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Acute Myeloid Leukemia

Clinical Practice Guidelines in Oncology

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Abstract

Acute myeloid leukemia (AML) remains 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. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AML provide recommendations on the diagnostic evaluation and workup for AML, risk assessment based on cytogenetic and molecular features, treatment options for induction and consolidation therapies for younger and older (age ≥ 65 years) adult patients, and key supportive care considerations. (*JNCCN* 2012;10:984–1021)

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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. It is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths from leukemias in the United States. An estimated 13,780 people will be diagnosed with AML in 2012, and 10,200 patients will die of the disease.[1] The median age of diagnosis is 67 years, with 54% of patients diagnosed at 65 years or older (and approximately a third of these diagnosed at ≥ 75 years of age).[2] Thus, as the population ages, the incidence of AML, along with myelodysplasia, seems to be rising. Environmental factors that have long been established to in-

Please Note

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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 page1021. (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.

crease the risks of myelodysplastic syndromes (MDS) and AML include prolonged exposure to petrochemicals; solvents such as benzene; pesticides; and ionizing radiation.[3] Equally disturbing is the increasing incidence of treatment-related myelodysplasia and acute leukemia in survivors of tumors of childhood and young adulthood. Therapy-related myeloid leukemia (secondary MDS/AML) is a well-recognized consequence of cancer treatment in a proportion of patients receiving cytotoxic therapy for solid tumors or hematologic malignancies.

Although the exact incidence of therapy-related MDS/AML is unknown, and varies depending on the types of treatment modalities used for a given primary tumor, recent reports suggest that therapy-related MDS/AML may account for 5% to 20% of patients with MDS/AML.[4–6] The rate of therapy-related MDS/AML is higher among patients with certain primary tumors, including breast cancer, gynecologic cancers, and lymphomas (both non-Hodgkin's lymphoma and Hodgkin lymphoma), largely owing to the more leukemogenic cytotoxic agents that are commonly used in the treatment of these tumors.[6–9] The 2 well-documented categories of cytotoxic agents associated with the development of therapy-related MDS/AML are alkylating agents (eg, cyclophosphamide, melphalan) and topoisomerase inhibitors/agents that interact with topoisomerase (eg, etoposide, doxorubicin, mitoxantrone).[4,7,8] Treatment with antimetabolites, such as the purine analog fludarabine, has also been associated with therapy-related MDS/AML in patients

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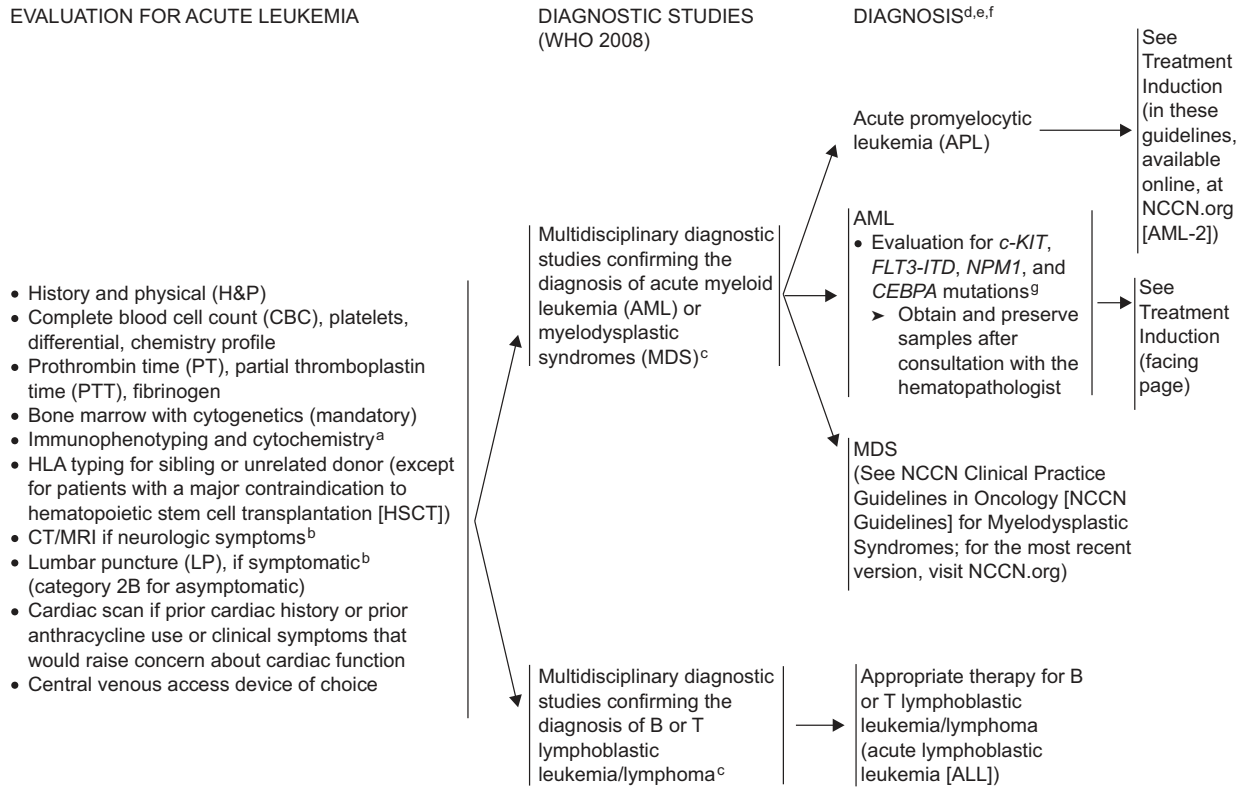

[a] Samples for both techniques should be taken at the time of initial sampling. Prioritization of these two complementary diagnostic procedures is left to the discretion of the pathology departments of the individual institutions. M0 can only be diagnosed by immunophenotyping.

[b] For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or CNS bleeding. LP should be performed if no mass/lesion is detected on the imaging study. Screening LP should be considered at first remission for patients with M5 or M4 morphology or WBC count > 100,000/mcL at diagnosis. See Evaluation and Treatment of CNS Leukemia (page 995).

[c] When presented with rare cases such as acute leukemias of ambiguous lineage including mixed phenotype acute leukemias (according to 2008 WHO classification), consultation with an experienced hematopathologist is strongly recommended.

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

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

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

[g] These molecular abnormalities are important for prognostication in a subset of patients (category 2A) and may guide therapeutic intervention (category 2B; see page 995). These are useful for patients with normal karyotype (especially *FLT3-ITD*, *NPM1* mutations) or core binding factor leukemia (especially *c-KIT* mutation). If a test is not available at an institution, pathology should be consulted about preserving material from the original diagnostic sample for future use at an outside reference laboratory after full cytogenetic data are available.

