk group of patients 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. [136]

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.[127] For those with significant residual blasts, escalation to high-dose cytarabine (2 g/m^2 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 initiation of salvage regimens (see *Postremission Surveillance and 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 *Postremission Surveillance and 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. 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. As above, if the patient has a hypoplastic marrow with a small quantity of residual blasts, additional therapy may be delayed for an additional 10 to 14 days and the marrow status reassessed before embarking on salvage therapy.

Occasionally, patients with both myeloid and lymphoid markers at diagnosis (biphenotypic leukemia) may experience response to ALL therapy if an AML induction regimen failed.[4] 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 CR 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^2, 400 mg/m^2, and 3 g/m^2 doses of cytarabine.[133] The 4-year DFS rate for patients receiving consolidation with 3 g/m^2 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 RFS (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 RFS rate was 78% for CBF AML, 40% for normal karyotype, and 21% for other cytogenetic categories.[135] Notably, 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.[33] 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%).[33] 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.[133] 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).[137] Patients were randomized to treatment with an "intermediate-dose" cytarabine regimen (cycle 1: cytarabine, 200 mg/m^2 × 7 days + idarubicin, 12 mg/m^2 × 3 days; cycle 2: cytarabine, 1 g/m^2 every 12 hours × 6 days + amsacrine, 120 mg/m^2 × 3 days) [12 g/m^2 cytarabine] or a "high-dose" cytarabine regimen (cycle 1: cytarabine, 1 g/m^2 every 12 hours × 5 days + idarubicin, 12 mg/m^2 × 3 days; cycle 2: cytarabine, 2 g/m^2 every 12 hours × 4 days + amsacrine, 120 mg/m^2 × 3 days) [26 g/m^2 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.[137] A similar proportion of patients in each treatment arm received consolidation, specifically 26% to 27% of third chemotherapy cycle patients, 10% to 11% of autologous HSCT patients, and 27% to 29% of allogeneic HSCT. 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%).[137] These results are comparable to those from the CALGB study with high-dose cytarabine.[133] 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).[137] 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%).[137] This study suggests that 2 cycles of intermediate-dose cytarabine (1 g/m^2 every 12 hours × 6 days; total dose 12 g/m^2 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^2 for 6 doses; total dose of 18 g/m^2 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 at initial consolidation whenever possible.

Previous versions of these guidelines have used cytogenetics as the major defining criteria for risk of relapse including chromosomal deletions, duplications, or substitutions. 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 years 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).[138] 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 patients 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).[22] 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.[139] 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 3 to 4 cycles of high-dose cytarabine afforded a lower risk of relapse and a somewhat higher DFS as consolidation for most patients with intermediate-risk cytogenetics. While 3 g/m^2 high-dose cytarabine is preferred, a range of 1 to 3 g/m^2 can be used to address patients who are less fit. The role of autologous HSCT in the intermediate-risk group outside of clinical trials is diminishing due to improvements in allotransplants, which are expanding the pool of potential donors outside the family setting. While autologous HSCT is still incorporated into the clinical trial design in Europe, this year the consensus of the NCCN AML Panel was that autologous HSCT should not be a recommended consolidation therapy outside that context. 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).[22] 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.[139] 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).[138] 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.[138] Other options for this group include clinical trials or multiple courses (3–4) of high-dose cytarabine consolidation.[140] Alternative regimens incorporating intermediate doses of cytarabine (1–2 g/m^2) 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%).[140] 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.[28] The presence of an isolated *NPM1* or *CEBPA* mutation improves prognosis only slightly less than for patients with CBF translocations (see *Evaluation of Acute Leukemia* 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[35] 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, for 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), RFS was more favorable with allogeneic HSCT (94 vs. 7.9 months without allogeneic HSCT).[71] 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.

Three tyrosine kinase inhibitors (TKIs) approved for other malignancies have in vitro activity against FLT3 – sunitinib, sorafenib, and ponatinib.[141-143] Phase II clinical trials have only evaluated the benefit of sorafenib in AML. Data from a phase I/II study of sorafenib in combination with idarubicin and cytarabine in younger patients showed improved CR rate, particularly in FLT3-mutated patients; however, CR duration and OS were not significantly improved.[144] A more recent phase II study from this group combined sorafenib with azacytidine to show that the combination was well-tolerated and that it led to improved survival.[145] The use of sorafenib in combination with chemotherapy was also studied in a randomized, placebo-controlled trial in elderly patients with AML. There was no improvement in EFS or OS and increased toxicity was observed.[146] Despite the latter study, greater investigation into the use of TKIs in patients of poor-risk disease is warranted. 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.[138] 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).[22]

The panel uniformly endorsed clinical trial participation or allogeneic HSCT with matched sibling or matched unrelated donor (including umbilical cord blood products) 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 Acute 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.[124,129] 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 rely 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.[147] 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.[147] 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, and >72 years), and type of leukemia (de novo, secondary). The algorithm can be accessed online at http://www.aml-score.org/.

Older adults with intact functional status (ie, ECOG score 0–2), minimal comorbidity, and non-adverse 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^2 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 non-adverse 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^2 × 3 days or intensified with 12 mg/m^2 × 4 days) compared with high-dose daunorubicin (up to 80 mg/m^2) yielded a significantly higher CR rate in patients aged 50 to 70 years (80% vs. 70%, respectively; *P* = .03). [126] 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.[126] The French ALFA-9803 study (N = 416) evaluated (during first randomization) induction with idarubicin (9 mg/m^2 × 4 days) compared with daunorubicin (45 mg/m^2 × 4 days) in patients aged 65 years or older.[148] In this trial, the CR rate after induction was 57% and induction death occurred in 10% of patients. The medial OS for all patients was 12 months; the estimated 2-year OS rate was 27%. No significant differences in these outcomes were seen between anthracycline treatment arms.[148] Long-term outcomes based on a combined analysis of data from the two French ALFA trials above (9801 and 9803 studies; N = 727) showed superior results with standard idarubicin induction (36 mg/m^2 total dose) compared with daunorubicin induction (240 mg/m^2 total dose for patients <65 years; 180 mg/m^2 total dose for patients ≥65 years) in older patients with AML (age ≥50 years).[149] At a median actuarial follow-up of 7.5 years, the median OS for all patients included

in the analysis was 14.2 months. The estimated 5-year OS rate was 15.3% and the overall cure rate was 13.3%. Induction with standard idarubicin was associated with a significantly higher cure rate compared with daunorubicin (16.6% vs. 9.8%; *P* = .018). In the group of patients younger than age 65 years, standard idarubicin was still associated with a significantly higher cure rate than daunorubicin despite the high dose (240 mg/m^2 total dose) of daunorubicin (27.4% vs. 15.9%; *P* =.049).[149]

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^2 × 3 days; n = 411) or dose-escalated daunorubicin (90 mg/m^2 × 3 days; n = 402), the CR rate was 54% and 64%, respectively (*P* = .002).[150] 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 mg/m^2 × 3 days) from the ALFA-9801 study, in which the 4-year EFS and OS rates were 21% and 32%, respectively.[126] 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.[150]

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.[151,152] 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 mg/m^2 × 3 days) and cytarabine (200 mg/m^2 continuous infusion × 7 days), with or without (control arm) fractionated gemtuzumab ozogamicin 3 mg/m^2 given on days 1, 4 and 7.[152] 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 mg/m^2 on day 1). The CR/CR with incomplete platelet recovery (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.[152] The gemtuzumab ozogamicin arm was associated with a higher incidence of hematologic toxicity (16% vs. 3%; *P* <.0001); this was not associated with an increase in the risk of death from toxicity.[152] 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) with or without (control) gemtuzumab ozogamicin (3 mg/m^2 on day 1 of course 1 of induction).[151] 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/CR incomplete (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.[151]

