

NCCN

Acute Myeloid Leukemia, Version 3.2017

Clinical Practice Guidelines in Oncology

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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 it accounts for the largest number of annual deaths from leukemias in the United States. An estimated 21,380 people will be diagnosed with and 10,590 pa-

Abstract

Acute myeloid leukemia (AML) is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths due to leukemias in the United States. This portion of the NCCN Guidelines for AML focuses on management and provides recommendations on the workup, diagnostic evaluation, and treatment options for younger (age <60 years) and older (age ≥60 years) adult patients.

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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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. [The full NCCN Guidelines for Acute Myeloid Leukemia are not printed in this issue of JNCCN but can be accessed online at NCCN.org.](#)

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Disclosures for the NCCN Acute Myeloid Leukemia Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Acute Myeloid Leukemia Panel members can be found on page 957. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit [NCCN.org](#).

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tients will die of AML in 2017.¹ Median age at diagnosis is 67 years, with 54% of patients diagnosed at ≥65 years of age (approximately one-third are diagnosed at ≥75 years).² Thus, as the population ages, the incidence of AML, along with myelodysplastic syndromes (MDS), seems to be increasing.

Therapy-related MDS/AML (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. Reports suggest that therapy-related MDS/AML may account for 5% to 20% of patients with MDS/AML.³⁻⁵ Two well-documented categories of cytotoxic agents associated with the development of therapy-related MDS/AML are alkylating agents and topoisomerase inhibitors.^{3,6,7} Treatment with antimetabolites, such as the purine analogue fludarabine, has also been associated

with therapy-related MDS/AML in patients with lymphoproliferative disorders, particularly when administered in combination with alkylating agents.^{8,9} Radiotherapy, especially in the context of myeloablative therapy (eg, total-body irradiation or radioimmunotherapy) given before autologous hematopoietic cell transplantation (HCT) may also increase the risk for therapy-related MDS/AML.^{10,11} 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.⁷

The NCCN AML Panel convenes annually to update recommendations for the diagnosis and treatment of AML in adults, which are based on a review of recently published clinical trials that have led to significant improvements in treatment

Text cont. on page 936.

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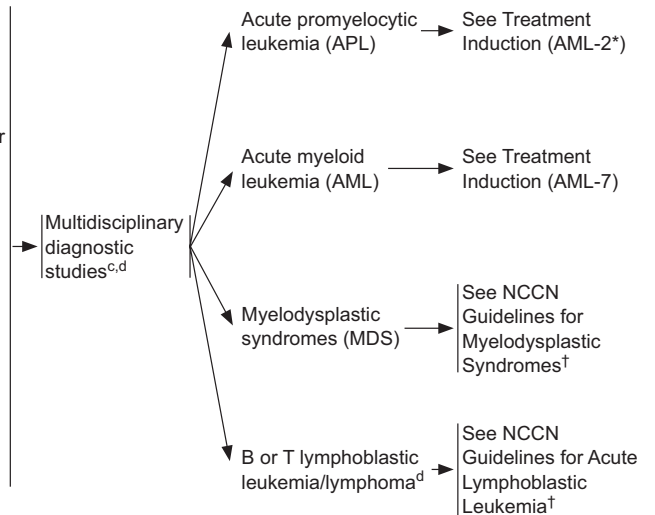
KEY:

*Discussion Section Writing Committee

Specialties: #Hematology/Hematology Oncology; #Bone
Marrow Transplantation; #Internal Medicine; †Medical
Oncology; #Pathology

EVALUATION FOR ACUTE LEUKEMIA

- History and physical (H&P)
- Complete blood count (CBC), platelets, differential, chemistry profile, uric acid, lactate dehydrogenase (LDH)
- Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen
- Bone marrow with cytogenetics (karyotype ± FISH) and molecular analyses (KIT, FLT3-ITD, NPM1, CEBPA, and other mutations)^a
- Immunophenotyping and cytochemistry
- Human leukocyte antigen (HLA) typing for patient with potential hematopoietic cell transplantation (HCT) in the future (except for patients with a major contraindication to HCT)
- CT of brain without contrast, if CNS hemorrhage suspected^b
- Brain MRI with contrast, if leukemic meningitis suspected^b
- PET/CT, if clinical suspicion for extramedullary disease
- 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 2016)DIAGNOSIS^{c,d,e,f}

*Available online, in the complete version of these guidelines, at NCCN.org.

†Available at NCCN.org.

^aMolecular abnormalities (KIT, FLT3-ITD, NPM1, CEBPA, and other mutations) are important for prognostication in a subset of patients (category 2A) and may guide therapeutic intervention (category 2B) (See AML-A*). Multiplex gene panels and sequencing assays are available for the assessment of other molecular abnormalities that have prognostic impact in AML or eligibility for clinical trial (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. Circulating blasts from peripheral blood can be used to detect molecular abnormalities in patients with blast counts >1000/mcL.

^bFor 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 before first consolidation for patients with monocytic differentiation, mixed phenotype acute leukemia, WBC >40,000/mcL at diagnosis, extramedullary disease, or high risk APL. Consider administration of one dose of IT chemotherapy (methotrexate or cytarabine) at time of diagnostic LP. See Evaluation and Treatment of CNS Leukemia (AML-B*).

^cThe WHO 2016 classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% 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.

^dWhen presented with rare cases such as acute leukemias of ambiguous lineage including mixed phenotype acute leukemias (according to 2016 WHO classification), consultation with an experienced hematopathologist is strongly recommended.

^eYoung 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.

^fPatients 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.

AML-1

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

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CLASSIFICATION

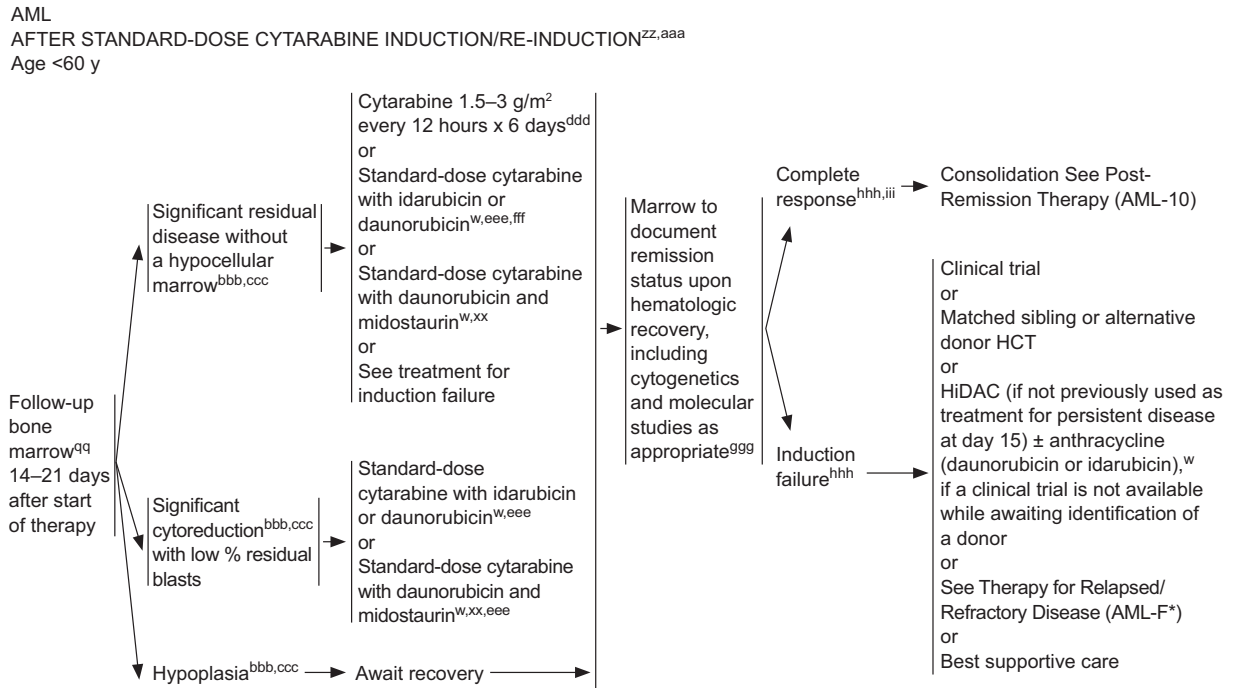
TREATMENT INDUCTION^{pp,qq}

<p>Age^{nn,oo} <60 y →</p>	<p>Clinical trial (preferred) or Standard-dose cytarabine 100–200 mg/m² continuous infusion x 7 days with idarubicin 12 mg/m² or daunorubicin 60–90 mg/m² x 3 days^{rr,ss} (category 1) or Standard-dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and cladribine 5 mg/m² x 5 days (category 2A)^{tt} or High-dose cytarabine (HiDAC)^{ss,uu} 2 g/m² every 12 hours x 6 days^{vv} or 3 g/m² every 12 h x 4 days^{www} with idarubicin 12 mg/m² or daunorubicin 60 mg/m² x 3 days (1 cycle) (category 1 for patients ≤45 y, category 2B for other age groups) or Standard dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and oral midostaurin 50 mg every 12 hours, days 8-21^{xx} (FLT3-mutated AML) or Fludarabine 30 mg/m² IV days 2–6, HiDAC 2 g/m² over 4 hours starting 4 hours after fludarabine on days 2–6, idarubicin 8 mg/m² IV days 4–6, and G-CSF SC daily days 1–7 (category 2B)^{yy}</p>	<p>→ See Follow-up (AML-8)</p> <p>→ See Follow-up (AML-9)</p> <p>→ See Follow-up (AML-8)</p> <p>→ See Follow-up (AML-9)</p>
<p>AML ≥60 y See AML-11</p>	<p>(This section is merged into the table above for better readability)</p>	<p>(This section is merged into the table above for better readability)</p>

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<p>ⁿⁿPatients with elevated blast counts 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.</p> <p>^{oo}Poor performance status and comorbid medical condition, in addition to age, are factors that influence ability to tolerate standard induction therapy.</p> <p>^{pp}See Supportive Care (AML-C 1 of 2*).</p> <p>^{qq}See Monitoring During Therapy (AML-E*).</p> <p>^{rr}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, et al. Anthracycline dose intensification in acute myeloid leukemia. <i>N Engl J Med</i> 2009;361:1249-1259. If there is residual disease on days 12–14, the additional daunorubicin dose is 45 mg/m² x 3 days. Burnett AK, et al. A randomized comparison of daunorubicin 90 mg/m² vs 60 mg/m² in AML induction: results from the UK NCRI AML17 trial in 1206 patients. <i>Blood</i> 2015;125:3878-3885.</p> <p>^{ss}For patients with impaired cardiac function, other cytarabine-based regimens alone or with other agents can be considered.</p> <p>^{tt}Holowiecki J, 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. <i>J Clin Oncol</i> 2012;30:2441-2448. Although this trial showed an advantage for the addition of cladribine to standard 7+3, bone marrow aspirates were not performed after the first cycle of induction until either counts recovered or blasts reappeared in the peripheral blood, which would delay administration of a second cycle of induction compared to standard practice in the United States.</p>	<p>^{uu}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. Kern W and Estey EH. High-dose cytarabine arabinoside in the treatment of acute myeloid leukemia: review of three randomized trials. <i>Cancer</i> 2006;107:116-124. However, one recent study showed that high-dose cytarabine may improve the outcome for younger patients. Willemze R, et al. High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: results of the EORTC-GIMEMA AML-12 trial. <i>J Clin Oncol</i> 2014;32:219-228.</p> <p>^{vv}Weick JK, 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. <i>Blood</i> 1996;88:2841-2851.</p> <p>^{ww}Bishop JF, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. <i>Blood</i> 1996;87:1710-1717.</p> <p>^{xx}This regimen is for FLT3 mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. The multi-kinase inhibitor midostaurin prolongs survival compared with placebo in combination with daunorubicin/cytarabine induction, high-dose consolidation, and as maintenance therapy in newly diagnosed acute myeloid leukemia patients age 18-60 with FLT3 mutations: an international prospective randomized placebo-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). <i>Blood</i> 2015;126:6.</p> <p>^{yy}Burnett AK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. <i>J Clin Oncol</i> 2013;31:3360-3368.</p>
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AML-7



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^wFor regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course.

^{qq}See Monitoring During Therapy (AML-E*).

^{xx}This regimen is for FLT3 mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. The multi-kinase inhibitor midostaurin prolongs survival compared with placebo in combination with daunorubicin/cytarabine induction, high-dose consolidation, and as maintenance therapy in newly diagnosed acute myeloid leukemia patients age 18-60 with FLT3 mutations: an international prospective randomized placebo-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). Blood 2015;126:6.

^{zz}Consider clinical trials for patients with targeted molecular abnormalities.

^{aaa}Begin alternate donor search (haploidentical, unrelated donor or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT.

^{bbb}If ambiguous, consider repeat bone marrow biopsy in 5–7 days before proceeding with therapy.

^{ccc}Hypoplasia is defined as cellularity less than 10%–20% of which the residual blasts are less than 5%–10% (ie, blast percentage of residual cellularity).

^{ddd}For re-induction, no data are available to show superiority with intermediate or high-dose cytarabine.

^{eee}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 if >50% cytoreduction.

^{fff}If daunorubicin 90 mg/m² was used in induction, the recommended dose for daunorubicin for reinduction prior to count recovery is 45 mg/m² for no more than 2 doses. Analogously, if idarubicin 12 mg/m² was used for induction, the early reinduction dose should be limited to 10 mg/m² for 1 or 2 doses.

^{ggg}MRD testing is under investigation and may have prognostic significance. See Discussion.

^{hhh}See Response Criteria for Acute Myeloid Leukemia (AML-D*).