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

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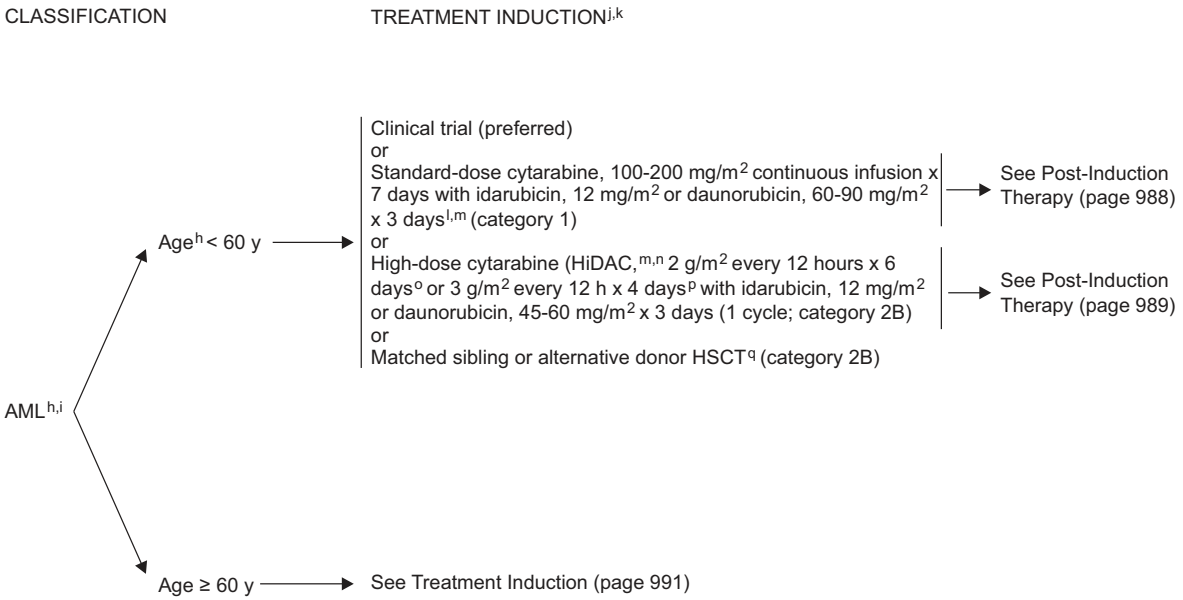


[h] Patients with blast counts > 50,000/mcL are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include apheresis or hydroxyurea. Prompt institution of definitive therapy is essential.

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

[j] See Supportive Care (page 996).

[k] See Monitoring During Therapy (page 998).

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

[m] For patients with impaired cardiac function, other regimens that combine a nonanthracycline (eg, fludarabine or topotecan) with cytarabine have been published.

[n] The use of high-dose cytarabine for induction outside the setting of a clinical trial is still controversial. Although the remission rates are the same for standard- and high-dose cytarabine, 2 studies have shown more rapid marrow blast clearance after 1 cycle of high-dose therapy and a disease-free survival advantage for patients aged ≤ 50 y who received the high-dose therapy (category 2B). Kern W, Estey EH. High-dose cytarabine arabinoside in the treatment of acute myeloid leukemia: review of three randomized trials. Cancer 2006;107:116-124. No data are available using more than 60 mg of daunorubicin or 12 mg of idarubicin with high-dose cytarabine.

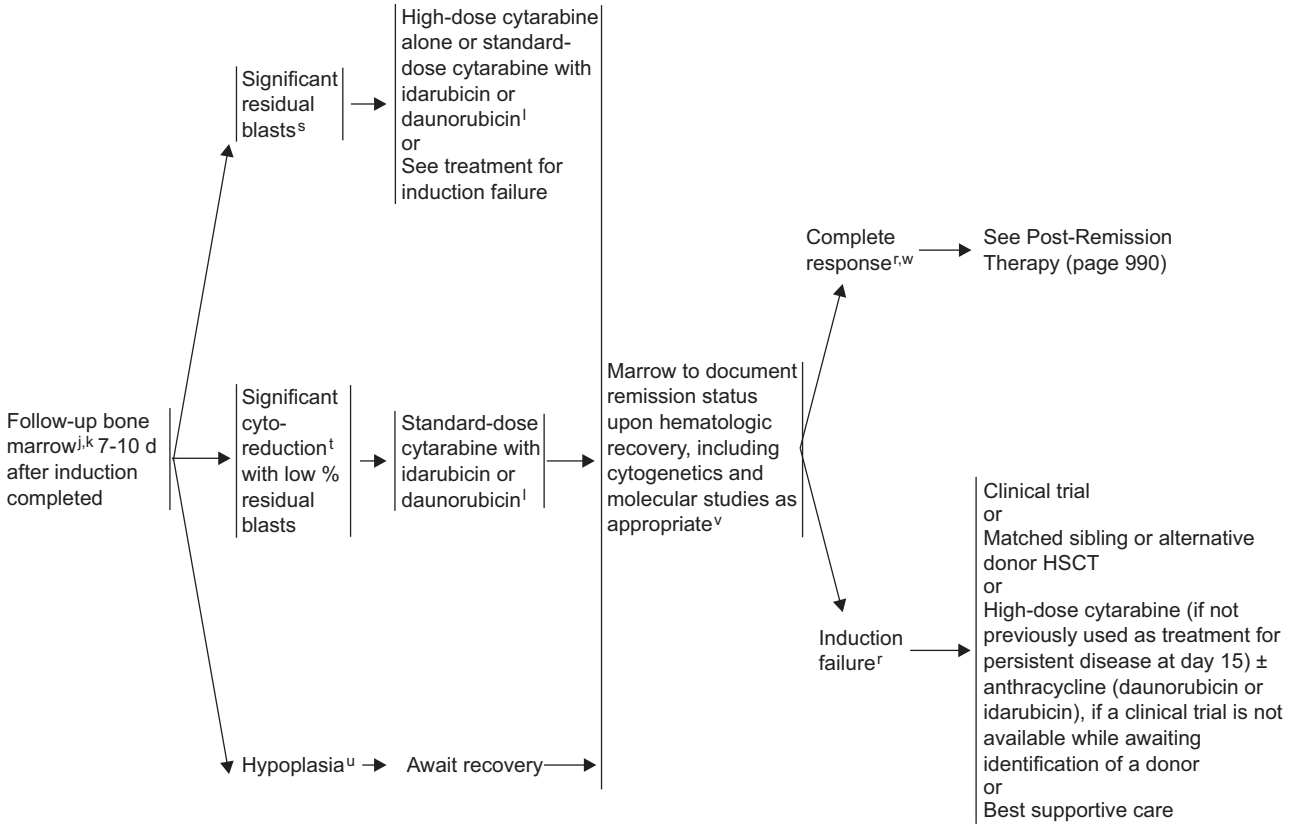
[o] Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. Blood 1996;88:2841-2851.