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 United States 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, older patients (n=112; age >60 years; median age 71 years), most of whom had additional risk factors, received clofarabine, 30 mg/m^2 intravenously for 5 days.[153] CR/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.[153] In a pooled analysis of data from two European phase II studies that also evaluated first-line clofarabine (30 mg/m^2 intravenously for 5 days, up to 4–6 courses) in older patients considered unsuitable for intensive chemotherapy (age ≥60 years; median age 71 years), monotherapy with clofarabine resulted in a CR in 32% of patients.[154] An additional 16% achieved CR with incomplete recovery of peripheral blood counts. Unfavorable risk cytogenetics were present in 30% of patients, and 36% had a WHO performance status score of 2 or worse. The 30-day mortality rate was 18% in this analysis. The median OS for all patients was 19 weeks; the median OS among the patients achieving a CR was 47 weeks.[154] A recent randomized trial from the United Kingdom National Cancer Research Institute (UK NCRI) compared the efficacy and safety of first-line therapy with clofarabine (20 mg/m^2 intravenously for 5 days, up to 4 courses) versus low-dose cytarabine (20 mg twice daily subcutaneously for 10 days, every 6 weeks up to 4 courses) in previously untreated older patients with AML and high-risk MDS (n=406; median age 74 years).[155] Treatment with clofarabine resulted in significantly higher overall response rate (ORR) (38% vs. 19%; $P < .0001$) and CR rate (22% vs. 12%; $P = .005$) compared with subcutaneous (low-dose) cytarabine. However, no differences were observed in the 2-year OS rate (13% vs. 12%, respectively). The 30-day mortality rate (induction death) was not significantly different (18% vs. 13%, respectively). Treatment with clofarabine was associated with significantly higher incidences of grade 3 or 4 gastrointestinal toxicities and hepatic toxicity, as well as higher mean number of days in the hospital and days on antibiotics, compared with subcutaneous cytarabine.[155] Several studies have evaluated the combination of clofarabine with subcutaneous cytarabine in older patients with AML. In an earlier study from the MD Anderson Cancer Center, older patients with previously untreated AML (age ≥60 years, median age 71 years) were randomized to receive induction with clofarabine alone (n=16; 30 mg/m^2 intravenously for 5 days) or clofarabine combined with subcutaneous cytarabine (n=54; 20 mg/m^2 subcutaneously for 14 days).[156] All patients were admitted to a laminar air flow room during induction (generally lasting 30 days), and anti-infective prophylaxis included antiviral and antifungal therapies. Patients received consolidation with 3 days of clofarabine, with or without 7 days of cytarabine. The combination regimen resulted in a significantly higher CR rate compared with clofarabine alone (63% vs. 31%; $P = .025$), with a lower induction mortality rate (19% vs. 31%; $P =$

NS). Although the combination regimen resulted in an improved EFS (median 7.1 vs. 1.7 months; *P* = .04), median OS was not significantly different (11.4 vs. 5.8 months) compared with clofarabine alone.[156] More recently, a phase II Spanish study evaluated the combination of clofarabine (20 mg/m^2 intravenously for 5 days) and subcutaneous cytarabine (20 mg/m^2 subcutaneously for 14 days) in older patients with previously untreated AML (age ≥60 years).[157] Patients with less than a CR with the first course could receive another induction course; consolidation comprised 5 days of clofarabine (15 mg/m^2) and 7 days of subcutaneous cytarabine (20 mg/m^2) up to 10 courses. The study was designed to enroll 75 patients. However, after enrolling 11 patients (median age 74 years), the study was discontinued due to high toxicity and unacceptable mortality rates. The mortality rate at 4 weeks was 46% (5 patients) and at 8 weeks was 73% (8 patients).[157] The poorer outcomes reported in this trial compared with the earlier MD Anderson trial may, in part, be explained by the older age and frequent comorbidity of patients in the recent study, as well as potential differences in the extent of monitoring (eg, outpatient versus inpatient) and supportive care practices (eg, anti-infective prophylaxis and infection monitoring) between the studies. Although the combination of clofarabine and subcutaneous cytarabine appears promising in older patients who may not be suitable for standard induction therapies, rigorous monitoring and supportive care measures are needed to minimize toxicities.

The role of clofarabine monotherapy compared with standard induction regimens in the treatment of older patients with AML remains undefined. 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-azacytadine and decitabine (alone or in combination with histone deacetylase inhibitors), or low-dose cytarabine.

An international, randomized, phase III study by Fenaux et al[158] 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%.[158,159] 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).[159] 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.[160] In a phase II study in previously untreated patients aged 60 years and older (N = 55; median age, 74 years), the overall CR rate with this agent (20 mg/m^2 for 5 days every 28 days) was 24% (including 6/25 patients [24%] with poor-risk cytogenetics), and the median EFS and OS were 6 and 8 months, respectively.[160] An earlier phase I study evaluated different dose schedules of decitabine in patients with relapsed/refractory leukemias (n=50; AML diagnosis, n=37).[161] In this study decitabine was

given at 5, 10, 15, or 20 mg/m^2 for 5 days per week for 2 to 4 consecutive weeks (ie, 10, 15, or 20 days). Decitabine dose of 15 mg/m^2 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.[161] In an open-label randomized phase III study, decitabine (20 mg/m^2 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.[162] 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).[162] 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%).[162] Both azacytidine and decitabine are approved by the FDA as treatment for patients with MDS.

The UK NCRI 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).[163] Patients were also randomized to receive 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.[163] 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 (20 mg/m^2 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).[164] 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 RFS was 14 months. The median OS for all patients was 12.7 months. Induction mortality rate was 7% at 8 weeks.[164] 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 idarubicin in conjunction with standard-dose cytarabine as the preferred treatment over daunorubicin or mitoxantrone 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 an ECOG performance status score of 0 to 2, with or without adverse features (such as

therapy-related AML/prior MDS or unfavorable cytogenic or molecular markers) may be managed with one of the following options: clinical trial, standard infusional cytarabine and anthracycline; or low-intensity therapy (eg, subcutaneous cytarabine, azacitidine, decitabine). Standard induction with infusional cytarabine combined with anthracycline may be an appropriate option for high-risk patients (eg, having adverse prognostic factors) who are candidates for subsequent HSCT, whereas low-intensity therapy may be more appropriate for elderly patients or patients with major comorbidities who cannot tolerate standard induction chemotherapy.

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. The panel also encourages participation in a clinical trial investigating novel agents for these patients, where appropriate and possible.

Novel regimens that incorporate non-chemotherapy agents are currently under investigation in the management of older patients with AML. Lenalidomide—a thalidomide analog—is an immunomodulating agent that has demonstrated activity against myeloid malignancies including MDS. In a phase I/II study that evaluated sequential therapy with 5-azacytidine followed by lenalidomide in older patients with previously untreated AML (n=18), the regimen resulted in a CR in 44% of patients (including CR with incomplete recovery of blood counts).[165] The median duration of response was approximately 6 months. The maximum tolerated dose of the regimen was not reached in this study. The most common adverse events included fatigue, injection site reactions, gastrointestinal events, and febrile neutropenia.[165] A recent trial evaluated this regimen with sequential 5-azacytidine and lenalidomide in older patients (age ≥60 years) with previously untreated AML not eligible for standard induction chemotherapy (n=45; n=42 evaluated).[166] Seven patients (17%) had a prior diagnosis of MDS, and five of these patients had received prior treatment with hypomethylating agents for MDS (5-azacytidine, n=5; decitabine, n=1). The ORR was 41%, including a CR in 19% and CR with incomplete recovery of blood counts in 9%.[166] The median duration of response was 28 weeks and the median OS for responding patients was 69 weeks. Early death (death within 4 weeks from start of treatment) occurred in 17% of patients. The median OS for all patients was 20 weeks.[166] The most common treatment-related adverse events included grade 1 or 2 gastrointestinal toxicities, injection site reactions, fatigue, and rash/pruritus; grade 3 adverse events were uncommon, and no grade 4 or 5 treatment-related toxicities were reported. Additional studies in a larger group of patients are needed to further evaluate the efficacy and safety profile of this combination approach.

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 CRi for

patients who have fewer than 5% marrow blasts but mild residual cytopenias.

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^2 × 7 days) plus the anthracycline to which they had been randomized for induction (idarubicin, 9 mg/m^2 × 4 days or daunorubicin, 45 mg/m^2 × 4 days) or 6 monthly courses of anthracycline (1 day only) at the above doses and 60 mg/m^2 of cytarabine every 12 hours as a subcutaneous infusion at home for 5 days each month.[148] 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.[148] 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^2/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.[167,168] 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.[167,168] 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.[167] 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[169] prospectively evaluated a protocol in which patients aged 50 years and older with unfavorable cytogenetics would be evaluated for a RIC allogeneic HSCT.[169] 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 RFS, and the authors concluded that this approach remains of interest.[169] 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.[170] This study showed similar rates of 4-year nonrelapse mortality (19% and 20%, respectively), and no difference was seen in relapse and OS rates.[170]

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).[171] 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 RFS 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%; $P = .012$).[171] 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 3-year OS rates of 63% and 61%, respectively.[171]

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).[172] 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 favoring allogeneic HSCT was seen.[172]

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.

Role of MRD Monitoring

Currently, NCCN does not provide recommendations on the use of MRD monitoring until further studies can provide consistent and reliable results; however, due to the rapidly evolving field and the undeniable need for monitoring, current trends in this field are discussed below.