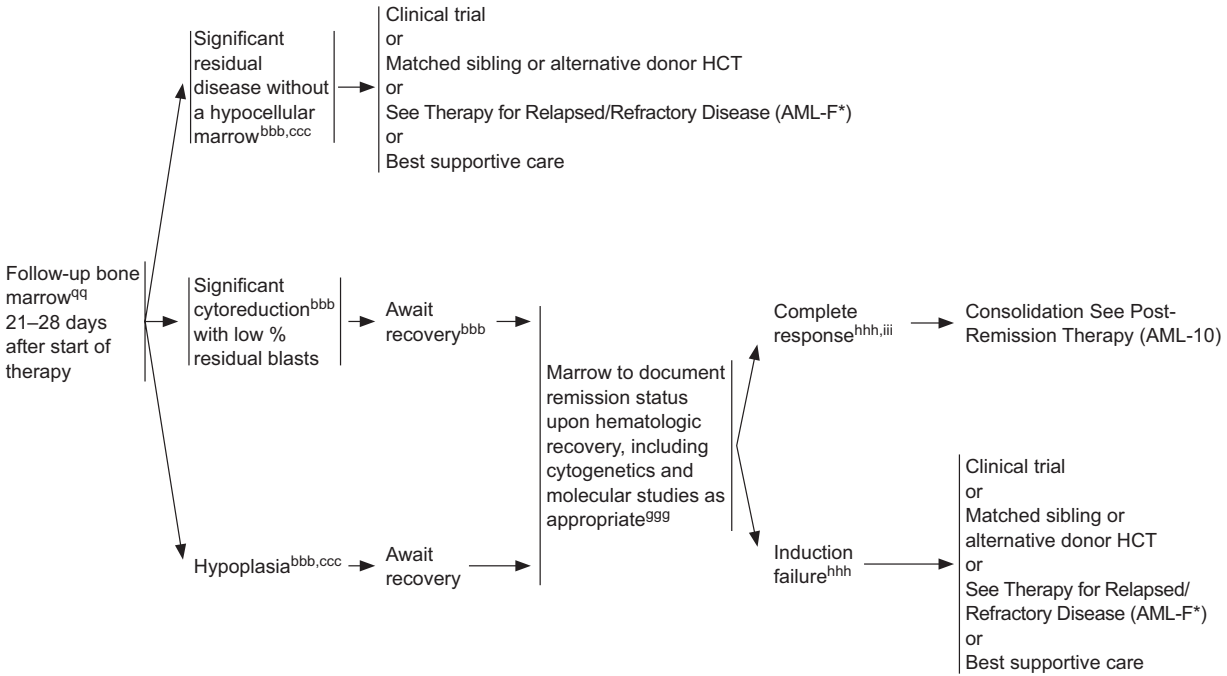
ⁱⁱⁱScreening LP should be considered at first remission before first consolidation for patients with monocytic differentiation, mixed phenotype acute leukemia, WBC >40,000/mcL at diagnosis, or extramedullary disease. See Evaluation and Treatment of CNS Leukemia (AML-B*).

AML-8

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

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AML
 AFTER HIGH-DOSE CYTARABINE INDUCTION/RE-INDUCTION^{zz,aaa}
 Age <60 y



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^{qq}See Monitoring During Therapy (AML-E*).

^{zz}Consider clinical trials for patients with targeted molecular abnormalities.

^{aaa}Begin alternate donor search (haploidentical, unrelated donor or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT.

^{bbb}If ambiguous, consider repeat bone marrow biopsy in 5–7 days before proceeding with therapy.

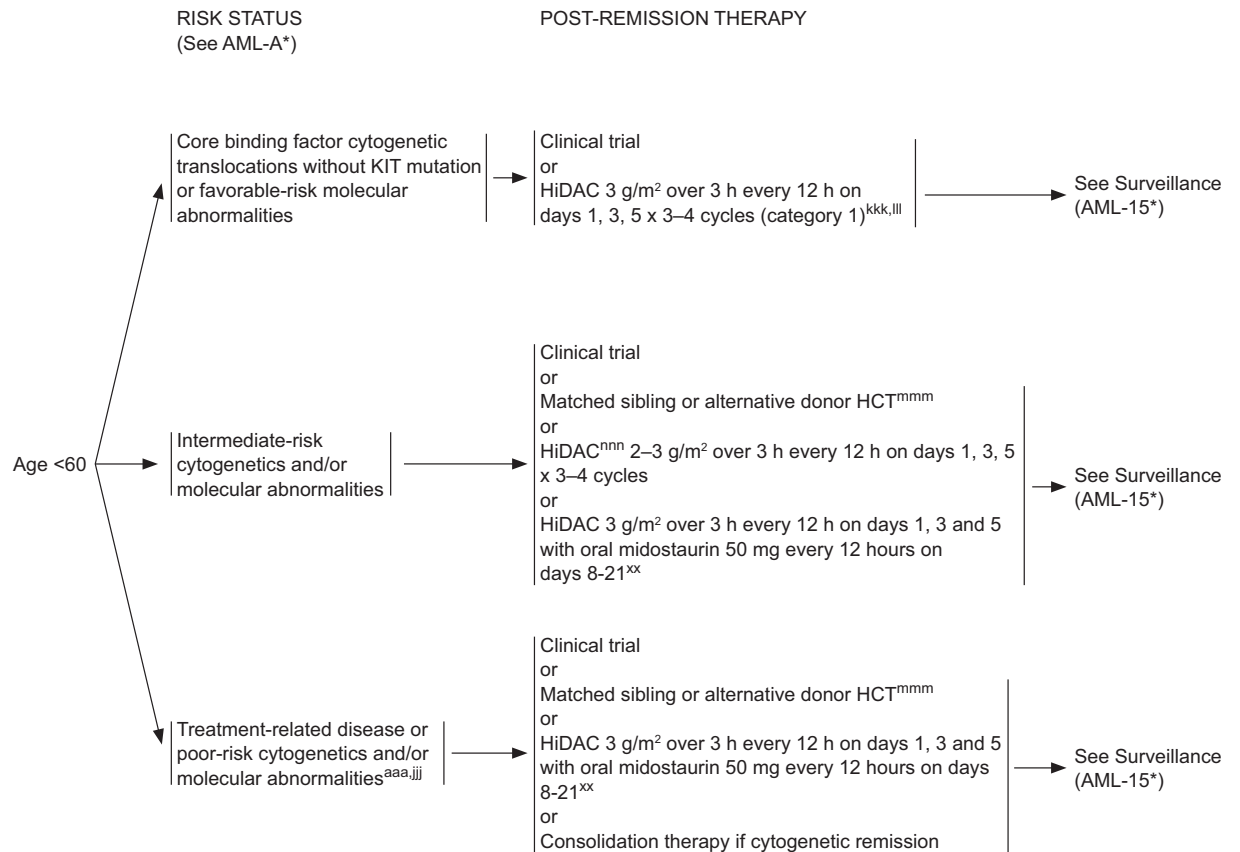
^{ccc}Hypoplasia is defined as cellularity less than 10%–20% of which the residual blasts are less than 5%–10% (ie, blast percentage of residual cellularity).

⁹⁹⁹MRD testing is under investigation and may have prognostic significance. See Discussion.

^{hhh}See Response Criteria for Acute Myeloid Leukemia (AML-D*).

ⁱⁱⁱScreening LP should be considered at first remission before first consolidation for patients with monocytic differentiation, mixed phenotype acute leukemia, WBC >40,000/mcL at diagnosis, or extramedullary disease. See Evaluation and Treatment of CNS Leukemia (AML-B*).

AML-9



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^{xx}This regimen is for FLT3 mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. The multi-kinase inhibitor midostaurin prolongs survival compared with placebo in combination with daunorubicin/cytarabine induction, high-dose consolidation, and as maintenance therapy in newly diagnosed acute myeloid leukemia patients age 18-60 with FLT3 mutations: an international prospective randomized placebo-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). *Blood* 2015;126:6.

^{aaa}Begin alternate donor search (haploidentical, unrelated donor or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT.

ⁱⁱⁱFLT3-ITD mutation is a poor-risk feature in the setting of otherwise normal karyotype, and these patients should be considered for clinical trials where available.

^{kkk}Mayer RJ, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. *N Engl J Med* 1994;331:896-903.

ⁱⁱⁱAlternate dosing of cytarabine for postremission therapy has been reported (see Discussion). Lowenberg B, et al. Cytarabine dose for acute myeloid leukemia. *N Engl J Med* 2011;364:1027-1036. Higher doses have not been evaluated in favorable-risk molecular abnormalities.

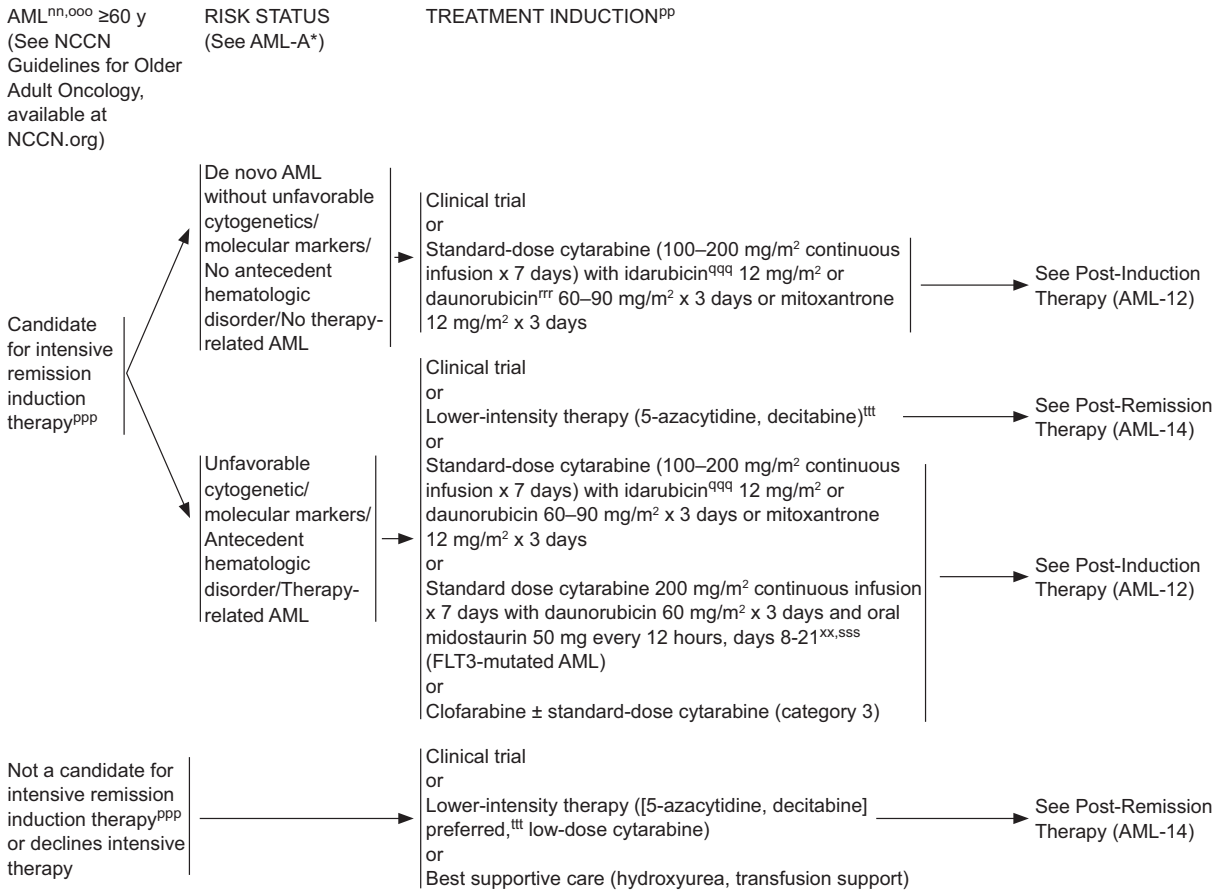
^{mmm}Patients may require at least one cycle of high-dose cytarabine consolidation while donor search is in progress to maintain remission. Patients may proceed directly to transplant following achievement of remission if a donor (sibling or alternative) is available.

ⁿⁿⁿThere is no evidence that HiDAC is superior to intermediate doses (1.5 g/m² daily x 5 days) of cytarabine in patients with intermediate-risk cytogenetics.

AML-10

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

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ⁿⁿPatients with elevated blast counts 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.

^{pp}See Supportive Care (AML-C 1 of 2*).

^{xx}This regimen is for FLT3 mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. The multi-kinase inhibitor midostaurin prolongs survival compared with placebo in combination with daunorubicin/cytarabine induction, high-dose consolidation, and as maintenance therapy in newly diagnosed acute myeloid leukemia patients age 18-60 with FLT3 mutations: an international prospective randomized placebo-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). *Blood* 2015;126:6.

^{ooo}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, 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.