[p] 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.

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

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

CONSOLIDATION THERAPY



[j] See Supportive Care (page 996).
[k] See Monitoring During Therapy (page 998).
[l] ECOG reported a significant increase in complete response rates and overall survival using daunorubicin, 90 mg/m^2 x 3 days versus 45 mg/m^2 x 3 days in patients < 60 years of age. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 2009;361:1249-1259. If residual disease is present on days 12-14, the additional daunorubicin dose is 45 mg/m^2 x 3 days.
[r] See Response Criteria for Acute Myeloid Leukemia (page 997).
[s] Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and the patient is a candidate for an allogeneic HSCT.
[t] If ambiguous, consider repeat bone marrow biopsy in 5-7 days before proceeding with therapy.
[u] Hypoplasia is defined as cellularity < 10%-20% and residual blasts < 5%-10%.
[v] The role of immunophenotyping in detecting minimal residual disease is being evaluated.
[w] Patients with an increased risk of meningeal involvement (initial WBC count > 100,000/mcL or monocytic histology) should be considered for CNS evaluation with a LP on achieving complete response. See Evaluation and Treatment of CNS Leukemia (page 995).

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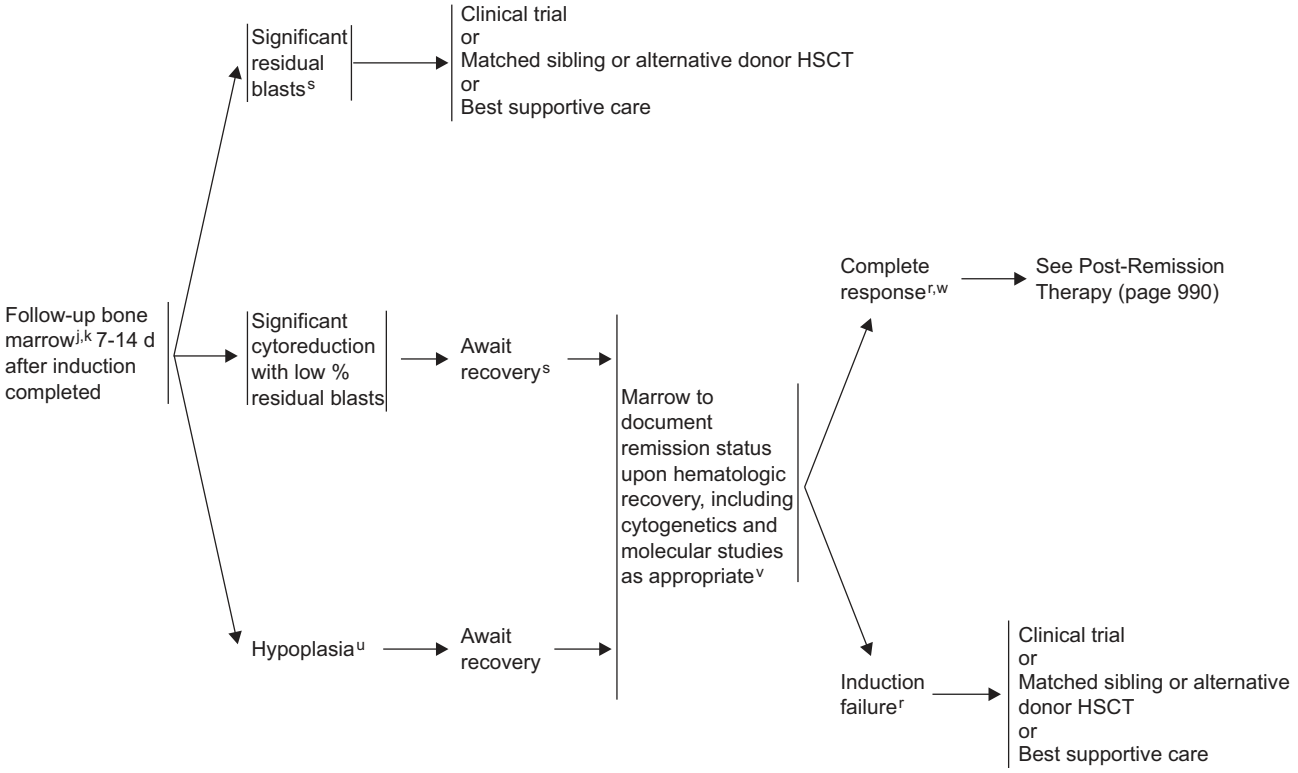
AML POST-INDUCTION THERAPY
AFTER HIGH-DOSE CYTARABINE
Age < 60 y