While morphologic assessment is the first step in a cure for AML, there remains a level of MRD that currently lacks any standardized method of monitoring. Two promising techniques are real-time quantitative PCR (RQ-PCR) and flow cytometry. RQ-PCR amplifies leukemia-associated genetic abnormalities, while flow cytometric profiling detects leukemia-associated immunophenotypes (LAIPs).[173-175] Both methods have a higher sensitivity than conventional morphology. RQ-PCR has a detection range of 1 in 1000 to 1 in 100,000, while flow cytometry has sensitivity between 10^{-4} to 10^{-5}. The challenge to incorporating these

techniques into routine practice is a lack of standardization and established cutoff values, though ongoing research is focused on addressing these limitations. Most of what is known about MDR monitoring has been done in the APL population;[176,177] however, these techniques are now expanding to include other AML subtypes. The data from these methods have been correlated with AML treatment outcome and the preliminary results are promising. Refinement of these methods to take into account variables including the intrinsic nature of the transcript as well as factors of the patient population, including age, disease severity, and treatment, will make MRD monitoring in patients with AML a more reliable option.

RQ-PCR

There are three classifications of RQ-PCR targets: leukemic fusion genes, mutations, and gene overexpression. The most investigated leukemic fusion genes are RUNX1-RUNX1T1, CBFB-MYH11, and MLL fusion transcripts. Gene fusions are found in 20% and 35% of adult and childhood non-APL AML cases, respectively.[178,179] Mutations in AML include NPM1, DNMT3A, and FLT3-ITD mutations. NPM1 mutations are seen in approximately one-third of adult AML, while less than 10% of childhood cases have this mutation.[180,181] Similarly, the DMNT3A mutation is found at a higher percentage in adult (15%–20%) compared to childhood (2%) AML.[63,182,183] The FLT3-ITD mutation is found in 25% of adult and 15% of childhood AML.[43,184] Two less well-studied mutations that may serve as MRD markers include CEBPA and MLL-partial tandem duplications.[185] Finally, the main target of gene overexpression in AML is the Wilms' tumor (WT1) gene. Taken together, these putative targets for MRD monitoring encompass the majority of AML cases.

A study of 29 patients with either RUNX1-RUNX1T1 or CBFB-MYH11 AML during postinduction and postconsolidation chemotherapy did not observe a correlation with survival.[186] However, the authors did correlate a greater than or equal to 1 log rise in RQ-PCR transcript relative to the remission bone marrow sample as indicative of inferior leukemia-free survival and imminent morphologic relapse, supporting the use of RQ-PCR .[186] Another study evaluated bone marrow from 53 patients during consolidation therapy and was the first to establish clinically relevant MRD cut-off values for the CBFB-MYH11 transcript to stratify patients with increased risk of relapse.[187] PCR negativity in at least one bone marrow sample during consolidation therapy was predictive of a 2-year RFS of 79% as compared to the 54% seen in PCR-positive patients. Similarly, Yin et al[3] found that a less than 3 log reduction in RUNX1-RUNX1T1 transcript in bone marrow or a greater than 10 CBFB-MYH11 copy number in peripheral blood after 1 course of induction chemotherapy was highly predictive of relapse.[3] A study in childhood AML of 15 patients also showed that RUNX1-RUNX1T1 increased transcript levels are predictive of relapse.[188] MLL fusion transcripts for MRD monitoring have also been analyzed in 19 patients with t(9;11)(q22;q23) AML. Eleven of these patients showed negative PCR for the MLL fusion transcripts, and this associated with a better outcome. While most studies have shown a correlation between transcript level and outcome, a study of childhood AML showed RQ-PCR of RUNX1-RUNX1T1 to be a poor marker for relapse and the method to be inferior to flow cytometry.[189] The different outcomes of the studies highlight the need for standardization of these methods. It also may be an indication of variability between adult and pediatric populations, a factor that must be taken into account when establishing methods and cutoffs.

The use of RQ-PCR in mutations is hampered by the inability to distinguish the number of cells containing transcript as each cell may have variable levels. Furthermore, these transcripts may still be

detected in cells that have differentiated in response to treatment and are no longer clonogenic, thereby giving a false positive.[190,191] Another caveat is the instability of mutations that may result in false negatives. This is particularly true for FLT3-ITD[192-194] and NPM1 mutations.[195-197] Despite these complications, several studies have investigated the relationship between NPM1 mutations and outcome.[196,198-203] In a small study of 25 patients, the use of a higher sensitivity RQ-PCR was shown to circumvent transcript instability, ultimately showing that FLT3-ITD MRD monitoring was predictive of relapse.[204] In comparison to FLT3-ITD, data suggest that NPM1 mutations may be more stable.[199] Schittger et al developed and tested primers for 17 different mutations of NPM1.[201] Serial analyses of 252 NPM1-mutated AML samples at four time points showed a strong correlation between the level of *NPM1*^{mut} and outcome. Kronke et al further modified this method to show that *NPM1*^{mut} levels after double induction and consolidation therapy reflected OS and cumulative incidence of relapse.[197] In 245 patients, PCR negativity had a 6.5% 4-year cumulative incidence of relapse versus 53% for patients with positive PCR.[197] This correlation was also seen when taken after completion of therapy. CEBPA and MLL-partial tandem duplications are two additional targets for MRD monitoring by RQ-PCR.[185,205] While data suggest both transcripts may be suitable MRD markers, the small sample sizes limit current use of these markers until data can be extrapolated to a larger population.

Gene overexpression studies have focused on WT1. Retrospective data show that a lower level of WT1 after induction therapy is associated with long-term remission.[206] WT1 was overexpressed in 86% of marrow and 91% of blood samples from 504 patients with AML when compared to 204 healthy donors.[207] However, when using the cutoff values of greater than 100-fold detection, only 46% of blood and 13% of marrow samples in the cohort were positive.[207] This reflects the outliers of the healthy population that have higher WT1 transcripts. Furthermore, only 19% of childhood AML samples met this criterion in a study from Willasch et al.[208] While WT1 is a strong candidate for MRD monitoring, early studies show that there is variability in the detection of this transcript that must first be addressed.

Flow Cytometry

Flow cytometry for the monitoring of AML measures the presence of tumor-specific antigens and abnormalities not found on normal bone marrow cells. Several known markers identify abnormal cells or cell maturation and when used as a panel, these markers can define cell populations.[209] Studies in both adult and childhood AML cases show a correlation between flow cytometry and relapse. Loken et al showed that 7 of 27 patients who had not achieved morphologic remission have negative MRD by flow cytometry. All 7 patients were long-term survivors when compared with the remaining 20 patients. Conversely, less than 5% of the 188 patients in morphologic remission had high levels of MRD by flow cytometry.[210] A larger study of 1382 follow-up bone marrow samples from 202 children with AML demonstrated MRD to be a predictor of relapse. In this study 28 of the 38 samples (74%) with greater than 15% myeloblasts had measurements of 0.1% or greater by flow cytometry. In patients with 5% to 15% myeloblasts, 43 of the 129 patients (33%) were detected by the same threshold and only 100 of the 1215 samples (8%) with less than 5% myeloblasts fell into this category. The ability of MRD monitoring to predict an unfavorable EFS was statistically significant ($P < .0001$).[189]

The most difficult issue facing flow cytometry as an effective method for MRD monitoring is standardization and training. Flow cytometry relies heavily on the expertise of the technician who must take into account variability in instruments, fluorochromes, analysis software, and individual antigens. Variations in the treatment schedule, dosing, type

of treatment, and time of draw are also potential variables. Despite the issues with flow cytometry, research is focused on improving the method. Defining threshold cutoff values[211-214] as well as generating standards to equalize data among different instruments and software programs will be essential. A recent study by Feller et al[215] further defined LAIPs and determined whether data from an established MRD monitoring laboratory could be replicated in four centers with no significant prior experience. Increased success rates of defining LAIPs were seen in all four centers after extensive group discussion. The inexperienced laboratories had a success rate of 82% to 93% for defining at least one LAIP in a sample from 35 evaluable samples. The missed LAIPs would have resulted in 7% to 18% of the patients being unevaluable by MRD in these centers. The number of samples incorrectly evaluated increases if it includes samples in which at least two LAIPs were identified by the primary lab, but the other labs only detected one LAIP. This accounted for an additional 9% to 20% of cases that would have resulted in false negatives. LAIPs with high specificity and sensitivity (MRD levels of 0.01%) were very well-defined in the multicenter analysis. With regard to the missed LAIPs, the authors proposed the design of redundant panels to account for immunophenotypic shift. Inconsistencies in LAIPs with MRD of 0.1% or lower may be resolved with the use of a greater number of fluorochromes.[216] Another important conclusion from this publication was the ability of these methods to be applied to different instruments. In this study, both the Becton Coulter and the Becton Dickinson were tested and obtained similar results. This multicenter study demonstrated the potential use of MRD monitoring but also highlighted areas that need improvement. This makes MRD monitoring a more likely option if performed in core facilities until greater research is done on the method to eliminate variability. Enrollment in clinical trials that provide MRD monitoring is encouraged. A currently enrolling trial is entitled, Monitoring Minimal Residual Disease Following Treatment of Patients with Acute Myeloid Leukemia (AML) or High Grade Myelodysplastic Syndrome (MDS) (NCT01311258)[217].