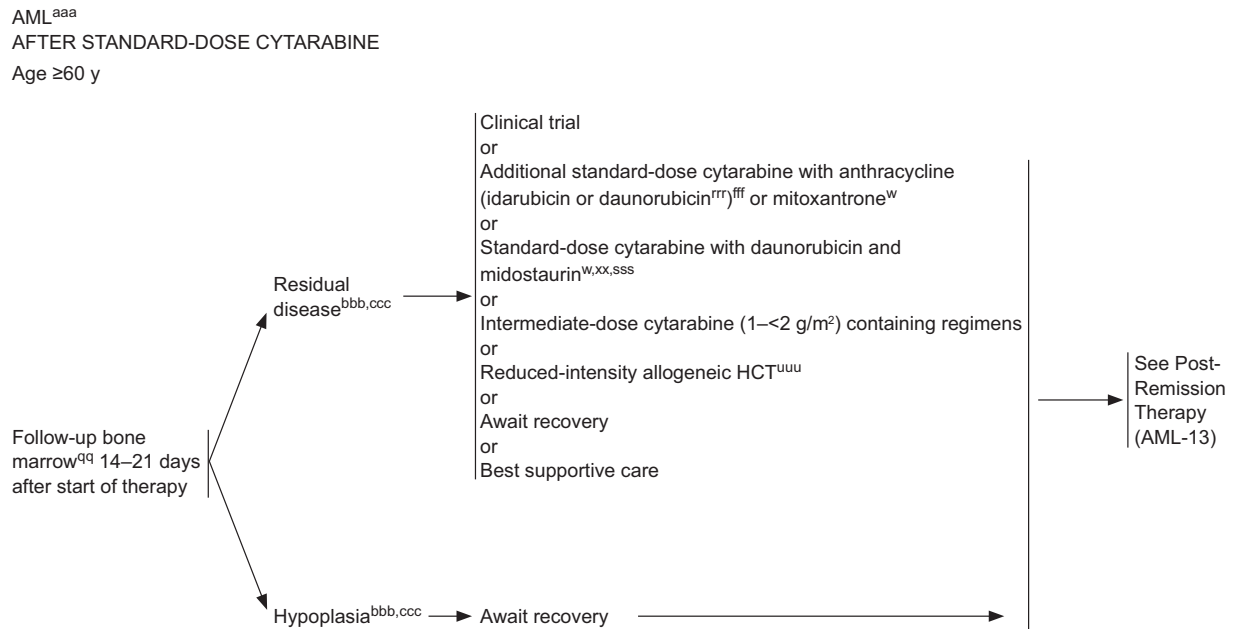
^{ppp}Factors in decisions about fitness for induction chemotherapy include age, performance status, functional status, and comorbid conditions.

^{qqq}For patients who exceed anthracycline dose or have cardiac issues but are still able to receive aggressive therapy, alternative non-anthracycline-containing regimens may be considered (eg, FLAG, CLAG).

^{rrr}The complete response rates and 2-year 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, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med* 2009;361:1235-1248).

^{sss}The RATIFY trial studied patients age 18-60y. An extrapolation of the data suggests that older patients who are fit to receive 7+3 should be offered midostaurin since it seems to provide a survival benefit without undue toxicity.

^{ttt}Response may not be evident before 3–4 cycles of treatment with hypomethylating agents (5-azacytidine, decitabine). Continue hypomethylating agents until progression if patient tolerating therapy. Similar delays in response are likely with novel agents on a clinical trial, but endpoints will be defined by the protocol.



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^wFor regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course.

^{qq}See Monitoring During Therapy (AML-E*).

^{xx}This regimen is for FLT3 mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. The multi-kinase inhibitor midostaurin prolongs survival compared with placebo in combination with daunorubicin/cytarabine induction, high-dose consolidation, and as maintenance therapy in newly diagnosed acute myeloid leukemia patients age 18-60 with FLT3 mutations: an international prospective randomized placebo-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). *Blood* 2015;126:6.

^{aaa}Begin alternate donor search (haploidentical, unrelated donor or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT.

^{bbb}If ambiguous, consider repeat bone marrow biopsy in 5–7 days before proceeding with therapy.

^{ccc}Hypoplasia is defined as cellularity less than 10%–20% of which the residual blasts are less than 5%–10% (ie, blast percentage of residual cellularity).

^{fff}If daunorubicin 90 mg/m² was used in induction, the recommended dose for daunorubicin for reinduction prior to count recovery is 45 mg/m² for no more than 2 doses. Analogously, if idarubicin 12 mg/m² was used for induction, the early reinduction dose should be limited to 10 mg/m² for 1 or 2 doses.

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^{sss}The RATIFY trial studied patients age 18-60y. An extrapolation of the data suggests that older patients who are fit to receive 7+3 should be offered midostaurin since it seems to provide a survival benefit without undue toxicity.

^{uuu}Reduced-intensity transplant is a reasonable option in patients with identified donors available to start conditioning within 4-6 weeks from start of induction therapy. Patients without an identified donor would most likely need some additional therapy as a bridge to transplant. Reduced-intensity HCT 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 <10% blasts). It is preferred that this approach be given in the context of a clinical trial.

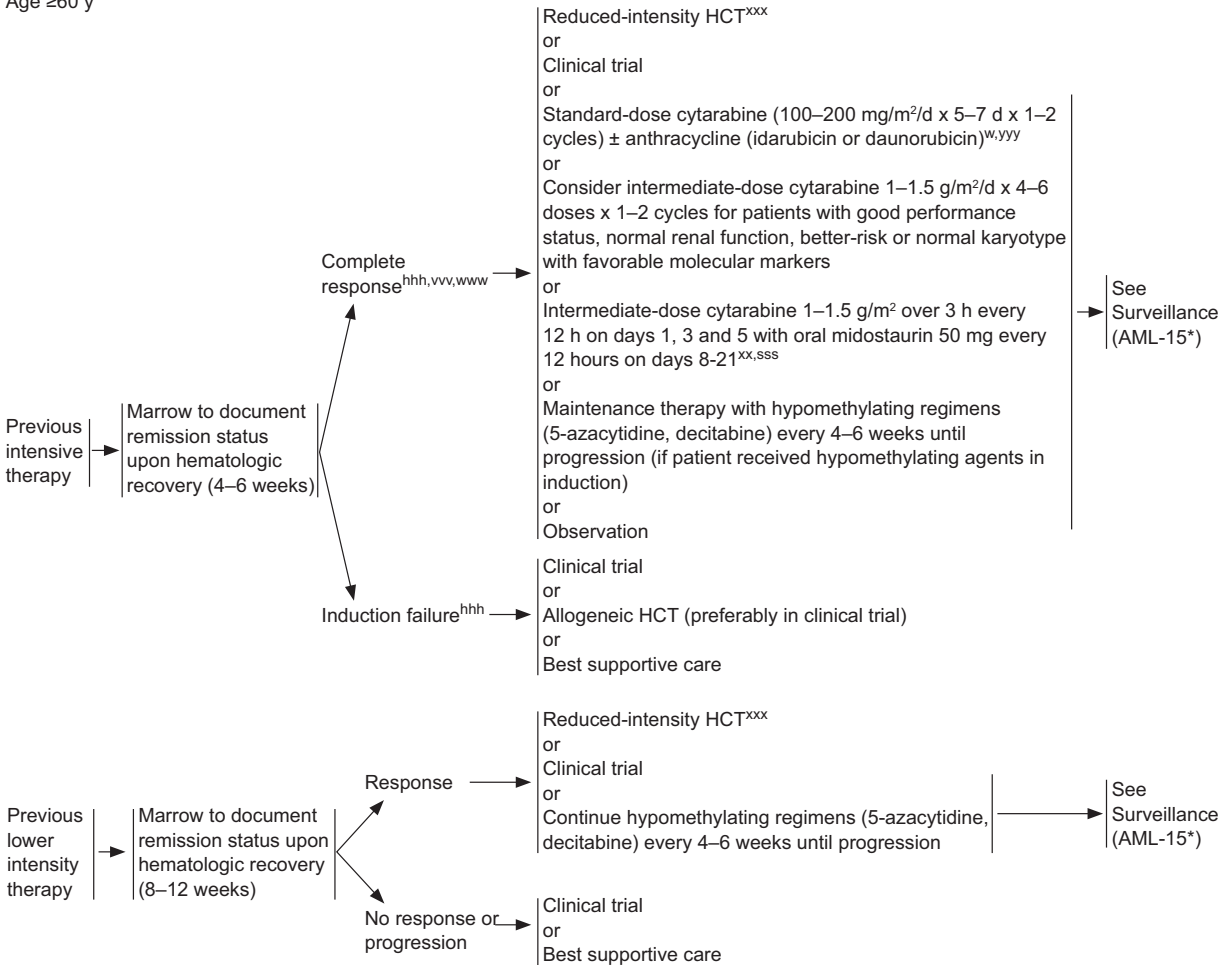
AML-12

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

Acute Myeloid Leukemia, Version 3.2017

AML POST-REMISSION THERAPY

Age ≥60 y



*Available online, in the complete version of these guidelines, at NCCN.org.

^wFor regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course.

^{xx}This regimen is for FLT3 mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. The multi-kinase inhibitor midostaurin prolongs survival compared with placebo in combination with daunorubicin/cytarabine induction, high-dose consolidation, and as maintenance therapy in newly diagnosed acute myeloid leukemia patients age 18-60 with FLT3 mutations: an international prospective randomized placebo-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). *Blood* 2015;126:6.

^{hhh}See Response Criteria for Acute Myeloid Leukemia (AML-D*).

^{sss}The RATIFY trial studied patients age 18-60y. An extrapolation of the data suggests that older patients who are fit to receive 7+3 should be offered midostaurin since it seems to provide a survival benefit without undue toxicity.

^{vvv}Patients in remission may be screened with LP if initial WBC count >40,000/mcL or monocytic histology. See Evaluation and Treatment of CNS Leukemia (AML-B*).

^{www}HLA-typing for patients considered strong candidates for allogeneic transplantation.

^{xxx}Patients who are deemed as strong candidates for HCT and who have an available donor should be transplanted in first remission.

^{yyy}An excellent outcome was reported for outpatient consolidation that provides another option for elderly patients. Gardin C, 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.

AML-13
AML-14

Cont. from page 927.

Acute Myeloid Leukemia, Version 3.2017

or have yielded new information regarding biologic factors that may have prognostic importance. This portion of the NCCN Guidelines discusses recommendations outlined for the workup and management of AML. To view the complete and most updated version of these guidelines, visit NCCN.org.

Workup

Evaluation and initial workup for suspected AML consists of a comprehensive medical history and physical examination. Laboratory evaluations include blood chemistry and a CBC including platelets and a differential of white blood cells (WBCs); serum uric acid and lactate dehydrogenase have prognostic relevance and should be evaluated.^{12,13} Bone marrow analysis with cytogenetics (karyotype ± fluorescence in situ hybridization) is necessary for risk stratification and to guide therapy of AML. A comprehensive evaluation of several molecular markers (eg, *FLT3*, *NPM1*, *CEBPA*, *KIT*, and other mutations) is important for risk assessment and prognostication in a subset of patients (category 2A), and may guide treatment decisions (category 2B). More comprehensive panel arrays are available and institutions may have established sequencing panels that include markers with currently unknown impact on prognosis or that do not determine clinical trial eligibility. Recent studies have reported on the prognostic impact of a number of molecular abnormalities in patients with AML (see “Molecular Markers and Risk Stratification” available online, in this guideline, at NCCN.org). Adequate marrow should be available at the time of diagnosis or relapse for molecular studies as per the institutional practice. A local pathologist should be consulted to discuss ways to optimize sample collection. If molecular testing is not available at the treatment center, evaluation at an outside reference laboratory or transfer to another institution is recommended. Circulating blasts from peripheral blood can be used to detect molecular abnormalities in patients with blast counts >1,000/mcL.

Extramedullary presentation, including central nervous system (CNS) disease, is uncommon in patients with AML; however, if suspected, a PET/CT is recommended. Patients with significant CNS signs or symptoms at presentation should be evaluated using appropriate imaging techniques, such as radiography, CT, or MRI, for the detection of intracranial

bleeding, leptomeningeal disease, or mass lesions in either the brain or spinal cord. If CNS hemorrhage is suspected, a brain CT without contrast is recommended. If leukemic meningitis is suspected, a brain MRI with contrast is recommended. 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, adequate platelet support is available, and the circulating disease has been cleared through the initiation of systemic therapy. Routine screening LPs are not warranted at diagnosis in patients with AML. However, for patients at high risk for CNS disease, such as those with monocytic differentiation or high WBC count (>40,000/mcL)¹⁴ at presentation, a diagnostic LP should be considered as part of the documentation of remission status. Screening LPs should be considered at first remission before first consolidation in patients with monocytic differentiation, mixed phenotype acute leukemia, WBC count >40,000/mcL at diagnosis, high-risk acute promyelocytic leukemia (APL), or extramedullary disease, particularly in those not receiving high-dose cytarabine (HiDAC; ie, older patients). Patients proceeding to transplant should also be considered for screening LPs. For those who present with solitary extramedullary disease (currently referred to as myeloid sarcoma, and historically as granulocytic sarcoma or chloroma) without overt marrow disease, 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 common at presentation in many leukemias; thus, it is standard clinical practice to screen for coagulopathy by evaluating prothrombin time, partial thromboplastin time, and fibrinogen activity as part of the initial evaluation and before performing any invasive procedure. The need for a cardiac evaluation (eg, echocardiogram or multiple gated acquisition [MUGA] scan) should be determined based on individual risk factors. Patients with a history or symptoms of cardiac disease, prior exposure to cardiotoxic drugs or thoracic radiation, or those of an older age, should have an echocardiogram. In younger patients who are otherwise asymp-

tomatic with no history of cardiac disease, an echocardiogram can be considered. For those who are acutely ill, treatment should not be delayed for an echocardiogram. In a small study of 76 patients with cancer who were screened for cardiac disease, only 4 patients with cardiac abnormalities were identified; of these, the presence of cardiac disease did not change the course of treatment.¹⁵

Human leukocyte antigen (HLA) typing should be performed in all patients with newly diagnosed AML for whom allogeneic HCT would be considered. HLA typing of family members is recommended for patients aged <60 years who do not have favorable-risk cytogenetics, and tissue typing should be broadened to include alternative donor searches. In patients with any nonfavorable risk, a donor search should begin while the patient is recovering from induction chemotherapy rather than waiting for remission. HLA typing is routinely used in many institutions to select platelet donors for patients who exhibit alloimmunization to HLA-specific antigens.

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 myelodysplasia, to refine prognostic subgroups that may define treatment strategies.¹⁶ 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 had set the threshold between high-grade MDS and AML at 30% blasts, whereas the WHO classification lowered the threshold for diagnosing AML to $\geq 20\%$ 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 to that of patients with >30% blasts. The WHO classification system further allowed AML to be diagnosed in patients with abnormal hematopoiesis and characteristic

clonal structural cytogenetic abnormalities with $t(15;17)$, $t(8;21)$, and $inv(16)$ or $t(16;16)$ regardless of marrow blast percentage.