CONSOLIDATION THERAPY



[j] See Supportive Care (page 996).
[k] See Monitoring During Therapy (page 998).
[r] See Response Criteria for Acute Myeloid Leukemia (page 997).
[s] Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and the patient is a candidate for an allogeneic HSCT.
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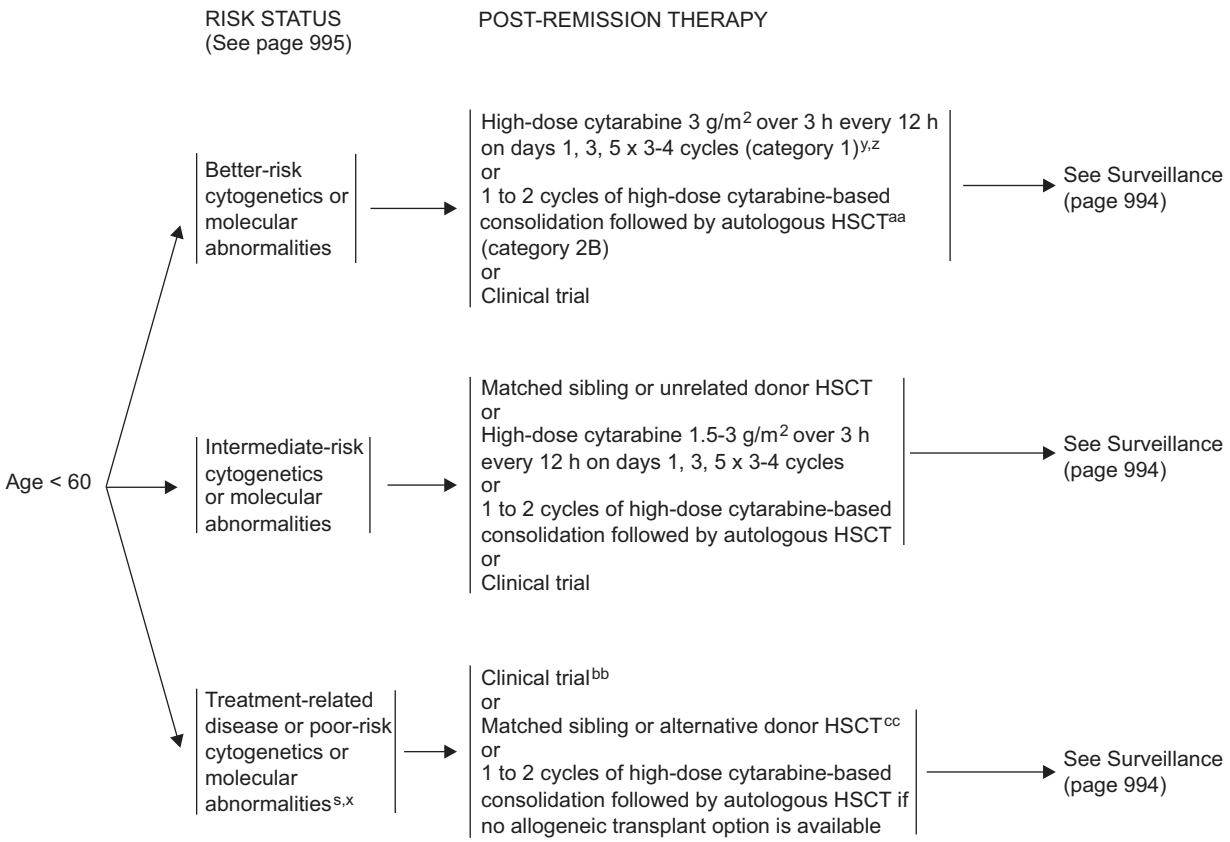

[s] Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and the patient is a candidate for an allogeneic HSCT.

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

[y] Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 1994;331:896-903.

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

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

[bb] Clinical trials, when available, are strongly recommended in the treatment of patients with poor prognostic features.

[cc] 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 after achievement of remission if a donor (sibling or alternative) is available.

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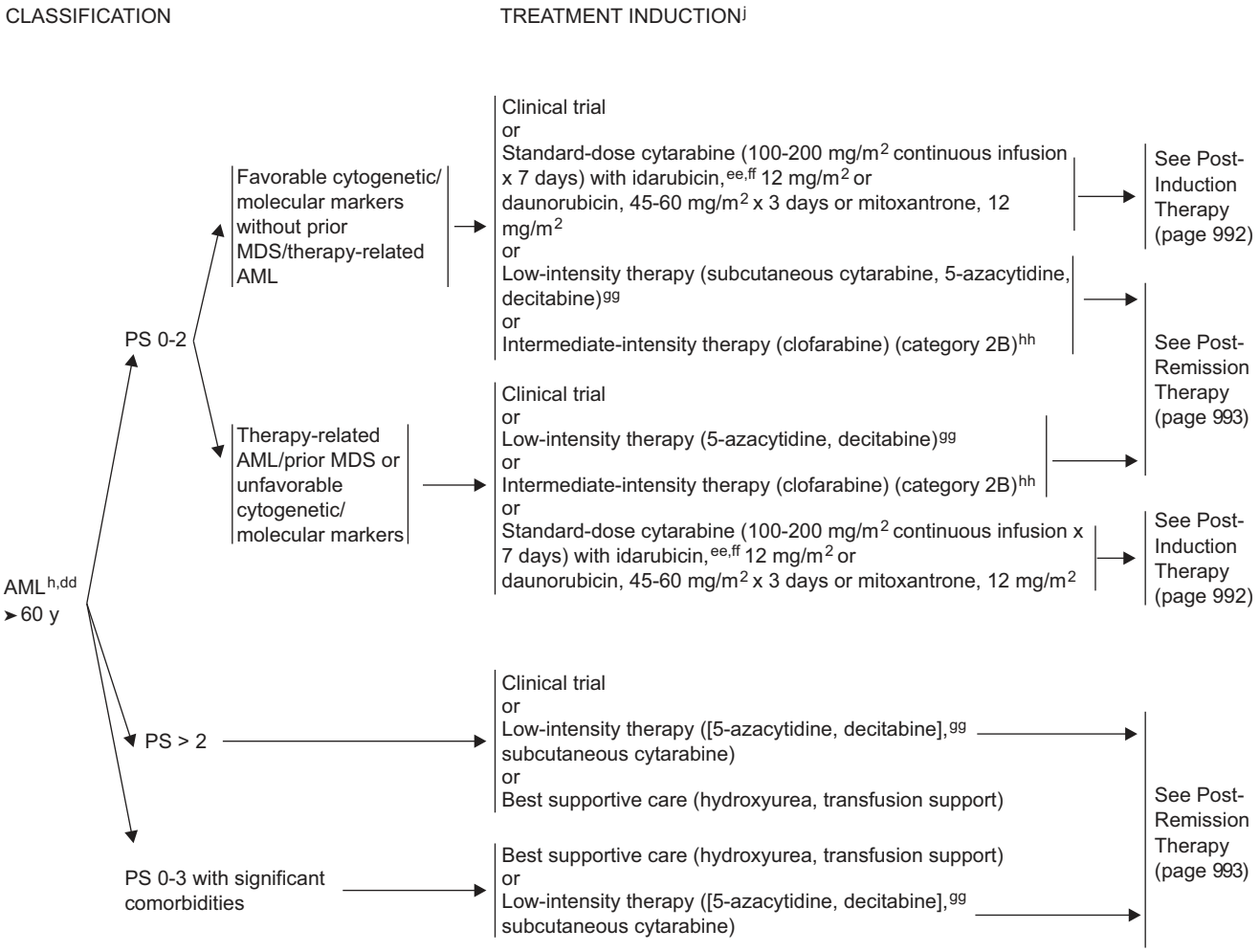


[h] Patients with blast counts > 50,000/mcL are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include apheresis or hydroxyurea. Prompt institution of definitive therapy is essential.

[j] See Supportive Care (page 996).