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 the bone marrow evaluation is being performed as part of a clinical research protocol.

A matched unrelated donor search (including umbilical 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); 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 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 U.S. 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[218,219]; 2) fludarabine, cytarabine, and G-CSF (FLAG regimen) with or without idarubicin[220,221]; 3) etoposide and cytarabine, with or without mitoxantrone[222]; 4) clofarabine (25 mg/m^2 daily for 5 days), cytarabine (2 g/m^2 daily for 5 days), and G-CSF[223]; or 5) clofarabine- and idarubicin-containing regimens with clofarabine (22.5 mg/m^2 daily for 5 days) and idarubicin (10 mg/m^2 daily for 3 days) or clofarabine (same as above) and idarubicin (6 mg/m^2 daily for 3 days) and cytarabine (0.75 g/m^2 daily for 5 days).[224] More recently, a regimen with clofarabine (40 mg/m^2) combined with cytarabine (2 g/m^2) 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.[225] 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[163,226] or hypomethylating agents.[159-162,227,228]

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, anti-infective 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 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.[229] 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.[230]

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 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 cytology should be sampled by LP. If the LP is negative for leukemic cells, the patient can be followed with a repeat LP if symptoms persist. If the LP is positive, intrathecal chemotherapy is recommended, given concurrently with systemic induction therapy. Intrathecal therapy may include agents such as methotrexate, cytarabine, and liposomal cytarabine, alone or combined with corticosteroids. The selection of agents (eg, single agent, combination, triple intrathecal therapy) and dose schedules for intrathecal therapy largely depend upon the specific clinical situation (eg, extent of CNS leukemia, symptoms, systemic therapies given concurrently) and institutional practices. Initially, intrathecal therapy is generally given twice weekly until the cytology shows no blasts, and then weekly for 4 to 6 weeks. Intrathecal therapy with the liposomal formulation of cytarabine, which has a longer half-life, offers the benefit of less frequent once weekly administration. Importantly, intrathecal therapy should only be administered by clinicians with experience and expertise in the delivery of intrathecal agents. High-dose cytarabine, when used as part of induction therapy, may substitute for intrathecal chemotherapy because it crosses the blood-brain barrier; the cerebrospinal fluid must then be reassessed after completion of induction therapy, and further intrathecal therapy should be given as appropriate.

If the initial CT/MRI identifies a mass effect or increased intracranial pressure due to a parenchymal lesion in the brain, a needle aspiration or biopsy should be considered. If the results are positive, then radiation therapy should be strongly considered, followed by intrathecal

therapy, as described earlier. 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 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.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: A Cancer Journal for Clinicians 2014;64:9-29. Available at: http://dx.doi.org/10.3322/caac.21208.

2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23335087.

3. Yin JA, O'Brien MA, Hills RK, et al. Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. Blood 2012;120:2826-2835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22875911.

4. Smith M, Barnett M, Bassan R, et al. Adult acute myeloid leukaemia. Crit Rev Oncol Hematol 2004;50:197-222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15182826.

5. Leone G, Pagano L, Ben-Yehuda D, Voso MT. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica 2007;92:1389-1398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17768113.

6. Pagana L, Pulsoni A, Tosti ME, et al. Clinical and biological features of acute myeloid leukaemia occurring as second malignancy: GIMEMA archive of adult acute leukaemia. Br J Haematol 2001;112:109-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11225603.

7. Pulsoni A, Pagano L, Lo Coco F, et al. Clinicobiological features and outcome of acute promyelocytic leukemia occurring as a second tumor: the GIMEMA experience. Blood 2002;100:1972-1976. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12200354.

8. Kayser S, Dohner K, Krauter J, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 2011;117:2137-2145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21127174.

9. Larson RA. Etiology and management of therapy-related myeloid leukemia. Hematology Am Soc Hematol Educ Program 2007:453-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024664.

10. Mauritzson N, Albin M, Rylander L, et al. Pooled analysis of clinical and cytogenetic features in treatment-related and de novo adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976-1993 and on 5098 unselected cases reported in the literature 1974-2001. Leukemia 2002;16:2366-2378. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12454741.

11. Carney DA, Westerman DA, Tam CS, et al. Therapy-related myelodysplastic syndrome and acute myeloid leukemia following fludarabine combination chemotherapy. Leukemia 2010;24:2056-2062. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20962860.

12. Czader M, Orazi A. Therapy-related myeloid neoplasms. Am J Clin Pathol 2009;132:410-425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19687318.

13. Hosing C, Munsell M, Yazji S, et al. Risk of therapy-related myelodysplastic syndrome/acute leukemia following high-dose therapy and autologous bone marrow transplantation for non-Hodgkin's lymphoma. Ann Oncol 2002;13:450-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11996478.

14. Lenz G, Dreyling M, Schiegnitz E, et al. Moderate increase of secondary hematologic malignancies after myeloablative radiochemotherapy and autologous stem-cell transplantation in patients with indolent lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group. J Clin Oncol 2004;22:4926-4933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15611507.

15. Borthakur G, Lin E, Jain N, et al. Survival is poorer in patients with secondary core-binding factor acute myelogenous leukemia compared

with de novo core-binding factor leukemia. Cancer 2009;115:3217-3221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19441109.

16. Beaumont M, Sanz M, Carli PM, et al. Therapy-related acute promyelocytic leukemia. J Clin Oncol 2003;21:2123-2137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12775738.

17. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835-3849. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10577857.

18. 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;21:4642-4649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14673054.

19. Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008.

20. Byrd JC, Mrozek K, Dodge RK, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood 2002;100:4325-4336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393746.

21. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. Blood 1998;92:2322-2333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9746770.

22. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood 2000;96:4075-4083. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11110676.

23. Breems DA, Van Putten WL, De Greef GE, et al. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. J Clin Oncol 2008;26:4791-4797. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18695255.

24. Medeiros BC, Othus M, Fang M, et al. Prognostic impact of monosomal karyotype in young adult and elderly acute myeloid leukemia: the Southwest Oncology Group (SWOG) experience. Blood 2010;116:2224-2228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20562328.

25. Perrot A, Luquet I, Pigneux A, et al. Dismal prognostic value of monosomal karyotype in elderly patients with acute myeloid leukemia: a GOELAMS study of 186 patients with unfavorable cytogenetic abnormalities. Blood 2011;118:679-685. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21622650.

26. Bienz M, Ludwig M, Leibundgut EO, et al. Risk assessment in patients with acute myeloid leukemia and a normal karyotype. Clin Cancer Res 2005;11:1416-1424. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15746041.

27. Cairoli R, Beghini A, Grillo G, et al. Prognostic impact of c-KIT mutations in core binding factor leukemias: an Italian retrospective study. Blood 2006;107:3463-3468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16384925.

28. Dohner K, Schlenk RF, Habdank M, et al. Mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interaction with other gene mutations. Blood 2005;106:3740-3746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16051734.

29. Falini B, Nicoletti I, Martelli MF, Mecucci C. Acute myeloid leukemia carrying cytoplasmic/mutated nucleophosmin (NPMc+ AML): biologic and clinical features. Blood 2007;109:874-885. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17008539.

30. Frohling S, Schlenk RF, Breitruck J, et al. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. Blood 2002;100:4372-4380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393388.

31. Frohling S, Schlenk RF, Stolze I, et al. CEBPA mutations in younger adults with acute myeloid leukemia and normal cytogenetics: prognostic relevance and analysis of cooperating mutations. J Clin Oncol 2004;22:624-633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14726504.

32. Pabst T, Mueller BU, Zhang P, et al. Dominant-negative mutations of CEBPA, encoding CCAAT/enhancer binding protein-alpha (C/EBPalpha), in acute myeloid leukemia. Nat Genet 2001;27:263-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11242107.

33. Paschka P, Marcucci G, Ruppert AS, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): A Cancer and Leukemia Group B Study. J Clin Oncol 2006;24:3904-3911. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921041.

34. Schnittger S, Schoch C, Kern W, et al. Nucleophosmin gene mutations are predictors of favorable prognosis in acute myelogenous leukemia with a normal karyotype. Blood 2005;106:3733-3739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16076867.

35. Schnittger S, Kohl TM, Haferlach T, et al. KIT-D816 mutations in AML1-ETO-positive AML are associated with impaired event-free and overall survival. Blood 2006;107:1791-1799. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16254134.

36. Thiede C, Koch S, Creutzig E, et al. Prevalence and prognostic impact of NPM1 mutations in 1485 adult patients with acute myeloid leukemia (AML). Blood 2006;107:4011-4020. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16455956.