In 2003, the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in AML, accepted the cytochemical and immunophenotypic WHO criteria as the standard for diagnosing AML, including the reporting of myelodysplasia according to morphology.¹⁷ However, no evidence shows that myelodysplasia 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 was added for molecular markers found to have a prognostic impact.¹⁸ 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), $inv(3)(q21q26.2)$ 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 abnormalities such as mutated *NPM1* or *CEBPA* genes.¹⁸ In 2016, WHO expanded the recurrent genetic abnormalities to include 2 provisional categories, AML with *BCR-ABL1* rearrangement and AML with *RUNX1* mutation. AML with *BCR-ABL1* rearrangement is a rare de novo AML that may benefit from therapies that entail tyrosine kinase inhibitors; AML with *RUNX1* mutation is associated with a poorer prognosis.

In accordance with the 2016 WHO classification,¹⁹ a diagnosis of AML is made based on the presence of $\geq 20\%$ blasts in the marrow or peripheral blood. Accurate classification of AML requires multidisciplinary diagnostic studies (using immunohistochemistry, cytochemistry, or both, in addition to molecular genetics analysis). The NCCN AML Panel suggests that complementary diagnostic techniques can be used at the discretion of the pathology department. Some cases may still show evidence of both myeloid and lymphoid antigen expression on the leukemic cells and are thusly defined as acute leukemias of ambiguous lineage. This is further subgrouped into

acute undifferentiated leukemia, mixed phenotypic acute leukemia (MPAL) with *BCR-ABL1* rearrangement, MPAL with rearranged *KMT2A*, MPAL with B-cell/myeloid features not otherwise specified, and MPAL with T-cell/myeloid features not otherwise specified. The expression of both cytochemical and/or immunophenotypic characteristics of both lineages on the same cells is defined as biphenotypic, whereas expression of lineage-specific characteristics on different populations of leukemia cells is termed bilineal. When presented with rare cases such as acute leukemias of ambiguous lineage as defined by the 2016 WHO classification,¹⁹ consultation with an experienced hematopathologist is preferred.

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 patients with AML has not yet been incorporated into postremission monitoring strategies, except in those with APL. However, ongoing research is moving MRD monitoring to the forefront for all patients with AML (see “Role of MRD Monitoring” available online, in this guideline, at NCCN.org).

Management of AML in Patients Aged <60 Years

Induction Therapy

Standard induction regimens used for patients aged <60 years are based on a backbone of cytarabine plus an anthracycline, and have changed little in the past 40 years. Historically, in most large cooperative group trials, daunorubicin has been the most commonly used anthracycline at doses of 45 to 60 mg/m² daily for 3 days. Idarubicin, which has a longer intracellular retention time, used at doses of 12 mg/m² daily for 3 days, has had comparable remission rates with fewer patients requiring additional therapy at day 15 to achieve remission. Complete response (CR) rates for patients aged ≤50 years 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 overall survival (OS; 24 vs 16 months; $P=.003$) using daunorubicin 90 mg/m² daily for 3 days ($n=327$) versus 45 mg/m² daily for 3 days ($n=330$) in patients aged <60 years with previously untreated AML.²⁰ 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 aged <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.²⁰ In an update of the E1900 trial, high-dose daunorubicin maintained a higher response than standard-dose daunorubicin in patients <50 years of age (hazard ratio [HR], 0.66; $P=.002$).²¹ This benefit was observed regardless of risk cytogenetics. In addition, patients with *FLT3-ITD*-, *DNMT3A*-, and *NPM1*-mutant AML had improved OS. Patients aged 50 to 60 years with *FLT3-ITD* or *NPM1* mutations also benefitted from high-dose daunorubicin.²¹ High-dose daunorubicin was previously evaluated in a European trial that compared idarubicin 12 mg/m² daily for 3 or 4 days versus daunorubicin 80 mg/m² daily for 3 days in patients aged 50 to 70 years; CR rates were 83% and 70%, respectively ($P=.024$).²² No difference was seen in relapse rate, event-free survival (EFS), or OS outcomes between the treatment arms.

A recent systematic review and meta-analysis of 29 randomized controlled trials compared idarubicin with daunorubicin.²³ Idarubicin had a lower remission failure rate versus daunorubicin (risk ratio, 0.81; 95% CI, 0.66–0.99; $P=.04$), but no difference in early death or overall mortality was observed. Furthermore, this benefit was only seen when the dose ratio between daunorubicin and idarubicin was <5. Both high-dose daunorubicin and idarubicin resulted in 5-year survival rates between 40% and 50%.²³

It has been suggested that a daunorubicin dose of 60 mg/m² may be equally as effective as 90 mg/m² and have a lower toxicity. A study from Burnett et al²⁴ compared these 2 doses in 1,206 patients predominantly aged <60 years. There was no difference in CR rate (73% vs 75%; odds ratio [OR], 1.07; 95% CI, 0.83–1.39; $P=.60$). The 60-day mortality was higher in those receiving 90 mg/m² (10% vs 5%; HR, 1.98; 95% CI, 1.30–3.02; $P=.001$), although the 2-year OS rate was similar (59% vs 60%; HR, 1.16; 95%

CI, 0.95–1.43; $P=.15$).²³ A phase III randomized trial from the Polish Adult Leukemia Group evaluated the efficacy and safety of adding a purine analogue to an induction regimen comprising daunorubicin and cytarabine in patients aged ≤ 60 years with previously untreated AML ($n=652$).²⁵ In this study, patients were randomized to daunorubicin and cytarabine (daunorubicin, 60 mg/m² daily for 3 days, cytarabine, 200 mg/m² continuous infusion for 7 days; DA arm); DA with cladribine (5 mg/m² daily for 5 days; DAC arm); and DA with fludarabine (25 mg/m² daily for 5 days; DAF arm). Patients who achieved a partial response after induction could receive a second cycle of the assigned induction regimen. Postremission treatment was the same in the 3 arms. Patients who achieved a CR after induction received consolidation with a course of intermediate-dose cytarabine (1.5 g/m² on days 1–3) and mitoxantrone (10 mg/m² on days 3–5), followed by a course of HiDAC (2 g/m² every 12 hours on days 1, 3, and 5).²⁵ A similar proportion of patients in the 3 arms proceeded to allogeneic HCT. 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 with DAC compared with DA were observed for patients aged ≥ 50 years, those with an initial WBC count $\geq 50 \times 10^9/L$, and patients with a high-risk karyotype.²⁵ No significant improvements in efficacy were observed in the overall DAF arm with regard 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 a high-risk karyotype. The incidence of hematologic toxicities and other adverse events (AEs) were similar among treatment arms.²⁵ Although this randomized trial showed an advantage for the addition of cladribine to a standard induction regimen, bone marrow aspirates were not performed after the first cycle of induction until either counts recovered or blasts reappeared in the peripheral blood, which would delay administration of a second cycle of induction compared with standard practice in the United States.

Emerging data have demonstrated improved survival for patients with newly diagnosed *FLT3*-mutation-positive AML when midostaurin is added

to standard chemotherapy as part of frontline treatment,^{26–28} which led to its breakthrough designation and FDA approval in April 2017. In the CALGB 10603/RATIFY Alliance trial, patients aged 18 to 60 years ($n=717$) with newly diagnosed *FLT3*-positive AML (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) were randomized to receive standard cytarabine therapy (200 mg/m² daily for 7 days via continuous infusion) and daunorubicin (60 mg/m² on days 1–3) with placebo or midostaurin (50 mg, twice daily on days 8–22).²⁸ If residual disease in the bone marrow was observed on day 21, patients were treated with a second blinded course. Patients who achieved a CR received 4 cycles of HiDAC (3 g/m² every 3 hours on days 1, 3, and 5) with placebo or midostaurin (50 mg, twice daily on days 8–22) followed by a year of maintenance therapy with placebo or midostaurin (50 mg, twice daily).²⁸ Patients who received midostaurin with standard induction and consolidation therapy experienced a significant improvement in OS compared with those on the placebo arm (HR, 0.77; 95% CI, 0.63–0.95; $P=.007$).²⁸

The use of HiDAC as induction therapy continues to be a controversial option. The most recent study from the EORTC-GIMEMA AML-12 trial suggests that HiDAC (3 g/m² every 12 hours on days 1, 2, 5, and 7) improves outcomes in patients aged < 46 years.²⁹ This study randomized 1,900 patients between ages 15 and 60 years into 2 treatment groups: HiDAC and standard-dose cytarabine (SDAC; 100 mg/m²/d by continuous infusion for 10 days). Both groups were also given daunorubicin (50 mg/m²/d on days 1, 3, and 5) and etoposide (50 mg/m²/d on days 1–5). Data from a median 6-year follow-up indicate an OS rate near statistical significance (HiDAC, 42.5% vs SDAC, 38.7%; $P=.06$), and when separated by age with a cutoff of 46 years, the benefit was relegated to the younger patient cohort (HiDAC, 51.9% vs SDAC, 43.3%; $P=.009$) compared with those aged ≥ 46 years (HiDAC, 32.9% vs SDAC, 33.9%; $P=.91$). Other populations that benefited from HiDAC were patients at high-risk including those with very poor-risk cytogenetic abnormalities and/or *FLT3*-ITD mutation or with secondary AML. There was no significant increase in grade 3 or 4 toxicities except for an increase in conjunctivitis (grade 2–3) with HiDAC (12.4%) versus SDAC (0.5%); the incidence of AEs was equivalent (SDAC, 67.6% vs HiDAC, 66.2%). Patients with a CR received a

single consolidation cycle of daunorubicin and cytarabine (500 mg/m² every 12 hours for 6 days) and subsequent HCT.²⁹

HiDAC therapy during induction was initially explored 2 decades ago in 2 large cooperative group trials. In an Australian Leukemia Study Group trial,^{30,31} patients aged <60 years (n=301) were randomized to receive either HiDAC (3 g/m² every 12 hours on days 1, 3, 5, and 7 for a total of 24 g/m²) or SDAC (100 mg/m² daily for 7 days via continuous infusion); patients in both arms received daunorubicin (50 mg/m² on days 1–3) and etoposide (75 mg/m² daily for 7 days). CR rates were equivalent in both arms (71% and 74%, respectively), with significantly higher 5-year relapse-free survival (RFS) rates with HiDAC (48% vs 25%; *P*=.007).³¹ Patients in both treatment arms received only 2 cycles of SDAC, 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.³⁰ However, treatment-related morbidity and mortality were higher in the HiDAC arm; 5-year OS rates were 33% in the high-dose arm compared with 25% in the standard-dose arm.³¹

In a large SWOG study,³² patients aged <65 years (n=665) were randomized to receive HiDAC (2 g/m² every 12 hours for 6 days for a total of 24 g/m²; patients aged <50 years were initially randomized to receive 3 g/m² on the same dose schedule before the high-dose arm was redefined to 2 g/m² due to toxicity concerns) or SDAC (200 mg/m² daily for 7 days); patients in both arms also received daunorubicin (45 mg/m² daily for 3 days). Patients in the HiDAC arm received a second high-dose cycle for consolidation, whereas those in the standard-dose arm were randomized to receive consolidation therapy with either 2 cycles of SDAC or 1 cycle of HiDAC plus daunorubicin. The CR rates were similar, with 55% for the high-dose arm compared with 58% for the standard-dose arm in patients aged <50 years, and 45% for HiDAC versus 53% for standard-dose therapy in patients aged 50 to 65 years. Disease-free survival (DFS; for patients with a CR) and OS (for all patients) at 4 years was not significantly different between treatment arms. Induction therapy with HiDAC was associated with significantly higher rates of treatment-related mortality (14% vs 5% for patients aged <50 years; 20% vs 12% for patients aged 50–64 years; *P*=.003) and grade 3 or higher

neurologic toxicity (8% vs 2% for patients aged <50 years; 5.0% vs 0.5% for patients aged 50–64 years; *P*<.0001).³² For patients aged <50 years, consolidation with HiDAC was associated with similar rates of treatment-related mortality (2% vs 0%) and grade 3 or higher neurologic toxicity (2% vs 0%) compared with the standard dose. For the original cohort of patients <50 years who received 3 g/m² HiDAC 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 aged <50 years who received 3 g/m² HiDAC 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.³²

Younger patients (age <50 years) who received HiDAC induction and consolidation in the SWOG trial had the highest 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).³² However, the percentage of patients who achieved a CR and did not proceed to consolidation was twice as high in the HiDAC induction arm.³² The risks for neurotoxicity and renal insufficiency are increased with HiDAC; therefore, both renal and neurologic function should be closely monitored in patients receiving this treatment. In a CALGB trial,³³ the subgroup of patients aged ≤60 years (n=156) who received standard-dose cytarabine–daunorubicin induction therapy and 4 courses of HiDAC consolidation (3 g/m² 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 HiDAC, the rates of treatment-related deaths and serious neurotoxicity were 5% and 12%, respectively.³³

Because the OS outcomes for the high-dose arm in the SWOG trial, which consisted of HiDAC induction and 2 cycles of HiDAC consolidation (4-year OS rate, 52% for patients aged <50 years), were comparable to those of the CALGB trial with infusional SDAC induction and 4 cycles of HiDAC consolidation (4-year OS rate, 52% for patients aged ≤60 years), the use of HiDAC in the induction phase outside of a clinical trial remains controversial. A

meta-analysis including 22 trials and 5,945 patients aged <60 years with de novo AML demonstrated improved RFS and reduced risk of relapse, particularly in favorable-risk cytogenetics, for patients receiving HiDAC versus standard chemotherapy.³⁴ However, toxicity was acknowledged as a limiting factor and emphasis was placed on the importance of future studies to define populations that would benefit most from HiDAC and to optimize dosing recommendations. The decision to use high-dose versus standard-dose cytarabine for induction might be influenced by consolidation strategies; fewer high-dose consolidation cycles may be needed for patients induced with HiDAC or for those who will undergo early autologous HCT. 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 who received high-dose therapy.³⁵ No data are available using more than 60 mg/m² of daunorubicin or 12 mg/m² of idarubicin with HiDAC. 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 HiDAC 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.³⁶