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

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

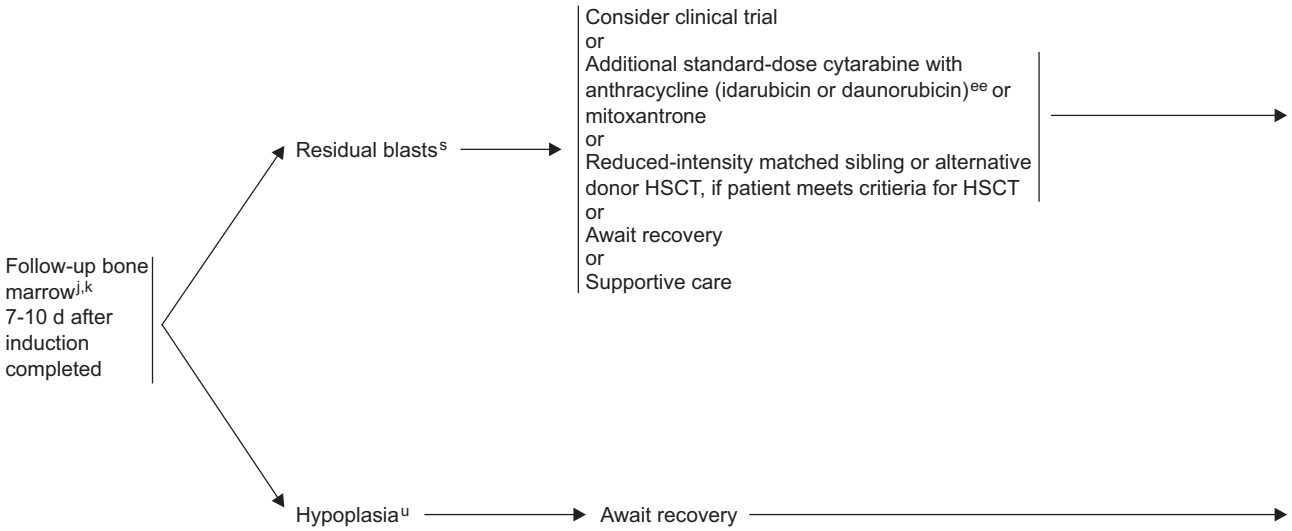
[ff] Patients older than 75 years with significant comorbidities usually do not benefit from conventional chemotherapy treatment. However, the rare patient with good or normal karyotype and no significant comorbidities may benefit from conventional chemotherapy treatment.

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

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

AML POST-INDUCTION THERAPY

Age ≥ 60 y



[j] See Supportive Care (page 996).
[k] See Monitoring During Therapy (page 998).
[s] Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and the patient is a candidate for an allogeneic HSCT.
[u] Hypoplasia is defined as cellularity < 10%-20% and residual blasts < 5%-10%.
[ee] Idarubicin treatment compared with high doses of daunorubicin up to 80 mg/m^2 yields higher complete response rate and more complete responses after one course. (Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia aged 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol 2010;28:808-814.) The complete response rates and 2-year overall survival in patients between 60 and 65 years of age treated with daunorubicin, 90 mg/m^2, is also comparable to the outcome for idarubicin, 12 mg/m^2; the higher dose daunorubicin did not benefit patients older than 65 years (Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 2009;361:1235-1248).

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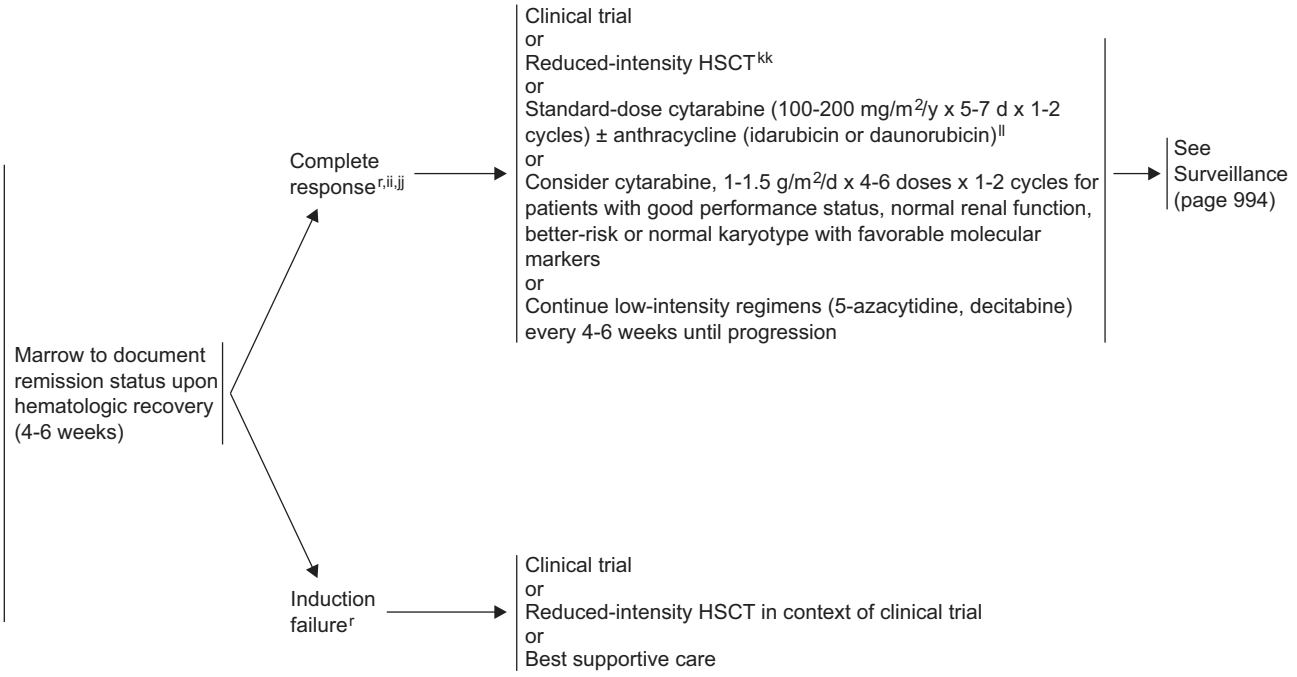
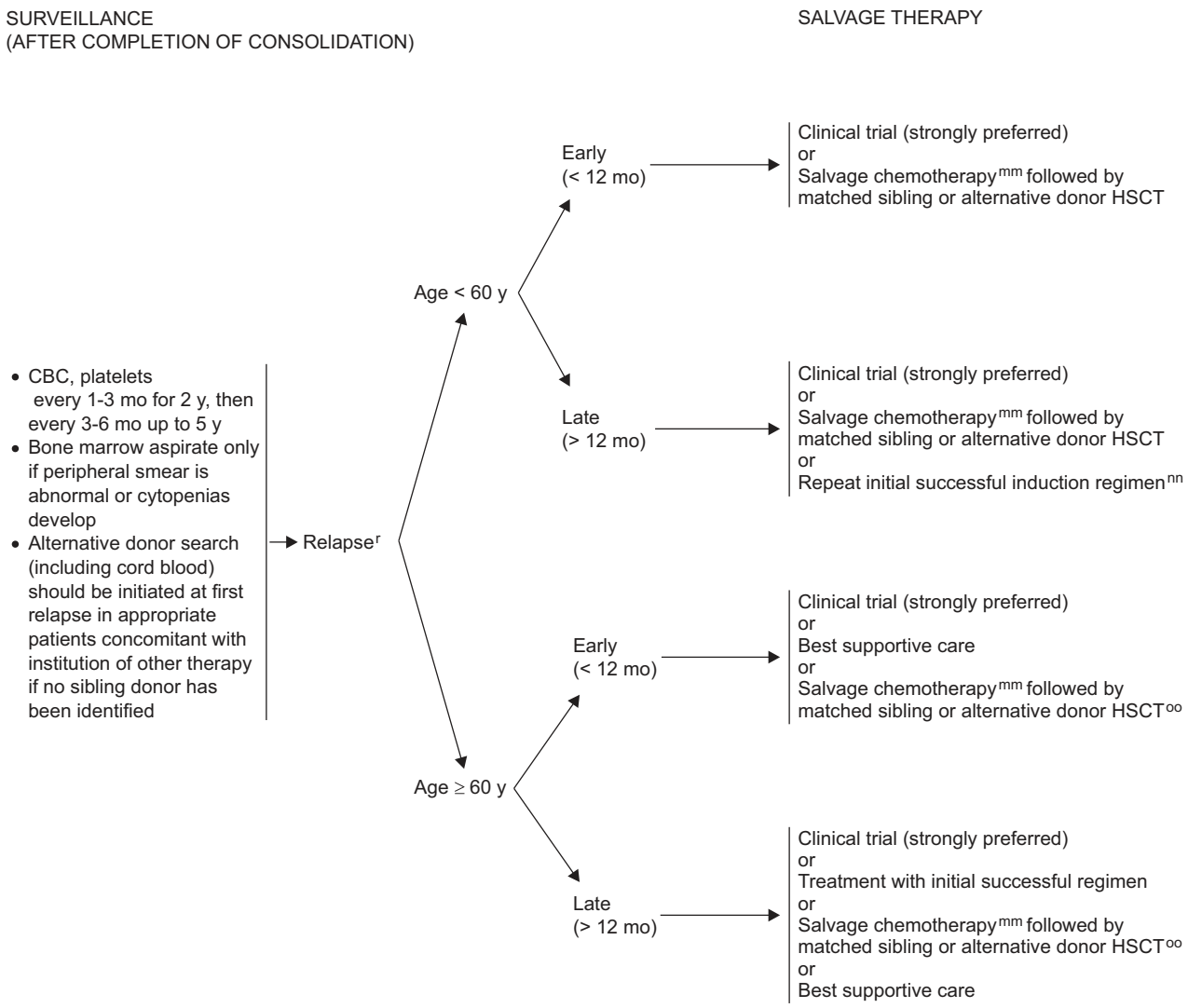
AML POST-REMISSION THERAPY
Age ≥ 60 y