37. Verhaak RG, Goudswaard CS, van Putten W, et al. Mutations in nucleophosmin (NPM1) in acute myeloid leukemia (AML): association with other gene abnormalities and previously established gene expression signatures and their favorable prognostic significance. Blood 2005;106:3747-3754. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16109776.

38. Falini B, Mecucci C, Tiacci E, et al. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med 2005;352:254-266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15659725.

39. Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med 2012;366:1079-1089. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22417203.

40. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med 2008;358:1909-1918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18450602.

41. Abu-Duhier FM, Goodeve AC, Wilson GA, et al. Identification of novel FLT-3 Asp835 mutations in adult acute myeloid leukaemia. Br J Haematol 2001;113:983-988. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11442493.

42. Kiyoi H, Naoe T, Nakano Y, et al. Prognostic implication of FLT3 and N-RAS gene mutations in acute myeloid leukemia. Blood 1999;93:3074-3080. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10216104.

43. Kottaridis PD, Gale RE, Frew ME, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood 2001;98:1752-1759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11535508.

44. Nakao M, Yokota S, Iwai T, et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia 1996;10:1911-1918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8946930.

45. Whitman SP, Archer KJ, Feng L, et al. Absence of the wild-type allele predicts poor prognosis in adult de novo acute myeloid leukemia with normal cytogenetics and the internal tandem duplication of FLT3: a cancer and leukemia group B study. Cancer Res 2001;61:7233-7239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11585760.

46. Yamamoto Y, Kiyoi H, Nakano Y, et al. Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. Blood 2001;97:2434-2439. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11290608.

47. Kainz B, Heintel D, Marculescu R, et al. Variable prognostic value of FLT3 internal tandem duplications in patients with de novo AML and a normal karyotype, t(15;17), t(8;21) or inv(16). Hematol J 2002;3:283-289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12522450.

48. Whitman SP, Maharry K, Radmacher MD, et al. FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood 2010;116:3622-3626. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20656931.

49. Whitman SP, Ruppert AS, Radmacher MD, et al. FLT3 D835/I836 mutations are associated with poor disease-free survival and a distinct gene-expression signature among younger adults with de novo cytogenetically normal acute myeloid leukemia lacking FLT3 internal tandem duplications. Blood 2008;111:1552-1559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17940205.

50. Santos FP, Jones D, Qiao W, et al. Prognostic value of FLT3 mutations among different cytogenetic subgroups in acute myeloid leukemia. Cancer 2011;117:2145-2155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21523727.

51. Bacher U, Haferlach C, Kern W, et al. Prognostic relevance of FLT3-TKD mutations in AML: the combination matters--an analysis of 3082 patients. Blood 2008;111:2527-2537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17965322.

52. Mead AJ, Linch DC, Hills RK, et al. FLT3 tyrosine kinase domain mutations are biologically distinct from and have a significantly more favorable prognosis than FLT3 internal tandem duplications in patients with acute myeloid leukemia. Blood 2007;110:1262-1270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17456725.

53. Barjesteh van Waalwijk van Doorn-Khosrovani S, Erpelinck C, Meijer J, et al. Biallelic mutations in the CEBPA gene and low CEBPA expression levels as prognostic markers in intermediate-risk AML. Hematol J 2003;4:31-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12692518.

54. Green CL, Koo KK, Hills RK, et al. Prognostic significance of CEBPA mutations in a large cohort of younger adult patients with acute myeloid leukemia: impact of double CEBPA mutations and the interaction with FLT3 and NPM1 mutations. J Clin Oncol 2010;28:2739-2747. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20439648.

55. Preudhomme C, Sagot C, Boissel N, et al. Favorable prognostic significance of CEBPA mutations in patients with de novo acute myeloid leukemia: a study from the Acute Leukemia French Association (ALFA). Blood 2002;100:2717-2723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12351377.

56. Abbas S, Lugthart S, Kavelaars FG, et al. Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value. Blood 2010;116:2122-2126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20538800.

57. Chotirat S, Thongnoppakhun W, Promsuwicha O, et al. Molecular alterations of isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) metabolic genes and additional genetic mutations in newly diagnosed acute myeloid leukemia patients. J Hematol Oncol 2012;5:5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22397365.

58. Chou WC, Hou HA, Chen CY, et al. Distinct clinical and biologic characteristics in adult acute myeloid leukemia bearing the isocitrate dehydrogenase 1 mutation. Blood 2010;115:2749-2754. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20097881.

59. Marcucci G, Maharry K, Wu YZ, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 2010;28:2348-2355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20368543.

60. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med 2009;361:1058-1066. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19657110.

61. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol 2010;28:3636-3643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20567020.

62. Chou WC, Lei WC, Ko BS, et al. The prognostic impact and stability of Isocitrate dehydrogenase 2 mutation in adult patients with acute myeloid leukemia. Leukemia 2011;25:246-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21079611.

63. Ley TJ, Ding L, Walter MJ, et al. DNMT3A mutations in acute myeloid leukemia. N Engl J Med 2010;363:2424-2433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21067377.

64. Thol F, Damm F, Ludeking A, et al. Incidence and prognostic influence of DNMT3A mutations in acute myeloid leukemia. J Clin Oncol 2011;29:2889-2896. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21670448.

65. Marcucci G, Metzeler KH, Schwind S, et al. Age-Related Prognostic Impact of Different Types of DNMT3A Mutations in Adults With Primary Cytogenetically Normal Acute Myeloid Leukemia. J Clin Oncol 2012;30:742-750. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22291079.

66. Markova J, Michkova P, Burckova K, et al. Prognostic impact of DNMT3A mutations in patients with intermediate cytogenetic risk profile acute myeloid leukemia. Eur J Haematol 2012;88:128-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21967546.

67. Renneville A, Boissel N, Nibourel O, et al. Prognostic significance of DNA methyltransferase 3A mutations in cytogenetically normal acute myeloid leukemia: a study by the Acute Leukemia French Association. Leukemia 2012;26:1247-1254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22289988.

68. Mendler JH, Maharry K, Radmacher MD, et al. RUNX1 Mutations Are Associated With Poor Outcome in Younger and Older Patients With Cytogenetically Normal Acute Myeloid Leukemia and With Distinct Gene and MicroRNA Expression Signatures. J Clin Oncol 2012;30:3109-3118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22753902.

69. Metzeler KH, Maharry K, Radmacher MD, et al. TET2 mutations improve the new European LeukemiaNet risk classification of acute

myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 2011;29:1373-1381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21343549.

70. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010;115:453-474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19880497.

71. Rollig C, Bornhauser M, Thiede C, et al. Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system. J Clin Oncol 2011;29:2758-2765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21632498.

72. Boissel N, Leroy H, Brethon B, et al. Incidence and prognostic impact of c-Kit, FLT3, and Ras gene mutations in core binding factor acute myeloid leukemia (CBF-AML). Leukemia 2006;20:965-970. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16598313.

73. 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 (AMLSG). Blood 2013;121:170-177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23115274.

74. Arber DA, Vardiman JW, Brunning RD, et al. Acute myeloid leukemia with recurrent genetic abnormalities. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon: IARC; 2008:110-123.

75. Powell BL. Arsenic trioxide in acute promyelocytic leukemia: potion not poison. Expert Rev Anticancer Ther 2011;11:1317-1319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21929304.

76. Tallman MS, Altman JK. Curative strategies in acute promyelocytic leukemia. Hematology Am Soc Hematol Educ Program 2008:391-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19074116.

77. Park JH, Qiao B, Panageas KS, et al. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. Blood 2011;118:1248-1254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21653939.

78. Howlader N NA, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. (http://seer.cancer.gov/csr/1975_2010/). Bethesda, MD; 2013. Available at: http://seer.cancer.gov/csr/1975_2010/browse_csr.php?sectionSEL=1&pageSEL=sect_01_table.12.html.

79. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood 1988;72:567-572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3165295.

80. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans-retinoic acid in acute promyelocytic leukemia. N Engl J Med 1997;337:1021-1028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9321529.

81. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. Blood 2002;100:4298-4302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393590.

82. Ades L, Guerci A, Raffoux E, et al. Very long-term outcome of acute promyelocytic leukemia after treatment with all-trans retinoic acid and chemotherapy: the European APL Group experience. Blood 2010;115:1690-1696. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20018913.

83. Ades L, 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;111:1078-1084. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17975017.

84. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20705755.

85. 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 outcome. Blood 2010;115:5137-5146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20393132.

86. 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 adults patients younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood 2010;116:3171-3179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20644121.

87. Fenaux P, Chastang C, Chevret S, et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood 1999;94:1192-1200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10438706.