In the MRC AML 15 trial, younger patients with untreated AML (median age, 49 years), were randomized to 2 induction courses of daunorubicin and cytarabine with or without etoposide (ADE; n=1,983) or ADE versus fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF), and idarubicin (FLAG-Ida; n=1,268), and to amsacrine, cytarabine, etoposide, and then mitoxantrone/cytarabine or HiDAC (3 g/m²; n=1,445).³⁷ Patients in the HiDAC arm received 1.5 g/m² in consolidation and were treated with or without a fifth course of cytarabine (n=227). There were no significant differences in the CR rate between ADE and FLAG-Ida (81% vs 84%, respectively), but FLAG-Ida significantly decreased relapse rates (FLAG-Ida, 38% vs ADE, 55%; *P*<.001).³⁷ A recent randomized phase III study from the HOVON/SAKK groups compared standard cytarabine/idarubicin induction with or without clofarabine (10 mg/m² on days 1–5) for patients with AML aged 18 to 65 years.³⁸ Although

there was no difference in OS and EFS in the group as a whole, there was a decrease in relapse rate counterbalanced by an increased rate of death in remission for the clofarabine arm. In subset analysis, there was a significant improvement in OS and EFS for the European LeukemiaNet (ELN) intermediate I group primarily in patients with *NPM1* wild-type/*FLT3*-ITD-negative subgroup with a 4-year EFS of 40% for the clofarabine arm versus 18% for the control arm.³⁸

The NCCN AML Panel recommends enrollment in a clinical trial for treatment induction of younger patients (age <60 years) with AML (preferred). For patients not enrolled in a clinical trial, infusional SDAC (100–200 mg/m² continuous infusion) for 7 days combined with either idarubicin (12 mg/m² for 3 days) or daunorubicin (60–90 mg/m² for 3 days) is a category 1 recommendation.²⁰ SDAC (200 mg/m² continuous infusion for 7 days) combined with daunorubicin (60 mg/m² for 3 days) and cladribine (5 mg/m² for 5 days) is a category 2A recommendation.²⁵ HiDAC plus an anthracycline as induction therapy is a category 1 recommendation for patients aged ≤45 years, though it remains a category 2B recommendation for other age groups.^{29,30,32,35} The study by Willemze et al,²⁹ which demonstrated improved OS for patients aged 15 to 45 years treated on this regimen, was integral in the recommendation change to category 1 for this age group. For patients with *FLT3*-positive AML, SDAC (200 mg/m² continuous infusion) for 7 days combined with daunorubicin (60 mg/m² for 3 days) and oral midostaurin (50 mg every 12 hours on days 8–21) is a category 2A recommendation.²⁸ Fludarabine (30 mg/m² intravenously for days 2–6) plus cytarabine (2 g/m²) over 4 hours starting 4 hours after fludarabine in combination with idarubicin (8 mg/m² intravenously on days 4–6) and G-CSF (subcutaneously daily on days 1–7) is a category 2B recommendation.³⁷ For patients with impaired cardiac function, other cytarabine-based regimens combined with noncardiotoxic agents can be considered.

Patients with antecedent hematologic disease or treatment-related AML 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 to be 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 onto a clinical trial (incorporating either chemotherapy or novel agents), if available, given that 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 conditioning (RIC) allogeneic HCT from a matched-sibling or an alternative donor, which constitutes the best option for long-term disease control.³⁹

Postinduction Therapy

To judge the efficacy of the induction therapy, a bone marrow aspirate and biopsy should be performed 14 to 21 days after therapy initiation. In patients who have received SDAC induction with or without midostaurin and have significant residual disease without hypoplasia (defined as cellularity <10%–20%, of which the residual blasts <5%–10% [ie, blast percentage of residual cellularity]), additional therapy with standard-dose cytarabine and anthracycline should be considered. SDAC with anthracycline and midostaurin may also be considered for patients with *FLT3*-positive AML.²⁸ If hypoplasia status is unclear, a repeat bone marrow biopsy should be considered 5 to 7 days before proceeding with therapy. Escalation to HiDAC (1.5–3.0 g/m² every 12 hours for 6 days) may be considered for reinduction; no data are available to determine superiority of SDAC or HiDAC. Treatments for induction failure (see following discussion) may also be considered.

For patients with significant cytoreduction and a low percentage of residual blasts, SDAC with idarubicin or daunorubicin is recommended. SDAC with anthracycline and midostaurin may also be considered for patients with *FLT3*-positive AML.²⁸ For patients who have residual blasts after induction with SDAC combined with daunorubicin and cladribine, a second cycle of the same induction regimen may be administered if >50% cytoreduction is observed. If daunorubicin (90 mg/m²) was used in induction, the recommended dose for reinduction of daunorubicin before count recovery is 45 mg/m² for no more than 2 doses. Similarly, if idarubicin (12 mg/m²) was used for induction, the early reinduction dose should be limited to 10 mg/m² for 1 or 2 doses. If the marrow is hypoplastic, additional treatment selection is

deferred until the remission status can be assessed. If hypoplasia status is unclear, a repeat bone marrow biopsy should be considered 5 to 7 days before proceeding with postinduction therapy. For patients who achieve CR with the additional postinduction therapy, consolidation therapy can be initiated upon count recovery. Screening LP should be considered at first remission before first consolidation for patients with monocytic differentiation, mixed phenotype acute leukemia, WBC count >40,000/mcL at diagnosis, or extramedullary disease.

Patients with persistent disease after 2 courses of therapy (including a reinduction attempt based on midcycle marrow) are considered to be induction failures. Treatment options include clinical trial or use of salvage chemotherapy regimens used for relapsed/refractory disease (see AML-F; available online, in this guideline, at NCCN.org). If the patient did not receive HiDAC for persistent disease at day 15, HiDAC with or without anthracycline may be used if a clinical trial is not available and a donor is not yet identified. If the patient has an identified sibling or alternative donor available, a transplant option should be explored. For patients whose clinical condition has deteriorated such that active treatment is not an option, best supportive care should be continued.

Patients initially treated with HiDAC and who have significant residual disease without a hypocellular marrow 21 to 28 days after therapy initiation are considered to have experienced induction failure. Additional HiDAC therapy at this time is unlikely to induce remission in these cases, and these patients should be considered for a clinical trial or salvage regimens used for relapsed/refractory disease (see AML-F; available online, in this guideline, at NCCN.org). If an HLA-matched sibling or alternative donor has been identified, an allogeneic HCT may be effective in 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 where active therapy would be detrimental, best supportive care may be the most appropriate option. If the patient has significant cytoreduction after HiDAC with a small quantity of residual blasts or hypoplasia, additional therapy should be delayed for an additional 10 to 14 days and the marrow status may be reassessed.

Occasionally, patients with both myeloid and lymphoid markers at diagnosis may experience response to ALL therapy if an AML induction regimen failed.⁴⁰ Treatment decisions for patients with significant reduction without hypoplasia or those with hypoplasia are deferred until blood counts recover and a repeat marrow is performed to document remission status. Response is then categorized as a 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) may be needed to reduce the residual abnormal cells to a level that can be contained by immune surveillance. For patients aged <60 years, postremission therapy is based on risk status defined by cytogenetics and molecular abnormalities (see AML-1; page 928).

In the 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 HCT); this was significantly higher than the 4-year DFS rate (18%; $P=.008$) among the no-donor group (n=94; 46% underwent HCT).⁴¹ The 4-year DFS rate among patients with intermediate-risk AML was 45% for the donor group (n=61; 75% underwent HCT) and 48.5% for the no-donor group (n=104; 62.5% underwent HCT).⁴¹ The incidence of relapse was 35% and 47%, respectively, and the incidence of death in complete remission was 20% and 5%, respectively. The 4-year OS rate among intermediate-risk patients was 53% for the donor group and 54% for the no-donor group.⁴¹

The SWOG/ECOG trial reported a 5-year survival rate (from time of CR) of 44% with allogeneic HCT (n=18; 61% underwent HCT) and 13% with autologous HCT (n=20; 50% underwent HCT) among the subgroup of patients with unfavorable cytogenetics. Moreover, the 5-year survival rate was similar between those allocated to autologous HCT and those intended for chemotherapy consolidation alone (13% and 15%, respectively).⁴² The 5-year survival rates (from time of CR) for patients with intermediate-risk cytogenetics was 52% for the allogeneic HCT group (n=47; 66% underwent HCT) and 36%

for the autologous HCT group (n=37; 59% underwent HCT).⁴²

In the UK MRC AML 10 trial, a significant benefit with allogeneic HCT 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 than the no-donor groups.⁴³

Since 1994, multiple (3–4) cycles of HiDAC therapy have been the standard consolidation regimen for patients aged <60 years with either good- or intermediate-risk cytogenetics. This consolidation therapy is based on a CALGB trial comparing 100 mg/m², 400 mg/m², and 3 g/m² doses of cytarabine.³³ The 4-year DFS rate for patients receiving consolidation with 3 g/m² of HiDAC 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 core-binding factor (CBF)-AML, 32% for patients with normal karyotype AML (NK-AML), and 15% for patients in other cytogenetic categories (overall $P<.001$). Among those who received HiDAC consolidation, the 5-year RFS rate was 78% for CBF-AML, 40% for NK-AML, and 21% for other cytogenetic categories.³⁶ Notably, in patients with CBF-AML who received postremission therapy with HiDAC, the presence of *KIT* mutations resulted in poorer outcomes.^{44,45}

In a multicenter study, patients with CBF-AML (n=67) were enrolled in intensive chemotherapy protocols that involved HiDAC postremission therapy.⁴⁴ At 24 months, a *KIT* mutation in the TKD at codon 816 (TKD⁸¹⁶) in patients with t(8;21) was associated with a significantly higher incidence of relapse (90% vs 35.3%; $P=.002$) and lower OS (25% vs 76.5%; $P=.006$) compared with patients with wild-type *KIT*.⁴⁴ In CBF-AML with inv(16), TKD⁸¹⁶ did not result in a significant difference in relapse incidence and OS.⁴⁴ The prognostic influence of other *KIT* mutations on CBF-AML, including mutations on exon 17 (mut*KIT17*) and exon 8 (mut*KIT17*), have been investigated.^{45,46} In an analysis of patients with CBF-AML treated on CALGB trials (n=110), *KIT* mutations (mut*KIT17* and mut*KIT8*) among

patients with *inv(16)* were associated with a higher cumulative incidence of relapse at 5 years (56% vs 29%; $P=.05$) and a decreased 5-year OS rate (48% vs 68%) compared with wild-type *KIT*; in multivariate analysis, the presence of *KIT* mutations remained a significant predictor of decreased OS in the subgroup with *inv(16)*. In patients with *t(8;21)*, *KIT* mutations were 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%).⁴⁵ The CALGB trial also included maintenance chemotherapy after the consolidation phase; however, not all patients in remission received maintenance (55% of patients with CR) after HiDAC consolidation.³³ Subsequent clinical trials have eliminated maintenance during 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-dose 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 ($n=860$).⁴⁷ Patients were randomized to treatment with an “intermediate-dose” cytarabine regimen (12 g/m² cytarabine; cycle 1: cytarabine, 200 mg/m² daily for 7 days + idarubicin, 12 mg/m² daily for 3 days; cycle 2: cytarabine, 1 g/m² every 12 hours for 6 days + amsacrine, 120 mg/m² daily for 3 days) or a “high-dose” cytarabine regimen (26 g/m² cytarabine; cycle 1: cytarabine, 1 g/m² every 12 hours for 5 days + idarubicin, 12 mg/m² daily for 3 days; cycle 2: cytarabine, 2 g/m² every 12 hours for 4 days + amsacrine, 120 mg/m² daily for 3 days). Patients who experienced a CR after both treatment cycles were eligible to receive consolidation with a third cycle of chemotherapy or autologous or allogeneic HCT.⁴⁷ A similar proportion of patients in each treatment arm received consolidation, specifically 26% to 27% of patients in the third chemotherapy cycle, 10% to 11% of patients who underwent autologous HCT, and 27% to 29% of patients who underwent allogeneic HCT. 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%).⁴⁷ These results are comparable to those from the CALGB study with HiDAC.³³ 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).⁴⁷ 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 patients in this subgroup receiving the intermediate dose. 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%).⁴⁷ This study suggests that 2 cycles of intermediate-dose cytarabine (1 g/m² every 12 hours for 6 days; total dose 12 g/m² per cycle) for each consolidation cycle may be a feasible alternative to the current NCCN recommendations of 3 cycles of HiDAC (3 g/m² for 6 doses; total dose of 18 g/m² per cycle). This study, as well as the MRC AML 15 study,³⁷ suggest that doses of 3 g/m² of cytarabine are not clearly more effective than lower doses of 1.5–3.0 g/m²; in the MRC AML 15 trial, the cumulative incidence of relapse was statistically less for higher-dose cytarabine, but this did not translate into better RFS.³⁷

During the past decade, “normal” cytogenetics have been shown to encompass several molecular abnormalities with divergent risk behaviors.⁴⁸ The presence of an isolated *NPM1* or biallelic *CEBPA* mutation improves prognosis to one only slightly less than that of patients with CBF translocations, placing these patients in the favorable-risk molecular abnormalities category.⁴⁸ In contrast, patients with an isolated *FLT3*-ITD mutation and NK-AML have an outlook similar to those with poor-risk cytogenetics.⁴⁹ In a report that evaluated the ELN risk classification in a large cohort of patients, for those in the intermediate I-risk group (which included all patients with NK-AML with *FLT3* abnormalities and those lacking both *FLT3* and *NPM1* mutations), RFS was more favorable with allogeneic HCT (94.0 vs 7.9 months without allogeneic HCT).⁵⁰ Studies using sorafenib have implicated *FLT3* inhibitors as actionable targets in AML.^{50–54} Long-term follow-up data from a phase II study of sorafenib in combination with idarubicin and cytarabine in younger patients showed an improved CR rate, particularly in patients with *FLT3*-mutated disease; however, this improvement was not statistically significant (95% vs