[r] See Response Criteria for Acute Myeloid Leukemia (page 997).
[ii] Patients in remission may be screened with LP if initial WBC count > 100,000/mcL or monocytic histology. See Evaluation and Treatment of CNS Leukemia (page 995).
[jj] HLA typing for patients considered strong candidates for allogeneic transplantation.
[kk] Patients who are deemed strong candidates for stem cell transplant and who have an available donor should be transplanted in first remission.
[ll] An excellent outcome was reported for outpatient consolidation that provides another option for elderly patients. Gardin C, Turlure P, Fagot T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. Blood 2007;109:5129-5135.



[r] See Response Criteria for Acute Myeloid Leukemia (page 997).
[mm] See Salvage Chemotherapy Regimen Options (page 998).
[nn] Reinduction therapy may be appropriate in certain circumstances, such as patients with long first remission. If a second complete response is achieved, then consolidation with allogeneic HSCT should be considered.
[oo] Transplant should only be considered in the context of a clinical trial or if a remission is achieved.

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

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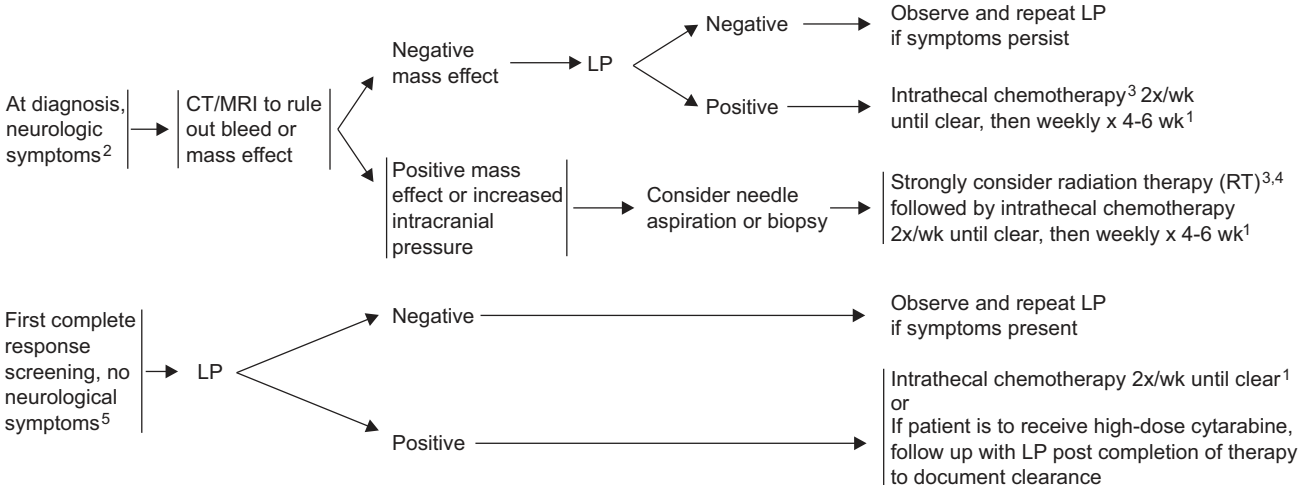
RISK STATUS BASED ON CYTOGENETICS AND MOLECULAR ABNORMALITIES

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

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

EVALUATION AND TREATMENT OF CNS LEUKEMIA[1]