88. Fenaux P, Le Deley MC, Castaigne S, et al. Effect of all transretinoic acid in newly diagnosed acute promyelocytic leukemia. Results of a multicenter randomized trial. European APL 91 Group. Blood 1993;82:3241-3249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8241496.

89. Mandelli F, Diverio D, Avvisati G, et al. Molecular remission in PML/RAR alpha-positive acute promyelocytic leukemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. Gruppo Italiano-Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed Oncologia Pediatrica Cooperative Groups. Blood 1997;90:1014-1021. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9242531.

90. Sanz MA, Martin G, Rayon C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. Blood 1999;94:3015-3021. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10556184.

91. Sanz MA, Lo Coco F, Martin G, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. Blood 2000;96:1247-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10942364.

92. Sanz MA, Martin G, Gonzalez M, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. Blood 2004;103:1237-1243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14576047.

93. Ades L, Chevret S, Raffoux E, et al. Is cytarabine useful in the treatment of acute promyelocytic leukemia? Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. J Clin Oncol 2006;24:5703-5710. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17116939.

94. Shen ZX, Chen GQ, Ni JH, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood 1997;89:3354-3360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9129042.

95. Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med 1998;339:1341-1348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9801394.

96. Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci U S A 2004;101:5328-5335. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15044693.

97. Estey E, Garcia-Manero G, Ferrajoli A, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. Blood 2006;107:3469-3473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16373661.

98. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19075265.

99. Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-1580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22715121.

100. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369:111-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23841729.

101. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12542484.

102. Ades L, Chevret S, Raffoux E, et al. Long-term follow-up of European APL 2000 trial, evaluating the role of cytarabine combined with ATRA and Daunorubicin in the treatment of nonelderly APL patients. Am J Hematol 2013;88:556-559. Available at:

103. Ades L, Raffoux E, Chevret S, et al. Arsenic Trioxide (ATO) In the Consolidation Treatment of Newly Diagnosed APL - First Interim Analysis of a Randomized Trial (APL 2006) by the French Belgian Swiss APL Group [abstract]. Blood 2010;116:Abstract 505. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;116/21/505.

104. Ades L, Chevret S, Raffoux E, et al. Arsenic Trioxide (ATO) Or ATRA For Consolidation Treatment Of Standard Risk Non Elderly Newly Diagnosed APL– Second Interim Analysis Of a Randomized Trial (APL 2006) By The French Belgian Swiss APL Group. Blood 2013;122:495. Available at: http://bloodjournal.hematologylibrary.org/content/122/21/495.abstract.

105. 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. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;120/21/6.

106. Asou N, Kishimoto Y, Kiyoi H, et al. A randomized study with or without intensified maintenance chemotherapy in patients with acute promyelocytic leukemia who have become negative for PML-RARalpha transcript after consolidation therapy: the Japan Adult Leukemia Study Group (JALSG) APL97 study. Blood 2007;110:59-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17374742.

107. Avvisati G, Petti M, Lo Coco F, et al. AIDA: The Italian way of treating acute promyelocytic leukemia (APL), final act. Blood 2003;102. Available at:

108. 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. Available at:

109. Coutre SE, Othus M, Powell B, et al. Arsenic trioxide during consolidation for patients with previously untreated low/intermediate risk acute promyelocytic leukaemia may eliminate the need for maintenance therapy. Br J Haematol 2014. Available at:

110. Lazo G, Kantarjian H, Estey E, et al. Use of arsenic trioxide (As2O3) in the treatment of patients with acute promyelocytic leukemia: the M. D. Anderson experience. Cancer 2003;97:2218-2224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12712474.

111. Leoni F, Gianfaldoni G, Annunziata M, et al. Arsenic trioxide therapy for relapsed acute promyelocytic leukemia: a bridge to transplantation. Haematologica 2002;87:485-489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12010661.

112. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol 2001;19:3852-3860. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11559723.

113. Thirugnanam R, George B, Chendamarai E, et al. Comparison of clinical outcomes of patients with relapsed acute promyelocytic leukemia induced with arsenic trioxide and consolidated with either an autologous stem cell transplant or an arsenic trioxide-based regimen. Biol Blood Marrow Transplant 2009;15:1479-1484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19822309.

114. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12805334.

115. de Botton S, Sanz MA, Chevret S, et al. Extramedullary relapse in acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. Leukemia 2006;20:35-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16307026.

116. Specchia G, Lo Coco F, Vignetti M, et al. Extramedullary involvement at relapse in acute promyelocytic leukemia patients treated or not with all-trans retinoic acid: a report by the Gruppo Italiano Malattie Ematologiche dell'Adulto. J Clin Oncol 2001;19:4023-4028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11600603.

117. de Botton S, Fawaz A, Chevret S, et al. Autologous and allogeneic stem-cell transplantation as salvage treatment of acute promyelocytic leukemia initially treated with all-trans-retinoic acid: a retrospective analysis of the European acute promyelocytic leukemia group. J Clin Oncol 2005;23:120-126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15534358.

118. Douer D, Hu W, Giralt S, et al. Arsenic trioxide (trisenox) therapy for acute promyelocytic leukemia in the setting of hematopoietic stem cell transplantation. Oncologist 2003;8:132-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12697938.

119. Lengfelder E, Lo-Coco F, Ades L, et al. Arsenic Trioxide-Based Therapy Of Relapsed Acute Promyelocytic Leukemia: Updated Results Of The European Registry Of Relapsed APL (PROMYSE) [abstract]. Presented at the 55th American Society of Hematology Annual Meeting and Exposition; December 7-10, 2013; New Orleans (LA). Abstract nr 1406.

120. De Botton S, Dombret H, Sanz M, et al. Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood 1998;92:2712-2718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9763554.

121. Tallman MS, Andersen JW, Schiffer CA, et al. Clinical description of 44 patients with acute promyelocytic leukemia who developed the retinoic acid syndrome. Blood 2000;95:90-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10607690.

122. Wiley JS, Firkin FC. Reduction of pulmonary toxicity by prednisolone prophylaxis during all-trans retinoic acid treatment of acute promyelocytic leukemia. Australian Leukaemia Study Group. Leukemia 1995;9:774-778. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7769839.

123. Kelaidi C, Chevret S, De Botton S, et al. Improved outcome of acute promyelocytic leukemia with high WBC counts over the last 15 years: the European APL Group experience. J Clin Oncol 2009;27:2668-2676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19414681.

124. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. Blood 2006;107:3481-3485. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16455952.

125. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in Acute myeloid leukemia. N Engl J Med 2009;361:1249-1259. Available at: http://content.nejm.org/cgi/content/abstract/361/13/1249.

126. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20048183.

127. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22508825.

128. Borthakur G, Kantarjian H, Wang X, et al. Treatment of core-binding-factor in acute myelogenous leukemia with fludarabine, cytarabine, and granulocyte colony-stimulating factor results in improved event-free survival. Cancer 2008;113:3181-3185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18932257.

129. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer 2006;106:1090-1098. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16435386.

130. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8634416.

131. Bishop JF, Matthews JP, Young GA, et al. Intensified induction chemotherapy with high dose cytarabine and etoposide for acute myeloid leukemia: a review and updated results of the Australian Leukemia Study Group. Leuk Lymphoma 1998;28:315-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9517503.

132. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8874180.

133. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. N Engl J Med 1994;331:896-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8078551.

134. Kern W, Estey EH. High-dose cytosine arabinoside in the treatment of acute myeloid leukemia: Review of three randomized trials. Cancer 2006;107:116-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16721819.

135. Bloomfield CD, Lawrence D, Byrd JC, et al. Frequency of prolonged remission duration after high-dose cytarabine intensification

in acute myeloid leukemia varies by cytogenetic subtype. Cancer Res 1998;58:4173-4179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9751631.

136. Al-Ali HK, Brand R, van Biezen A, et al. A retrospective comparison of autologous and unrelated donor hematopoietic cell transplantation in myelodysplastic syndrome and secondary acute myeloid leukemia: a report on behalf of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Leukemia 2007;21:1945-1951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17611571.

137. Lowenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. N Engl J Med 2011;364:1027-1036. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21410371.

138. Suciu S, Mandelli F, de Witte T, et al. Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMAAML-10 trial. Blood 2003;102:1232-1240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12714526.

139. Burnett AK, Wheatley K, Goldstone AH, et al. The value of allogeneic bone marrow transplant in patients with acute myeloid leukaemia at differing risk of relapse: results of the UK MRC AML 10 trial. Br J Haematol 2002;118:385-400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12139722.

140. Farag SS, Ruppert AS, Mrozek K, et al. Outcome of induction and postremission therapy in younger adults with acute myeloid leukemia with normal karyotype: a cancer and leukemia group B study. J Clin Oncol 2005;23:482-493. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15534356.