83%; $P=.23$).^{55,56} Sorafenib with azacitidine has been shown to be well-tolerated and results in improved survival.^{57,58} Studies using *FLT3* inhibitor, midostaurin, have demonstrated improved survival in young patients with *FLT3*-positive AML when combined with standard chemotherapy as part of frontline and consolidation treatment.^{26–28} Two other *FLT3* inhibitors, quizartinib and gilteritinib, are in clinical trials for patients with *FLT3*-positive AML.^{59,60}

The NCCN panel has provided the following options for consolidation therapy for patients with favorable-risk cytogenetics (those with CBF leukemia, without *KIT* mutations, or favorable-risk molecular abnormalities): (1) participation on a clinical trial, or (2) 3 to 4 cycles of HiDAC (category 1). There are not sufficient data to evaluate the use of allogeneic HCT in first remission for patients with AML and favorable-risk cytogenetics outside of a clinical trial.⁶¹ Data suggest that the response to treatment is similar regardless of whether the favorable-risk cytogenetics are de novo and treatment-related.⁶¹ However, outcomes in patients with favorable-risk disease who have *KIT* mutations are more similar to those in 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-designed plan for relapse therapy with either a matched-sibling or alternative donor HCT 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 HCT) or 3 to 4 cycles of HiDAC afforded a lower risk of relapse and a somewhat higher DFS when given as consolidation for patients with intermediate-risk cytogenetics. Although 2 to 3 g/m² HiDAC is preferred, a range of 1 to <2 g/m² can be used to accommodate patients who are less fit. The role of autologous HCT in the intermediate-risk group outside of clinical trials is diminishing due to improvements in allogeneic transplants, which are expanding the pool of potential donors outside the family setting. Although autologous HCT is still incorporated into the clinical trial design in Europe, the consensus of the NCCN AML Panel was that autologous HCT should not be a recommended consolidation therapy outside the setting of a clinical trial. Clinical trial participation is encouraged. Other options for this

group include clinical trials or multiple courses (3–4) of HiDAC consolidation.⁶² HiDAC (3 g/m²) with midostaurin may also be considered for patients with *FLT3*-positive AML.²⁸ Alternative regimens incorporating intermediate doses of cytarabine (1.5 g/m²) may be reasonable in patients with intermediate-risk disease. Comparable 5-year DFS rates were reported in patients aged <60 years with NK-AML after either 4 cycles of intermediate- or high-dose cytarabine (41%) or autologous HCT (45%).⁶² At this time, there is no evidence that HiDAC (2–3 g/m²) is superior to intermediate-dose (1.5 g/m²) cytarabine in patients with intermediate-risk AML.

The panel strongly recommends clinical trials as standard therapy for patients with poor prognostic features, which include *FLT3* abnormalities in the setting of otherwise NK-AML, high WBC (>50,000/mcL) at diagnosis, or 2 cycles of induction therapy needed to achieve CR. If cytogenetic remission is observed, consolidation therapy is recommended. Allogeneic HCT with matched-sibling or matched-alternative donor (including umbilical cord blood products) as consolidation therapy for patients with poor-risk cytogenetics or molecular abnormalities is a treatment option. For patients with *FLT3*-positive AML, HiDAC-based consolidation with midostaurin²⁸ may be considered to maintain remission while searching for a potential matched donor.

Management of AML in Patients Aged >60 Years

Induction Therapy

The creation of separate guidelines for patients aged >60 years recognizes the poor outcomes in this group treated with standard cytarabine and an anthracycline. In this patient population, the proportion of those with favorable CBF translocations decreases, in addition to those with isolated *NPM1* mutations, whereas the number of patients with unfavorable karyotypes and mutations increases. However, it should be noted that *NPM1* mutations in older patients remain a positive prognostic factor, as seen in the UK National Cancer Research Institute (NCRI) AML 16 trial wherein this age group had higher remission rates irrespective of the treatment approach.⁶³ Similar to younger patients, only the combined wild-type *FLT3* and *NPM1* mutant

group had improved survival. This same study also demonstrated that the *FLT3* mutation did not affect remission rates, although there was an association with inferior survival. Secondary AML, related to either prior MDS 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 aged <60 years during the past 3 decades, no similar improvement was observed for the older population.^{64,65} Treatment-related mortality frequently exceeds any expected transient response in this group, particularly in patients >75 years or those who have significant comorbid conditions or ECOG performance status >2.

For older patients (age >60 years) with AML, the panel recommends using patient performance status, in addition to adverse features (eg, de novo AML without favorable cytogenetics or molecular markers; therapy-related AML; antecedent hematologic disorder) and comorbid conditions, to select treatment options rather than rely on a patient's chronologic age alone. Comprehensive geriatric assessments are complementary to assessment of comorbid conditions and are emerging as better predictive tools of functional status.^{66,67} A treatment decision-making algorithm for previously untreated, medically fit, elderly patients (age ≥60 years) with AML was developed by the German AML cooperative group. Based on data from a large study in elderly patients (n=1,406), patient and disease factors significantly associated with CR and/or early death were identified and risk scores were developed based on multivariate regression analysis.⁶⁸ 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.⁶⁸ The factors included in the algorithm are body temperature (≤38°C and >38 °C), hemoglobin levels (≤10.3 and >10.3 g/dL), platelet counts (≤28K, >28K to ≤53K, >53K to ≤10K, and >10K counts/mcL), fibrinogen levels (≤150 and >150 mg/dL), age at diagnosis (60–64, >64–67, >67–72, and >72

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

Another comprehensive predictive model for early death after induction in patients with newly diagnosed AML suggests that age may be a reflection of other covariants, and the evaluation of these factors may provide a more accurate predictive model. The model includes performance score, age, platelet count, serum albumin, presence or absence of secondary AML, WBC count, peripheral blood blast percentage, and serum creatinine. These factors, when taken together, result in a predictive accuracy based on the area under the curve (AUC) of 0.82 (a perfect correlation is an AUC of 1.0).⁶⁹ This model is complex, and currently there is not a tool available to implement this model. A shortened form of the model was based on covariants that include age, performance status, and platelet count. The simplified model provides an AUC of 0.71, which is less accurate than the complex model but may be more accurate than decision-making strategies based solely on age.⁶⁹

Older adults with intact functional status (ie, ECOG score 0–2), minimal comorbidity, and de novo AML without unfavorable cytogenetics or molecular markers, without antecedent hematologic disorder, and without therapy-related AML may benefit from standard therapies regardless of chronologic age. A reasonable treatment regimen for these patients includes SDAC (100–200 mg/m² by continuous infusion per day for 7 days) along with 3 days of anthracycline. Although patients aged >75 years with significant comorbidities generally do not benefit from conventional chemotherapy treatment, the rare patient with favorable-risk or NK-AML 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 study from the Acute Leukemia French Association (ALFA)-9801 study (n=468) showed that idarubicin induction (the standard 12 mg/m² daily for 3 days or intensified with 12 mg/m² daily for 4 days) compared with high-dose daunorubicin (up to 80 mg/m²) yielded a significantly higher CR rate in patients aged 50 to 70 years (80% vs 70%, respectively; *P*=.03).²² The median OS for all patients was 17 months. The estimated 2-year EFS and OS rates were 23.5% and 38%, respectively, and the estimat-

ed 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.²²

The ALFA-9803 study (n=416) evaluated (during first randomization) induction with idarubicin (9 mg/m² daily for 4 days) compared with daunorubicin (45 mg/m² daily for 4 days) in patients aged ≥65 years.⁷⁰ In this trial, the CR rate after induction was 57% and induction death occurred in 10% of patients. The median 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.⁷⁰ Long-term outcomes based on a combined analysis of data from the ALFA-9801 and -9803 trials (n=727) showed superior results with standard idarubicin induction (36 mg/m² total dose) compared with daunorubicin induction (240 mg/m² total dose for patients aged <65 years; 180 mg/m² total dose for patients aged ≥65 years) in older patients with AML (age ≥50 years).⁷¹ 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 aged <65 years, standard idarubicin was still associated with a significantly higher cure rate than daunorubicin despite the high dose (240 mg/m² total dose) of daunorubicin (27.4% vs 15.9%; *P*=.049).⁷¹

In the HOVON trial, which randomized patients aged ≥60 years to induction therapy with SDAC combined with either standard-dose daunorubicin (45 mg/m² daily for 3 days; n=411) or dose-escalated daunorubicin (90 mg/m² daily for 3 days; n=402), the CR rates were 54% and 64%, respectively (*P*=.002).⁷² 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/m² daily for 3 days) from the ALFA-9801 study, in which the 4-year EFS and OS rates were

21% and 32%, respectively.²² In the HOVON trial, the benefit in OS outcomes for the dose-escalated daunorubicin group was observed only in patients aged ≤65 years or in those with CBF translocations.⁷²

There are conflicting data about the use of gemtuzumab ozogamicin (GO) for older patients with AML. Three phase III randomized trials evaluated the efficacy and safety of adding the anti-CD33 antibody-drug conjugate GO to induction therapy with daunorubicin and cytarabine in older patients with previously untreated AML.^{73,74} In the phase III ALFA-0701 trial, patients aged 50 to 70 years with de novo AML (n=280) were randomized to receive induction with daunorubicin (60 mg/m² daily for 3 days) and cytarabine (200 mg/m² continuous infusion for 7 days), with or without (control arm) fractionated GO at 3 mg/m² given on days 1, 4, and 7.⁷⁴ Patients with persistent marrow blasts at day 15 received additional daunorubicin and cytarabine. Patients with a CR/CRi with incomplete recovery of peripheral blood counts (CRi) after induction received 2 consolidation courses with daunorubicin and cytarabine, with or without GO (3 mg/m² on day 1). The CR/CRi after induction was similar between the GO and control arms (81% vs 75%). The GO 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.⁷⁴ The GO 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.⁷⁴ In another multicenter, phase III, randomized trial from the United Kingdom and Denmark (AML 16 trial), patients aged >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) GO (3 mg/m² on day 1 of course 1 of induction).⁷³ Median age was 67 years (range, 51–84 years) and 98% of patients were aged ≥60 years; 31% were aged ≥70 years. The CR/CRi rate after induction was similar between the GO and control arms (70% vs 68%). The GO arm was associated with significantly lower 3-year cumulative incidence of relapse (68% vs 76%; *P*=.007) and higher rates of 3-year RFS (21% vs 16%; *P*=.04) and OS (25% vs 20%; *P*=.05) 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 increase in AEs were observed with GO.⁷³ These 2 trials suggest that the addition of GO to standard induction regimens reduced the risk of relapse and improved OS outcomes in older patients with previously untreated AML.

The third phase III trial combining GO with chemotherapy showed a different result than the other 2. In this study, patients between the ages of 61 and 75 years were given chemotherapy consisting of mitoxantrone, cytarabine, and etoposide (n=472).⁷⁵ Half of the patients were given 6 mg/m² GO before chemotherapy on days 1 and 15. In remission, treatment included 2 courses of consolidation with or without 3 mg/m² GO on day 0. The OS between the groups was similar (GO, 45% vs no GO, 49%), but the induction and 60-day mortality rates were higher in the patients given GO (17% vs 12% and 22% vs 18%, respectively). Only a small subgroup of patients <70 years of age with secondary AML showed any benefit of treatment. Combined with the increased toxicity, the results of this study suggest that GO does not provide an advantage over standard chemotherapy for older patients with AML.⁷⁵

Conflicting studies have led to the publication of several recent systematic reviews and meta-analyses. A larger systematic review, inclusive of any randomized controlled trials that investigated the benefit of anti-CD33 antibody therapy regardless of whether treatment was in de novo or secondary disease, concluded that the data from 11 trials showed increased induction deaths ($P=.02$) and reduced residual disease ($P=.0009$).⁷⁶ Despite improved RFS (HR, 0.90; 95% CI, 0.84–0.98; $P=.01$), no OS benefit was measured (HR, 0.96; 95% CI, 0.90–1.02; $P=.2$). Two other meta-analyses showed improved RFS, although induction death was elevated.^{77,78} Conversely, a fourth meta-analysis evaluating 5 trials with 3,325 patients aged ≥ 15 years showed a reduced risk of relapse ($P=.0001$) and improved 5-year OS (OR, 0.90; 95% CI, 0.82–0.98; $P=.01$) with the addition of GO to conventional induction therapy.⁷⁹ It was noted that the greatest survival benefit was seen in patients with favorable cytogenetics; some benefit was seen in patients with intermediate cytogenetics, but no benefit was reported with the addition of GO in patients with adverse cytogenetics. These studies underscore the need for further investigation into the possible benefits of GO for the treatment of AML. As previously mentioned, GO 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 about early, nonrelapse mortality rates in clinical trials in younger patients, further complicating its use.