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

SUPPORTIVE CARE

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

General

- Blood products:
  - Leukocyte-depleted products used for transfusion.
  - Irradiated blood products for patients receiving immunosuppressive therapy (ie, fludarabine, HSCT).
  - Transfusion thresholds: red blood cell (RBC) counts for Hgb ≤ 8 g/dL or per institutional guidelines or symptoms of anemia; platelets for patients with platelets < 10,000/mcL or with any signs of bleeding.[1]
  - Cytomegalovirus (CMV) screening for potential HSCT candidates may be considered.
- Tumor lysis prophylaxis: hydration with diuresis, and urine alkalinization (may be contraindicated with increased phosphate) and allopurinol or rasburicase. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence of impaired renal function.
- Patients receiving high-dose cytarabine therapy (particularly those with impaired renal function) are at risk for cerebellar toxicity. Neurologic assessment, including tests for nystagmus, slurred speech, and dysmetria, should be performed before each dose of cytarabine.
  - In patients exhibiting rapidly rising creatinine because of tumor lysis, high-dose cytarabine should be discontinued until creatinine normalizes.
  - In patients who develop cerebellar toxicity, cytarabine should be stopped. The patient should not be rechallenged with high-dose cytarabine in future treatment cycles. (Smith GA, Damon LE, Rugo HS, et al. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. J Clin Oncol 1997;15:833-839.)
- Saline or steroid eye drops should be administered to both eyes 4 times daily for all patients undergoing high-dose cytarabine therapy until 24 hours after completion of cytarabine.
- Growth factors may be considered as a part of supportive care for postremission therapy. Note that this use may confound interpretation of the bone marrow evaluation. Patients should be off granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor (G-CSF) for a minimum of 7 days before obtaining bone marrow to document remission.
- Decisions regarding use and choice of antibiotics should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns. Posaconazole has been shown to significantly decrease fungal infections when compared with fluconazole.[2] Outcomes with other azoles, such as voriconazole, echinocandins, or amphotericin B, may produce equivalent results. Azoles should not be given during anthracyline chemotherapy because they impair drug metabolism and can increase toxicity.

[1] Patients who are allo-immunized should receive cross-match compatible and/or HLA-specific blood products.
[2] Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348-359.

Acute Myeloid Leukemia, Version 2.2012

RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA[1]

- Morphologic leukemia-free state
  - Bone marrow < 5% blasts in an aspirate with spicules
  - No blasts with Auer rods or persistence of extramedullary disease
- If there is a question of residual leukemia, a bone marrow aspirate/biopsy should be repeated in 1 week.
- A bone marrow biopsy should be performed if spicules are absent from the aspirate sample.
- Complete remission
  - Morphologic complete response (CR) - patient independent of transfusions
    - Absolute neutrophil count > 1000/mcL
    - Platelets ≥ 100,000/mcL
    - No residual evidence of extramedullary disease
  - Cytogenetic CR - cytogenetics normal (in those with previously abnormal cytogenetics)
  - Molecular CR - molecular studies negative[2]
  - CR with incomplete count recovery (CRi) - Some clinical trials, particularly those that focus on the elderly or those with antecedent myelodysplasia, include a variant of complete response referred to as CRp or CRi. This has been loosely defined as < 5% marrow blasts and transfusion independence but with persistence of cytopenia (usually thrombocytopenia).
- Partial remission[3]
  - Decrease of at least 50% in the percentage of blasts to 5%-25% in the bone marrow aspirate and the normalization of blood counts, as noted above.
- Patients failing to achieve a CR are considered treatment failures.
- Relapse after CR is defined as reappearance of leukemic blasts in the peripheral blood or the finding of > 5% blasts in the bone marrow, not attributable to another cause (eg, bone marrow regeneration after consolidation therapy) or extramedullary relapse.

[1] Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21:4642-4649.
[2] This is currently clinically relevant only in APL and Ph+ leukemia.
[3] Partial remissions are only useful in assessing potential activity of new investigational agents, usually in phase I trials, and should not be considered a therapy goal for standard therapy.

MONITORING DURING THERAPY

Induction:

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

Postremission therapy:

- CBC, platelets 2x/wk during chemotherapy.
- Chemistry profile, electrolytes daily during chemotherapy.
- Outpatient monitoring post chemotherapy: CBC, platelets, differential, and electrolytes 2-3x/wk until recovery.
- Bone marrow only if peripheral blood counts are abnormal or if there is failure to recover counts within 5 wk.
- Patients with high-risk features, including poor-prognosis cytogenetics, therapy-related AML, prior MDS, or possibly 2 or more inductions to achieve a complete response, are at increased risk for relapse and may be considered for early unrelated donor search, as indicated on page 987.

SALVAGE CHEMOTHERAPY REGIMEN OPTIONS[1]

- Cladribine + cytarabine + G-CSF ± mitoxantrone or idarubicin[2,3]
- High-dose cytarabine (if not received previously in treatment) ± anthracycline
- Fludarabine + cytarabine + G-CSF ± idarubicin[4,5]
- Etoposide + cytarabine ± mitoxantrone[6]
- Clofarabine + cytarabine + G-CSF[7]

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

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

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

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

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

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

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

Text continued from p. 985

with lymphoproliferative disorders, particularly when administered in combination with alkylating agents.[10,11] Radiotherapy, especially in the context of myeloablative therapy (eg, total-body irradiation or radioimmunotherapy) given before autologous stem cell transplantation, may also increase the risk of therapy-related MDS/AML.[12,13]

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.[8] Importantly, clinical outcomes in patients with therapy-related AML have been shown to be significantly inferior (both in terms of relapse-free and overall survivals) compared with patients with de novo cases,[7,14] except those with the therapy-related acute promyelocytic leukemia (APL) subtype[6,15] or the favorable-risk core binding factor (CBF) translocations. The proportion of patients with unfavorable cytogenetics tends to be higher in the population with therapy-related AML. Even among the subgroup with favorable karyotypes, those with therapy-related AML tend to do less well.

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

Initial Evaluation

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

Diagnosis

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

In 1999, the WHO developed a newer classification system, which incorporates information from cytogenetics and evidence of dysplasia to refine prognostic subgroups that may define treatment strategies.[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 (1976) had set the threshold between high-grade MDS and AML at 30% blasts, whereas the WHO classification lowered the threshold for diagnosing AML to 20% or more blasts; this was based on the finding that the biologic behavior (and survival outcomes) of the FAB MDS subgroup of "refractory anemia with excess blasts in transformation (RAEB-T)" with 20% to 30% blasts was equally grim compared with that of patients with greater than 30% blasts. In addition, the WHO classification system allows AML to be diagnosed regardless of the percentage of marrow blasts in patients with abnormal hematopoiesis and characteristic clonal structural cytogenetic abnormalities with t(15;17), t(8;21), and inv(16) or t(16;16).