141. O'Farrell AM, Foran JM, Fiedler W, et al. An innovative phase I clinical study demonstrates inhibition of FLT3 phosphorylation by SU11248 in acute myeloid leukemia patients. Clin Cancer Res 2003;9:5465-5476. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14654525.

142. Zhang W, Konopleva M, Shi YX, et al. Mutant FLT3: a direct target of sorafenib in acute myelogenous leukemia. J Natl Cancer Inst 2008;100:184-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18230792.

143. Shah NP, Talpaz M, Deininger MW, et al. Ponatinib in patients with refractory acute myeloid leukaemia: findings from a phase 1 study. Br J Haematol 2013;162:548-552. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23691988.

144. Ravandi F, Cortes JE, Jones D, et al. Phase I/II study of combination therapy with sorafenib, idarubicin, and cytarabine in younger patients with acute myeloid leukemia. J Clin Oncol 2010;28:1856-1862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20212254.

145. Ravandi F, Alattar ML, Grunwald MR, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. Blood 2013;121:4655-4662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23613521.

146. Serve H, Krug U, Wagner R, et al. Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial. J Clin Oncol 2013;31:3110-3118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23897964.

147. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21131036.

148. 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;109:5129-5135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17341661.

149. Gardin C, Chevret S, Pautas C, et al. Superior long-term outcome with idarubicin compared with high-dose daunorubicin in patients with acute myeloid leukemia age 50 years and older. J Clin Oncol 2013;31:321-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23248249.

150. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19776405.

151. Burnett AK, Russell NH, Hills RK, et al. Addition of Gemtuzumab Ozogamicin to Induction Chemotherapy Improves Survival in Older Patients With Acute Myeloid Leukemia. J Clin Oncol 2012;30:3924-3931. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22851554.

152. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012;379:1508-1516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22482940.

153. Kantarjian HM, Erba HP, Claxton D, et al. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. J Clin Oncol 2010;28:549-555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20026805.

154. Burnett AK, Russell NH, Kell J, et al. European development of clofarabine as treatment for older patients with acute myeloid leukemia considered unsuitable for intensive chemotherapy. J Clin Oncol 2010;28:2389-2395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20385984.

155. Burnett AK, Russell NH, Hunter AE, et al. Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival. Blood 2013;122:1384-1394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23838349.

156. Faderl S, Ravandi F, Huang X, et al. A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome. Blood 2008;112:1638-1645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18565853.

157. Martinez-Cuadron D, Montesinos P, Oriol A, et al. Phase II trial to assess the safety and efficacy of clofarabine in combination with low-dose cytarabine in elderly patients with acute myeloid leukemia. Ann Hematol 2014;93:43-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24081577.

158. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10:223-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19230772.

159. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 2010;28:562-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20026804.

160. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. J Clin Oncol 2010;28:556-561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20026803.

161. Issa JP, Garcia-Manero G, Giles FJ, et al. Phase 1 study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in hematopoietic malignancies. Blood

2004;103:1635-1640. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14604977.

162. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, Randomized, Open-Label, Phase III Trial of Decitabine Versus Patient Choice, With Physician Advice, of Either Supportive Care or Low-Dose Cytarabine for the Treatment of Older Patients With Newly Diagnosed Acute Myeloid Leukemia. J Clin Oncol 2012;30:2670-2677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22689805.

163. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer 2007;109:1114-1124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17315155.

164. Faderl S, Ravandi F, Huang X, et al. Clofarabine plus low-dose cytarabine followed by clofarabine plus low-dose cytarabine alternating with decitabine in acute myeloid leukemia frontline therapy for older patients. Cancer 2012;118:4471-4477. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22282348.

165. Pollyea DA, Kohrt HE, Gallegos L, et al. Safety, efficacy and biological predictors of response to sequential azacitidine and lenalidomide for elderly patients with acute myeloid leukemia. Leukemia 2012;26:893-901. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22033493.

166. Pollyea DA, Zehnder J, Coutre S, et al. Sequential azacitidine plus lenalidomide combination for elderly patients with untreated acute myeloid leukemia. Haematologica 2013;98:591-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23242596.

167. Herr AL, Labopin M, Blaise D, et al. HLA-identical sibling allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning compared to autologous peripheral blood stem cell transplantation for elderly patients with de novo acute myeloid leukemia. Leukemia 2007;21:129-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17128198.

168. Storb R. Can reduced-intensity allogeneic transplantation cure older adults with AML? Best Pract Res Clin Haematol 2007;20:85-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17336258.

169. Estey E, de Lima M, Tibes R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). Blood 2007;109:1395-1400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17038533.

170. Martino R, Valcarcel D, Brunet S, et al. Comparable non-relapse mortality and survival after HLA-identical sibling blood stem cell transplantation with reduced or conventional-intensity preparative regimens for high-risk myelodysplasia or acute myeloid leukemia in first remission. Bone Marrow Transplant 2008;41:33-38. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17982504.

171. Kurosawa S, Yamaguchi T, Uchida N, et al. Comparison of allogeneic hematopoietic cell transplantation and chemotherapy in elderly patients with non-M3 acute myelogenous leukemia in first complete remission. Biol Blood Marrow Transplant 2011;17:401-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20667478.

172. Farag SS, Maharry K, Zhang MJ, et al. Comparison of reduced-intensity hematopoietic cell transplantation with chemotherapy in patients age 60-70 years with acute myelogenous leukemia in first remission. Biol Blood Marrow Transplant 2011;17:1796-1803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21699879.

173. Shook D, Coustan-Smith E, Ribeiro RC, et al. Minimal residual disease quantitation in acute myeloid leukemia. Clin Lymphoma Myeloma 2009;9 Suppl 3:S281-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19778853.

174. Grimwade D, Vyas P, Freeman S. Assessment of minimal residual disease in acute myeloid leukemia. Curr Opin Oncol 2010;22:656-663. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20805746.

175. Buccisano F, Maurillo L, Del Principe MI, et al. Prognostic and therapeutic implications of minimal residual disease detection in acute myeloid leukemia. Blood 2012;119:332-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22039260.

176. Sanz MA, Lo-Coco F. Modern approaches to treating acute promyelocytic leukemia. J Clin Oncol 2011;29:495-503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21220600.

177. Grimwade D, Tallman MS. Should minimal residual disease monitoring be the standard of care for all patients with acute promyelocytic leukemia? Leuk Res 2011;35:3-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20674017.

178. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood 2010;116:354-365. Available at: http://www.hubmed.org/display.cgi?uids=20385793.

179. Harrison CJ, Hills RK, Moorman AV, et al. Cytogenetics of childhood acute myeloid leukemia: United Kingdom Medical Research Council Treatment trials AML 10 and 12. J Clin Oncol 2010;28:2674-2681. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20439644.

180. Falini B, Martelli MP, Bolli N, et al. Acute myeloid leukemia with mutated nucleophosmin (NPM1): is it a distinct entity? Blood 2011;117:1109-1120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21030560.

181. Hollink IH, Zwaan CM, Zimmermann M, et al. Favorable prognostic impact of NPM1 gene mutations in childhood acute myeloid leukemia, with emphasis on cytogenetically normal AML. Leukemia 2009;23:262-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19020547.

182. Hollink IH, Feng Q, Danen-van Oorschot AA, et al. Low frequency of DNMT3A mutations in pediatric AML, and the identification of the OCI-AML3 cell line as an in vitro model. Leukemia 2012;26:371-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21836609.

183. Hou HA, Kuo YY, Liu CY, et al. DNMT3A mutations in acute myeloid leukemia: stability during disease evolution and clinical implications. Blood 2012;119:559-568. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22077061.

184. Meshinchi S, Woods WG, Stirewalt DL, et al. Prevalence and prognostic significance of Flt3 internal tandem duplication in pediatric acute myeloid leukemia. Blood 2001;97:89-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11133746.

185. Weisser M, Kern W, Schoch C, et al. Risk assessment by monitoring expression levels of partial tandem duplications in the MLL gene in acute myeloid leukemia during therapy. Haematologica 2005;90:881-889. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15996925.

186. Lane S, Saal R, Mollee P, et al. A >or=1 log rise in RQ-PCR transcript levels defines molecular relapse in core binding factor acute myeloid leukemia and predicts subsequent morphologic relapse. Leuk Lymphoma 2008;49:517-523. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18297529.

187. Corbacioglu A, Scholl C, Schlenk RF, et al. Prognostic impact of minimal residual disease in CBFB-MYH11-positive acute myeloid leukemia. J Clin Oncol 2010;28:3724-3729. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20625124.

188. Viehmann S, Teigler-Schlegel A, Bruch J, et al. Monitoring of minimal residual disease (MRD) by real-time quantitative reverse transcription PCR (RQ-RT-PCR) in childhood acute myeloid leukemia

with AML1/ETO rearrangement. Leukemia 2003;17:1130-1136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12764380.