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), who frequently had additional risk factors present, received clofarabine (30 mg/m² intravenously for 5 days).⁸⁰ CR/CRi 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.⁸⁰ In a pooled analysis of data from 2 European phase II studies that also evaluated first-line clofarabine (30 mg/m² 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.⁸¹ An additional 16% achieved CRi. 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.⁸¹ A recent randomized trial from the UK NCRI compared the efficacy and safety of first-line therapy with clofarabine (20 mg/m² 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).⁸² Treatment with clofarabine resulted in a significantly higher overall response rate (ORR; 38% vs 19%; $P<.0001$) and CR rate (22% vs 12%; $P=.005$) compared with low-dose cytarabine. However, no differences were observed in the 2-year OS rate (13% vs 12%, respectively), and 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 a higher mean number of days in the hospital and days on antibiotics compared with low-dose cytarabine.⁸²

Several studies have evaluated the combination of clofarabine with low-dose 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 either clofarabine alone (n=16; 30 mg/m² intravenously for 5 days) or clofarabine combined with low-dose cytarabine (n=54; 20 mg/m² subcutaneously for 14 days).⁸³ 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 = not significant). 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.⁸³

A phase II Spanish study evaluated the combination of clofarabine (20 mg/m² intravenously for 5 days) and cytarabine (20 mg/m² subcutaneously for 14 days) in older patients with previously untreated AML (age ≥ 60 years).⁸⁴ Patients with less than a CR with the first course could receive another induction course; consolidation comprised 5 days of clofarabine (15 mg/m²) and 7 days of low-dose cytarabine (20 mg/m²) 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 because of high toxicity and unacceptable mortality rates. The mortality rate at 4 weeks was 46% (n=5) and at 8 weeks was 73% (n=8).⁸⁴ 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 former study, as well as potential differences in the extent of monitoring (eg, outpatient vs inpatient) and supportive care practices (eg, anti-infective prophylaxis and infection monitoring)

between the studies. Although the combination of clofarabine and low-dose 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. The ECOG-ACRIN Cancer Research Group phase III trial was designed to compare induction therapy with single-agent clofarabine versus cytarabine/daunorubicin in patients aged >60 years (n=727).^{85,86} Patients received either continuation of clofarabine or intermediate-dose cytarabine as consolidation therapy. At median follow-up (7.6 months), 374 patients had died (174 in the cytarabine/daunorubicin arm and 200 in the clofarabine arm).⁸⁵ Although the CR and induction mortality were similar between the groups, a significantly inferior OS was measured in the clofarabine monotherapy treatment arm (HR, 1.41; 95% CI, 1.12–1.78).⁸⁵ In an updated analysis with longer median follow-up (18.3 months), treatment arm ($P=.003$), adverse cytogenetic risk group ($P=.02$), increasing age ($P=.03$), and baseline WBC count ($<10,000/\text{mL}$; $P=.03$) were each independently associated with higher risk of receiving a second cycle of induction, but there was no significant differences between CR/CRi or median OS in patients receiving 1 or 2 induction cycles.⁸⁶

An international, randomized, phase III study by Fenaux et al⁸⁷ compared the hypomethylating agent 5-azacitidine 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 percentages between 20% and 30%.^{87,88} In the subgroup of these patients with AML, a significant survival benefit was found with 5-azacitidine compared with conventional care regimens, with a median OS of 24.5 versus 16 months (HR, 0.47; 95% CI, 0.28–0.79; $P=.005$).⁸⁸ The 2-year OS rates were 50% and 16%, respectively ($P=.001$).

Another hypomethylating agent, decitabine, has also been evaluated as remission induction therapy for older patients with AML.⁸⁹ In a phase II study in

previously untreated patients aged ≥ 60 years ($n=55$; median age, 74 years), the overall CR rate with this agent (20 mg/m² for 5 days every 28 days) was 24% (including 6 of 25 patients [24%] with poor-risk cytogenetics), and the median EFS and OS were 6 and 8 months, respectively.⁸⁹ An earlier phase I study evaluated different dose schedules of decitabine in patients with relapsed/refractory leukemias ($n=50$; AML diagnosis, $n=37$).⁹⁰ In this study, decitabine was given at 5, 10, 15, or 20 mg/m² for 5 days per week for 2 to 4 consecutive weeks (ie, 10, 15, or 20 days). The decitabine dose of 15 mg/m² for 10 days ($n=17$) was associated with the highest response rates, with an ORR of 65% and a CR rate of 35%. Among the patients with relapsed/refractory AML ($n=37$), the ORR was 22%, with a CR of 14% across all dose levels.⁹⁰ Results of a phase II study targeting older patients (age ≥ 60 years) with AML who were not candidates for or refused intensive therapy, in which subjects received a decitabine dose of 20 mg/m² for 10 days, demonstrated a CR rate of 47% ($n=25$) after a median of 3 cycles of therapy.⁹¹

In an open-label randomized phase III study, decitabine (20 mg/m² 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.⁹² 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 CRi) rate was significantly higher with decitabine (18% vs 8%; $P=.001$).⁹² The most common treatment-related AEs 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%).⁹² Both azacitidine and decitabine are approved by the FDA for the treatment of 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 $<10,000/\text{mcL}$).⁹³ Patients were also randomized to receive all-trans retinoic acid (ATRA) or no ATRA. Low-dose cytarabine resulted in a CR rate of 18% (vs 1% with hydroxyurea) and a survival benefit compared with hydroxyurea in patients with favorable or NK-AML. No advantage was observed with the addition of ATRA. Median DFS in patients who achieved a CR with low-dose cytarabine was 8 months.⁹³ 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 phase II study evaluated a regimen with low-dose cytarabine (20 mg twice daily for 10 days) combined with clofarabine (20 mg/m² daily for 5 days) in patients aged ≥ 60 years with previously untreated AML ($n=60$; median age, 70 years; range, 60–81 years).⁹⁴ Patients with a response received consolidation (up to 17 courses) with clofarabine plus low-dose cytarabine alternated 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. The induction mortality rate was 7% at 8 weeks.⁹⁴ Although this regimen appeared to be active in older patients with AML, the authors noted that the benefits of prolonged consolidation remain unknown.

Novel regimens that incorporate nonchemotherapy agents are currently under investigation in the management of older patients with AML. Lenalidomide—a thalidomide analogue—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-azacitidine followed by lenalidomide in older patients with previously untreated AML ($n=18$), the regimen resulted in a CR in 44% of patients (including CRi).⁹⁵ 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 AEs included fatigue, injection site reactions, gastrointestinal events, and febrile neutropenia.⁹⁵ A recent trial evaluated this regimen with sequential 5-azacitidine and lenalidomide in older patients (age ≥ 60 years) with previously untreated AML not eligible for stan-

dard induction chemotherapy (n=45; n=42 evaluated)⁹⁶; 7 patients (17%) had a prior diagnosis of MDS, and 5 of these patients had received prior treatment with hypomethylating agents for MDS (5-azacitidine, n=5; decitabine, n=1). The ORR was 41%, including a CR in 19% and CRi in 9% of patients.⁹⁶ The median duration of response was 28 weeks and the median OS for patients with cancer that responded to treatment was 69 weeks. Early death (death within 4 weeks from start of treatment) occurred in 17% of patients; median OS for all patients was 20 weeks.⁹⁶ The most common treatment-related AEs included grade 1 or 2 gastrointestinal toxicities, injection site reactions, fatigue, and rash/pruritus; grade 3 AEs were uncommon, and no grade 4 or 5 treatment-related toxicities were reported. Additional studies with larger numbers of patients are needed to further evaluate the efficacy and safety profile of this combination approach.

Recent studies are investigating the liposomal combination of daunorubicin and low-dose cytarabine (CPX-351) as a novel method of administering therapy and have found it to be efficacious in older patients with secondary AML.^{97,98} In a phase II trial that randomized 2:1 newly diagnosed older patients (age ≥ 60 years) with AML (n=126) to first-line CPX-351 or 7+3 treatment,⁹⁸ CPX-351 produced higher response rates (CPX-351, 66.7% vs 7+3, 51.2%; $P=.07$); however, differences in EFS and OS were not statistically significant.⁹⁸ A planned analysis of the secondary AML subgroup showed an improved response rate (57.6% vs 31.6%; $P=.06$) and prolongation of EFS (HR, 0.59; $P=.08$).⁹⁸ Phase III studies are ongoing in patients with newly diagnosed secondary AML.

Older adults with newly diagnosed AML who are candidates for intensive remission induction therapy may be managed with one of the following options: clinical trial or standard infusional cytarabine and anthracycline. For patients who exceed anthracycline dose guidelines or have cardiac issues but who are still fit enough to receive aggressive therapy, alternative non-anthracycline-containing regimens may be considered. For patients with unfavorable cytogenetic/molecular markers, antecedent hematologic disorder, or therapy-related AML, treatment options include clinical trial, lower-intensity therapy with hypomethylating agents (eg, 5-azacitidine or decitabine), standard infusional cytarabine and anthracycline, or clofarabine with or without SDAC

(category 3 recommendation). Data from the CALBG 10603/RATIFY study suggest a survival benefit with SDAC and anthracycline with midostaurin for patients with *FLT3*-positive AML²⁸; therefore, this regimen may also be considered.

For patients who are not candidates for intensive remission induction therapy or if a patient declines intensive therapy, treatment options include a clinical trial, lower-intensity therapy with hypomethylating drugs 5-azacitidine and decitabine, or low-dose cytarabine, which has been the comparator arm in several clinical trials in older unfit patients. In this context, the hypomethylating agents are preferred. Best supportive care with hydroxyurea and transfusion support should also be considered.

Postinduction Therapy

Similar to younger patients, older patients who receive standard cytarabine/anthracycline induction with or without midostaurin receive a bone marrow evaluation 14 to 21 days after start of therapy and are categorized according to the presence of blasts or hypoplasia. Patients with hypoplasia should await recovery of counts before continuing to postremission therapy. Patients with residual disease without hypoplasia may receive additional SDAC with an anthracycline or mitoxantrone. Alternatively, patients with *FLT3*-mutation-positive AML may receive additional SDAC with daunorubicin and midostaurin.²⁸ If daunorubicin (90 mg/m²) was used in induction, the recommended dose for reinduction before count recovery is 45 mg/m² for no more than 2 doses. Similarly, if idarubicin (12 mg/m²) was used for induction, the early reinduction dose should be limited to 10 mg/m² for 1 or 2 doses. Intermediate-dose cytarabine-containing regimens, RIC allogeneic HCT, or best supportive care are also treatment options. Reduced-intensity transplant is a reasonable option in patients with identified donors available to start conditioning within 4 to 6 weeks from start of induction therapy. Patients without an identified donor would most likely need some additional therapy as a bridge to transplant. Additionally, it is acceptable to await recovery in these patients, because many will enter remission without further treatment. Regardless of treatment, all patients receiving postinduction therapy after SDAC should have a repeat bone marrow evaluation 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 <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-azacitidine) 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 same agents. The French ALFA 9803 trial randomized patients aged ≥ 65 years who experienced remission ($n=164$; randomized for postremission therapy) to consolidation with either 1 additional course of SDAC (200 mg/m² daily for 7 days) plus the anthracycline to which they had been randomized for induction (idarubicin, 9 mg/m² daily for 4 days or daunorubicin, 45 mg/m² daily for 4 days) or 6 monthly courses of anthracycline (1 day only) at the above doses and 60 mg/m² of cytarabine every 12 hours as a subcutaneous infusion at home for 5 days each month.⁷⁰ 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 those receiving 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 difference was observed in the cumulative relapse rate between arms.⁷⁰ 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/m² daily for 4–6 doses) without an anthracycline.

The role of myeloablative allogeneic HCT is limited in older patients because of significant comorbidities; however, ongoing interest has been shown in RIC allogeneic HCT as consolidation therapy.^{99,100} 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.^{99,100} In a retrospective analysis comparing outcomes with RIC allogeneic HCT and autologous HCT in patients aged ≥ 50 years based on large registry data, RIC allogeneic HCT was associated with lower risk for relapse and superior DFS and OS relative to autologous HCT.⁹⁹ The authors also noted that a survival benefit was not observed in the subgroup of patients undergoing RIC allogeneic HCT in first CR because of an increased incidence of nonrelapse mortality.

Estey et al¹⁰¹ prospectively evaluated a protocol in which patients aged ≥ 50 years with unfavorable cytogenetics would be evaluated for a RIC allogeneic HCT.¹⁰¹ Of the 259 initial patients, 99 experienced a CR and were therefore eligible for HCT 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 HCT with those from matched subjects receiving conventional-dose chemotherapy. This analysis suggested that RIC allogeneic HCT was associated with improved RFS, and the authors concluded that this approach remains of interest.¹⁰¹ In an analysis of outcomes between 2 different strategies for matched sibling allogeneic HCT, outcomes in younger patients (age ≤ 50 years; $n=35$) receiving conventional myeloablative allogeneic HCT were compared with those in older patients (age >50 years; $n=39$) receiving RIC allogeneic HCT.¹⁰² This study showed similar rates of 4-year nonrelapse mortality (19% and 20%, respectively), and no difference was seen in relapse and OS rates.¹⁰²

A retrospective study based on data in older patients (range, 50–70 years) with AML compared outcomes in patients who underwent allogeneic HCT (either myeloablative conditioning or RIC; $n=152$) and those who did not receive HCT in first CR (chemotherapy only; $n=884$).¹⁰³ Allogeneic HCT in first CR was associated with a significantly lower 3-year cumulative relapse rate (22% vs 62%; $P<.001$) and a

higher 3-year RFS rate (56% vs 29%; $P < .001$) compared with the non-HCT group. Although HCT was associated with a significantly higher rate of non-relapse mortality (21% vs 3%; $P < .001$), the 3-year OS rate showed a survival benefit with HCT (62% vs 51%; $P = .012$).¹⁰³ Among the patients who underwent allogeneic HCT, myeloablative conditioning was used in 37%, whereas RIC was used in 61%. Survival outcomes between these groups were similar, with 3-year OS rates of 63% and 61%, respectively.¹⁰³

Another study evaluating treatment in older patients (range, 60–70 years) compared outcomes between RIC allogeneic HCT reported to the Center for International Blood and Marrow Transplant Research ($n = 94$) and standard chemotherapy induction and postremission therapy from the CALGB studies ($n = 96$).¹⁰⁴ Allogeneic HCT in first CR was associated with significantly lower 3-year relapse rates (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 HCT 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 there was a trend favoring allogeneic HCT.¹⁰⁴ A prospective multicenter phase II study examined the efficacy of RIC allogeneic HCT in older patients (range, 60–74 years) with AML in first CR ($n = 114$).¹⁰⁵ After allogeneic HCT, DFS and OS at 2 years were 42% (95% CI, 33%–52%) and 48% (95% CI, 39%–58%), respectively, for the entire group.¹⁰⁵ A time-dependent analysis of 4 successive prospective HOVON/SAKK AML trials examined data from patients aged ≥ 60 years who experienced a first CR after induction chemotherapy ($n = 640$).¹⁰⁶ For patients who received allogeneic HCT as postremission therapy ($n = 97$), the 5-year OS rate was 35% (95% CI, 25%–44%).¹⁰⁶

Collectively, these studies suggest that RIC allogeneic HCT is a feasible treatment option for patients aged ≥ 60 years, 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 alternative donor options/searches should be explored earlier in the disease management. The guidelines note that RIC allogeneic HCT is considered an additional option for

patients aged ≥ 60 years as postremission therapy in those experiencing a CR to induction therapy.

For patients who had previously received intensive therapy, a marrow evaluation to document remission status upon hematologic recovery should be performed after 4 to 6 weeks. If a CR is observed, a clinical trial, SDAC with or without an anthracycline, intermediate-dose cytarabine (for patients who are more fit), intermediate-dose cytarabine and midostaurin for patients with *FLT3*-mutation–positive AML,²⁸ maintenance therapy with hypomethylating regimens (ie, 5-azacitidine, decitabine) if the patient received hypomethylating agents in induction, or observation may be appropriate. Observation is recommended, because some patients have been able to maintain a CR without further treatment. For patients with induction failure, a clinical trial, allogeneic HCT preferably in the context of a clinical trial, or best supportive care are recommended treatment options. Emerging data are exploring the use of lower-intensity maintenance therapies to prolong remission duration and improve survival of elderly patients with AML after intensive treatment.¹⁰⁷ A multicenter, phase III randomized study investigated the survival benefit of adding androgens to maintenance therapy in patients with AML aged ≥ 60 years ($n = 330$).¹⁰⁸ In this study, induction therapy included cytarabine (100 mg/m² on days 1–7), idarubicin (8 mg/m² on days 1–5), and lomustine (200 mg/m² on day 1). Patients in CR or PR ($n = 247$) were treated with 6 reinduction courses, alternating idarubicin on day 1, cytarabine on days 1 to 5, and a regimen of methotrexate and mercaptopurine, and randomized to receive androgen, norethandrolone (10 or 20 mg/d) according to body weight, or no norethandrolone for a 2-year maintenance therapy regimen. Compared with the arm that received no androgens, norethandrolone improved rates of 5-year DFS (31.2% vs 16.2%, respectively), EFS (21.5% vs 12.9%, respectively), and OS (26.3% vs 17.2%, respectively).¹⁰⁸

For patients who previously received lower-intensity therapy, a marrow evaluation to document remission status on hematologic recovery should be performed after 8 to 12 weeks. If a response is observed, a clinical trial, reduced-intensity HCT, or continuation with hypomethylating regimens (every 4–6 weeks until progression) may be appropriate. If no response or progression is seen, a clinical trial or best supportive care are recommended treatment options.

Summary of Principles of AML Treatment

Current management of AML is divided into induction chemotherapy and postremission (eg, consolidation) therapy. The induction strategy is influenced by individual patient characteristics, such as age, presence of comorbid conditions affecting performance status, and preexisting MDS. Although obtaining 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 in order to achieve durable disease control. Strategies for postremission are based on the potential risk of relapse, with higher-risk patients receiving therapy that is more aggressive. Consistent with NCCN philosophy, participation in clinical trials is always encouraged. If a clinical trial is not an option, then low-intensity therapy or supportive care may be the appropriate choice.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.
2. National Cancer Institute. SEER 18, 2009-2013; Cancer Stat Facts: Acute Myeloid Leukemia (AML). Available at: <https://seer.cancer.gov/statfacts/html/amyl.html>. Accessed March 30, 2017.
3. Leone G, Pagano L, Ben-Yehuda D, Voso MT. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. *Haematologica* 2007;92:1389–1398.
4. 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.
5. 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.
6. 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.
7. Larson RA. Etiology and management of therapy-related myeloid leukemia. *Hematology Am Soc Hematol Educ Program* 2007:453–459.
8. 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.
9. Czader M, Orazi A. Therapy-related myeloid neoplasms. *Am J Clin Pathol* 2009;132:410–425.
10. 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.
11. 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.
12. Ferrara F, Mirto S. Serum LDH value as a predictor of clinical outcome in acute myelogenous leukaemia of the elderly. *Br J Haematol* 1996;92:627–631.
13. Yamauchi T, Negoro E, Lee S, et al. A high serum uric acid level is associated with poor prognosis in patients with acute myeloid leukemia. *Anticancer Res* 2013;33:3947–3951.
14. Cassileth PA, Sylvester LS, Bennett JM, Begg CB. High peripheral blast count in adult acute myelogenous leukemia is a primary risk factor for CNS leukemia. *J Clin Oncol* 1988;6:495–498.
15. Bryant A, Sheppard D, Sabloff M, et al. A single-institution analysis of the utility of pre-induction ejection fraction measurement in patients newly diagnosed with acute myeloid leukemia. *Leuk Lymphoma* 2015;56:135–140.
16. 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.
17. 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.
18. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO classification of tumours of haematopoietic and lymphoid tissues, 4th ed. Lyon, France: IARC; 2008.
19. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391–2405.
20. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med* 2009;361:1249–1259.
21. Luskun MR, Lee JW, Fernandez HF, et al. Benefit of high-dose daunorubicin in AML induction extends across cytogenetic and molecular groups. *Blood* 2016;127:1551–1558.
22. 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.
23. Teuffel O, Leibundgut K, Lehrnbecher T, et al. Anthracyclines during induction therapy in acute myeloid leukaemia: a systematic review and meta-analysis. *Br J Haematol* 2013;161:192–203.
24. Burnett AK, Russell NH, Hills RK, et al. A randomized comparison of daunorubicin 90 mg/m² vs 60 mg/m² in AML induction: results from the UK NCRI AML17 trial in 1206 patients. *Blood* 2015;125:3878–3885.
25. 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.
26. Fischer T, Stone RM, Deangelo DJ, et al. Phase IIB trial of oral Midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3. *J Clin Oncol* 2010;28:4339–4345.
27. Stone RM, Fischer T, Paquette R, et al. Phase IB study of the FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. *Leukemia* 2012;26:2061–2068.
28. Stone RM, Mandrekar S, Sanford BL, et al. The multi-kinase inhibitor midostaurin (M) prolongs survival compared with placebo (P) in combination with daunorubicin (D)/cytarabine (C) induction (ind), high-dose C consolidation (consol), and as maintenance (maint) therapy in newly diagnosed acute myeloid leukemia (AML) patients (pts) age 18–60 with FLT3 mutations (muts): an international prospective randomized (rand) P-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]) [abstract]. *Blood* 2015;126:Abstract 6.
29. Willemze R, Suciu S, Meloni G, et al. High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: results of the EORTC-GIMEMA AML-12 trial. *J Clin Oncol* 2014;32:219–228.
30. 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.
31. 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.
32. 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.

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33. 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.
34. Li W, Gong X, Sun M, et al. High-dose cytarabine in acute myeloid leukemia treatment: a systematic review and meta-analysis. *PLoS One* 2014;9:e110153.
35. 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.
36. 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.
37. Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol* 2013;31:3360–3368.
38. Lowenberg B, Pabst T, Maertens J, et al. Therapeutic value of clofarabine in younger and middle-aged (18–65 years) adults with newly diagnosed AML. *Blood* 2017;129:1636–1645.
39. 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.
40. Smith M, Barnett M, Bassan R, et al. Adult acute myeloid leukaemia. *Crit Rev Oncol Hematol* 2004;50:197–222.
41. Suci 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. Park SH, Chi HS, Min SK, et al. Prognostic impact of c-KIT mutations in core binding factor acute myeloid leukemia. *Leuk Res* 2011;35:1376–1383.
47. Lowenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. *N Engl J Med* 2011;364:1027–1036.
48. 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.
49. 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.
50. 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.
51. 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.
52. Rollig C, Serve H, Huttmann A, et al. Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): a multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 2015;16:1691–1699.
53. 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.
54. 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.
55. Ravandi F, Arana Yi C, Cortes JE, et al. Final report of phase II study of sorafenib, cytarabine and idarubicin for initial therapy in younger patients with acute myeloid leukemia. *Leukemia* 2014;28:1543–1545.
56. 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.
57. Ravandi F, Alattar ML, Grunwald MR, et al. Phase 2 study of azacitidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. *Blood* 2013;121:4655–4662.
58. 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.
59. Altman JK, Perl AE, Cortes JE, et al. Antileukemic activity and tolerability of ASP2215 80 mg and greater in FLT3 mutation-positive subjects with relapsed or refractory acute myeloid leukemia: results from a phase 1/2, open-label, dose-escalation/dose-response study. *Blood* 2015;126:321.
60. Hills RK, Gammon G, Trone D, Burnett AK. Quizartinib significantly improves overall survival in FLT3-ITD positive AML patients relapsed after stem cell transplantation or after failure of salvage chemotherapy: a comparison with historical AML database (UK NCRI data). *Blood* 2015;126:2557.
61. Aldoss I, Pullarkat V. Therapy-related acute myeloid leukemia with favorable cytogenetics: still favorable? *Leuk Res* 2012;36:1547–1551.
62. 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.
63. Lazenby M, Gilkes AF, Marrin C, et al. The prognostic relevance of *flt3* and *npm1* mutations on older patients treated intensively or non-intensively: a study of 1312 patients in the UK NCRI AML16 trial. *Leukemia* 2014;28:1953–1959.
64. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood* 2006;107:3481–3485.
65. 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.
66. Klepin HD, Geiger AM, Tooze JA, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood* 2013;121:4287–4294.
67. Sherman AE, Motyckova G, Fega KR, et al. Geriatric assessment in older patients with acute myeloid leukemia: a retrospective study of associated treatment and outcomes. *Leuk Res* 2013;37:998–1003.
68. 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.
69. Walter RB, Othus M, Borthakur G, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol* 2011;29:4417–4423.
70. 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.
71. 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.
72. 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.
73. 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.
74. 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.
75. Amadori S, Suci S, Stasi R, et al. Sequential combination of gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed acute myeloid leukemia: results of a randomized phase III trial by the EORTC and GIMEMA consortium (AML-17). *J Clin Oncol* 2013;31:4424–4430.

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76. Loke J, Khan JN, Wilson JS, et al. Mylotarg has potent anti-leukaemic effect: a systematic review and meta-analysis of anti-CD33 antibody treatment in acute myeloid leukaemia. *Ann Hematol* 2015;94:361–373.
77. Kharfan-Dabaja MA, Hamadani M, Reljic T, et al. Gemtuzumab ozogamicin for treatment of newly diagnosed acute myeloid leukaemia: a systematic review and meta-analysis. *Br J Haematol* 2013;163:315–325.
78. Li X, Xu SN, Qin DB, et al. Effect of adding gemtuzumab ozogamicin to induction chemotherapy for newly diagnosed acute myeloid leukemia: a meta-analysis of prospective randomized phase III trials. *Ann Oncol* 2014;25:455–461.
79. Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol* 2014;15:986–996.
80. 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.
81. 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.
82. 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.
83. 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.
84. 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.
85. Foran JM, Sun Z, Claxton DF, et al. North American leukemia, Intergroup phase III randomized trial of single agent clofarabine as induction and post-remission therapy, and decitabine as maintenance therapy in newly-diagnosed acute myeloid leukemia in older adults (age ≥60 years): a trial of the ECOG-ACRIN Cancer Research Group [abstract]. Presented at the 2015 ASH Annual Meeting; December 5–8, 2015; Orlando, Florida. Abstract 217.
86. Foran JM, Sun Z, Claxton DF, et al. Importance of achieving complete remission (CR) after intensive therapy for acute myeloid leukemia (AML) in older adults age ≥60 years: analysis of risk factors for early mortality and re-induction, and impact of quality of response on overall survival (OS) in the ECOG-ACRIN E2906 randomized trial [abstract]. Presented at the 2016 ASH Annual Meeting; December 3–6, 2016; San Diego, California. Abstract 613.
87. 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.
88. 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.
89. 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.
90. 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.
91. Blum W, Garzon R, Klisovic RB, et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proc Natl Acad Sci U S A* 2010;107:7473–7478.
92. 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.
93. 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.
94. 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.
95. 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.
96. 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.
97. Cortes JE, Goldberg SL, Feldman EJ, et al. Phase II, multicenter, randomized trial of CPX-351 (cytarabine:daunorubicin) liposome injection versus intensive salvage therapy in adults with first relapse AML. *Cancer* 2015;121:234–242.
98. Lancet JE, Cortes JE, Hogge DE, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood* 2014;123:3239–3246.
99. 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.
100. Storb R. Can reduced-intensity allogeneic transplantation cure older adults with AML? *Best Pract Res Clin Haematol* 2007;20:85–90.
101. 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.
102. 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.
103. 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.
104. 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.
105. Devine SM, Owzar K, Blum W, et al. Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first complete remission using a reduced-intensity conditioning regimen: results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trial Network 0502. *J Clin Oncol* 2015;33:4167–4175.
106. Versluis J, Hazenberg CL, Passweg JR, et al. Post-remission treatment with allogeneic stem cell transplantation in patients aged 60 years and older with acute myeloid leukaemia: a time-dependent analysis. *Lancet Haematol* 2015;2:e427–436.
107. Jurcic JG. Androgen maintenance therapy for acute myeloid leukemia. *J Clin Oncol* 2017;35:381–383.
108. Pigneux A, Bene MC, Guardiola P, et al. Addition of androgens improves survival in elderly patients with acute myeloid leukemia: a GOELAMS study. *J Clin Oncol* 2017;35:387–393.

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The NCCN Guidelines Staff have no conflicts to disclose.