189. Inaba H, Coustan-Smith E, Cao X, et al. Comparative analysis of different approaches to measure treatment response in acute myeloid leukemia. J Clin Oncol 2012;30:3625-3632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22965955.

190. Varella-Garcia M, Hogan CJ, Odom LF, et al. Minimal residual disease (MRD) in remission t(8;21) AML and in vivo differentiation detected by FISH and CD34+ cell sorting. Leukemia 2001;15:1408-1414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11516101.

191. Sexauer A, Perl A, Yang X, et al. Terminal myeloid differentiation in vivo is induced by FLT3 inhibition in FLT3/ITD AML. Blood 2012;120:4205-4214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23012328.

192. Cloos J, Goemans BF, Hess CJ, et al. Stability and prognostic influence of FLT3 mutations in paired initial and relapsed AML samples. Leukemia 2006;20:1217-1220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16642044.

193. Chou WC, Hou HA, Liu CY, et al. Sensitive measurement of quantity dynamics of FLT3 internal tandem duplication at early time points provides prognostic information. Ann Oncol 2011;22:696-704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20693296.

194. Schiller J, Praulich I, Krings Rocha C, Kreuzer KA. Patient-specific analysis of FLT3 internal tandem duplications for the prognostication and monitoring of acute myeloid leukemia. Eur J Haematol 2012;89:53-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22458420.

195. Suzuki T, Kiyoi H, Ozeki K, et al. Clinical characteristics and prognostic implications of NPM1 mutations in acute myeloid leukemia. Blood 2005;106:2854-2861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15994285.

196. Papadaki C, Dufour A, Seibl M, et al. Monitoring minimal residual disease in acute myeloid leukaemia with NPM1 mutations by quantitative PCR: clonal evolution is a limiting factor. Br J Haematol 2009;144:517-523. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19055671.

197. Kronke J, Schlenk RF, Jensen KO, et al. Monitoring of minimal residual disease in NPM1-mutated acute myeloid leukemia: a study from the German-Austrian acute myeloid leukemia study group. J Clin Oncol 2011;29:2709-2716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21555683.

198. Kristensen T, Moller MB, Friis L, et al. NPM1 mutation is a stable marker for minimal residual disease monitoring in acute myeloid leukaemia patients with increased sensitivity compared to WT1 expression. Eur J Haematol 2011;87:400-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21707751.

199. Gorello P, Cazzaniga G, Alberti F, et al. Quantitative assessment of minimal residual disease in acute myeloid leukemia carrying nucleophosmin (NPM1) gene mutations. Leukemia 2006;20:1103-1108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16541144.

200. Barragan E, Pajuelo JC, Ballester S, et al. Minimal residual disease detection in acute myeloid leukemia by mutant nucleophosmin (NPM1): comparison with WT1 gene expression. Clin Chim Acta 2008;395:120-123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18590714.

201. Schnittger S, Kern W, Tschulik C, et al. Minimal residual disease levels assessed by NPM1 mutation-specific RQ-PCR provide important prognostic information in AML. Blood 2009;114:2220-2231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19587375.

202. Stahl T, Badbaran A, Kroger N, et al. Minimal residual disease diagnostics in patients with acute myeloid leukemia in the post-transplant period: comparison of peripheral blood and bone marrow

analysis. Leuk Lymphoma 2010;51:1837-1843. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20849383.

203. Miglino M, Colombo N, Grasso R, et al. Nucleophosmin gene-based monitoring in de novo cytogenetically normal acute myeloid leukemia with nucleophosmin gene mutations: comparison with cytofluorimetric analysis and study of Wilms tumor gene 1 expression. Leuk Lymphoma 2012;53:2214-2217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22475129.

204. Schnittger S, Schoch C, Dugas M, et al. Analysis of FLT3 length mutations in 1003 patients with acute myeloid leukemia: correlation to cytogenetics, FAB subtype, and prognosis in the AMLCG study and usefulness as a marker for the detection of minimal residual disease. Blood 2002;100:59-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12070009.

205. Smith LL, Pearce D, Smith ML, et al. Development of a quantitative real-time polymerase chain reaction method for monitoring CEBPA mutations in normal karyotype acute myeloid leukaemia. Br J Haematol 2006;133:103-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16512836.

206. Cilloni D, Messa F, Arruga F, et al. Early prediction of treatment outcome in acute myeloid leukemia by measurement of WT1 transcript levels in peripheral blood samples collected after chemotherapy. Haematologica 2008;93:921-924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18443273.

207. Cilloni D, Renneville A, Hermitte F, et al. Real-time quantitative polymerase chain reaction detection of minimal residual disease by standardized WT1 assay to enhance risk stratification in acute myeloid leukemia: a European LeukemiaNet study. J Clin Oncol 2009;27:5195-5201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19752335.

208. Willasch AM, Gruhn B, Coliva T, et al. Standardization of WT1 mRNA quantitation for minimal residual disease monitoring in childhood AML and implications of WT1 gene mutations: a European multicenter study. Leukemia 2009;23:1472-1479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19322206.

209. Venditti A, Buccisano F, Del Poeta G, et al. Level of minimal residual disease after consolidation therapy predicts outcome in acute myeloid leukemia. Blood 2000;96:3948-3952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11090082.

210. Loken MR, Alonzo TA, Pardo L, et al. Residual disease detected by multidimensional flow cytometry signifies high relapse risk in patients with de novo acute myeloid leukemia: a report from Children's Oncology Group. Blood 2012;120:1581-1588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22649108.

211. Buccisano F, Maurillo L, Gattei V, et al. The kinetics of reduction of minimal residual disease impacts on duration of response and survival of patients with acute myeloid leukemia. Leukemia 2006;20:1783-1789. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16838027.

212. Maurillo L, Buccisano F, Del Principe MI, et al. Toward optimization of postremission therapy for residual disease-positive patients with acute myeloid leukemia. J Clin Oncol 2008;26:4944-4951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18606980.

213. Maurillo L, Buccisano F, Spagnoli A, et al. Monitoring of minimal residual disease in adult acute myeloid leukemia using peripheral blood as an alternative source to bone marrow. Haematologica 2007;92:605-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17488683.

214. Al-Mawali A, Gillis D, Lewis I. The use of receiver operating characteristic analysis for detection of minimal residual disease using five-color multiparameter flow cytometry in acute myeloid leukemia identifies patients with high risk of relapse. Cytometry B Clin Cytom 2009;76:91-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18727068.

215. Feller N, van der Velden VH, Brooimans RA, et al. Defining consensus leukemia-associated immunophenotypes for detection of

minimal residual disease in acute myeloid leukemia in a multicenter setting. Blood Cancer J 2013;3:e129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23912609.

216. Voskova D, Schnittger S, Schoch C, et al. Use of five-color staining improves the sensitivity of multiparameter flow cytomeric assessment of minimal residual disease in patients with acute myeloid leukemia. Leuk Lymphoma 2007;48:80-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17325851.

217. Zalewska-Szewczyk B, Gach A, Wyka K, et al. The cross-reactivity of anti-asparaginase antibodies against different L-asparaginase preparations. Clin Exp Med 2009;9:113-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19184328.

218. Martin MG, Augustin KM, Uy GL, et al. Salvage therapy for acute myeloid leukemia with fludarabine, cytarabine, and idarubicin with or without gemtuzumab ozogamicin and with concurrent or sequential G-CSF. Am J Hematol 2009;84:733-737. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19806665.

219. 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;80:115-126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18076637.

220. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9625576.

221. 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;99:939-944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9432047.

222. 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;9:1210-1214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2045861.

223. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21848522.

224. Faderl S, Ferrajoli A, Wierda W, et al. Clofarabine combinations as acute myeloid leukemia salvage therapy. Cancer 2008;113:2090-2096. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18756533.

225. Faderl S, Wetzler M, Rizzieri D, et al. Clofarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukemia: results from the CLASSIC I Trial. J Clin Oncol 2012;30:2492-2499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22585697.

226. Jensen MK, Johansen P, Stentoft J. Salvage therapy with low-dose cytosine arabinoside in refractory or relapsed acute non-lymphocytic leukaemia: a report on 25 patients. Eur J Haematol 1994;52:236-239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8005235.

227. Al-Ali HK, Jaekel N, Junghanss C, et al. Azacitidine in patients with acute myeloid leukemia medically unfit for or resistant to chemotherapy: a multicenter phase I/II study. Leuk Lymphoma 2012;53:110-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21767242.

228. Blum W, Klisovic RB, Hackanson B, et al. Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia. J Clin Oncol 2007;25:3884-3891. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17679729.

229. 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;15:833-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9053511.

230. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17251531.