In 2003, the International Working Group for the Diagnosis and Standardization of Response Criteria accepted the cytochemical and immunophenotypic criteria of WHO as the standard for diagnosing AML, including the reporting of dysplasia according to morphology.[17] However, no evidence shows that dysplasia represents an independent risk factor, because it is frequently linked to poor-risk cytogenetics.

In 2008, the WHO revised the diagnostic and response criteria for AML to include additional recurrent genetic abnormalities created by reciprocal translocations/inversions, and a new provisional category for some of the molecular markers that have been found to have prognostic impact.[18] In the 2008 WHO classification, the category of AML with recurrent genetic abnormalities was expanded to include the following: t(9;11)(p22;q23), t(6;9)(p23;q34) (provisional entity), inv(3)(q21;q26.2) or inv(3;3)(q21;q26.2) (provisional entity), and

t(1;22)(p13;q13) (provisional entity), in addition to the previously recognized t(8;21)(q22;q22); inv(16)(p13;1q22) or t(16;16)(p13.1;q22); and t(15;17)(q22;q12) [APL subtype]. In addition, AML with molecular lesions such as mutated *NPM1* or *CEBPA* genes are considered provisional entities (further information on these genetic lesions is provided later).[18]

The accurate classification of AML requires multidisciplinary diagnostic studies (using immunohistochemistry, cytochemistry, or both, in addition to molecular genetics analysis) in accordance with the 2008 WHO classification. The NCCN AML Panel suggests that complementary diagnostic techniques can be used at the discretion of the pathology departments of the individual institutions. Some cases may still show evidence of both myeloid and lymphoid antigen expression on the leukemic cells. When presented with rare cases such as acute leukemias of ambiguous lineage (including mixed phenotype acute leukemias, as defined by the 2008 WHO classification), consultation with an experienced hematopathologist should be sought. Aberrant expression of differentiation antigens present at diagnosis may allow tracking of residual blasts through flow cytometry in follow-up samples that may appear normal according to conventional morphology. The use of immunophenotyping and molecular markers to monitor minimal residual disease (MRD) in adult AML has not yet been incorporated into postremission monitoring strategies, except in patients with APL.

Cytogenetics and Risk Stratification: Although cytogenetic information is often unknown when treatment is initiated in patients with de novo AML, karyotype represents the single most important prognostic factor for predicting remission rate, relapse risks, and overall survival (OS) outcomes. The cytogenetic risk categories adopted by these guidelines are primarily based on analyses of large datasets from major cooperative group trials (see "Risk Status Based on Cytogenetics and Molecular Abnormalities," page 995).[19–21] In an analysis of data from pediatric and adult patients with AML (N = 1612) enrolled on the United Kingdom Medical Research Council (UK MRC) AML 10 trial, the 5-year survival rates for those with favorable, intermediate-risk, and poor-risk cytogenetics were 65%, 41%, and 14%, respectively.[20] In a review of data from adult patients treated on a phase III SWOG/ECOG intergroup study (N = 609), the 5-year survival rates for those with favorable, intermediate-risk, and unfavorable cytogenetics were 55%, 38%, and 11%, respectively.[21] Similarly, in a retrospective review of adult patients with AML treated on CALGB protocols (N = 1213), the 5-year survival rates for those with favorable, intermediate-risk, and poor-risk cytogenetics were 55%, 24%, and 5%, respectively.[19]

Therefore, the importance of obtaining adequate samples of marrow or peripheral blood at diagnosis for full karyotyping and fluorescence in situ hybridization (FISH) cytogenetic analysis for the most common abnormalities cannot be overemphasized. Although FISH studies for common cytogenetic abnormalities may provide a rapid screening to identify either favorable or unfavorable risk groups, they do not provide a full picture of the genetic factors, which contribute to risk.

In the past 5 years, the presence of autosomal chromosome monosomies in AML has emerged as an important prognostic factor associated with extremely poor prognosis.[22–24] Data from 3 large studies have identified monosomal karyotypes (defined as having ≥ 2 autosomal monosomies, or a single monosomy with additional structural abnormalities) as a subset of unfavorable cytogenetic prognosticators. Although complex karyotype (having ≥ 3 clonal cytogenetic abnormalities) and −5 or −7 monosomies are categorized in the high-risk/unfavorable cytogenetics group, the presence of a monosomal karyotype was found to confer further negative prognostic influence within the high-risk group. The first study to identify this high-risk subgroup was HOVON. In a joint study conducted by the Dutch-Belgian and Swiss cooperative groups (HOVON/SAKK) evaluating the correlation between cytogenetics and OS outcomes in patients aged 60 years or younger with AML (N = 1975), the 4-year OS rate in patients with monosomal karyotype was 4% compared with 26% in those with complex karyotype (but without monosomal karyotype).[22]

These findings were confirmed in subsequent analyses from other large cooperative group studies. In an analysis of data from patients treated on SWOG protocols (N = 1344; age 16–88 years), 13% of patients were found to have monosomal karyotype; nearly all of these cases (98%) occurred within the unfavorable cytogenetics category.[23] The incidence of monosomal karyotype increased with

age, from 4% in patients aged 30 years or younger to 20% in those older than 60 years. Among patients with unfavorable cytogenetics, the 4-year OS rate in the subgroup of patients with monosomal karyotype was 3% compared with 13% in the subgroup without monosomal karyotype. In patients with monosomy 7, monosomal karyotype did not appear to influence outcomes (4-year OS, 0%–3%); the 4-year OS rates for patients with inv(3)/t(3;3) and t(6;9) and those without monosomal karyotype, were 0% and 9%, respectively.[23] In a recent retrospective study that evaluated the prognostic impact of monosomal karyotype in older patients (age > 60 years; N = 186) with unfavorable cytogenetics treated on a GOELAMS trial, the 2-year OS rate was significantly decreased among patients with monosomal karyotype compared with those without this abnormality (7% vs. 22%; $P < .0001$); similar outcomes were observed within the subgroup of patients with complex karyotype.[24]

These studies show that monosomal karyotype, independent of other unfavorable cytogenetic factors, confers very poor prognosis in both young and older patients with AML.

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

Molecular profiling is increasing the ability to identify mutations at the molecular level, which carry prognostic impact. Thus, in addition to basic cytogenetic analysis, new molecular markers help to refine prognostics groups, particularly in patients with a normal karyotype. These markers include FMS-like tyrosine kinase 3 (*FLT3*), *c-KIT*, nucleophosmin (*NPM1*), and *CEBPA* gene mutations.[25–36] Tests for these molecular markers are becoming more common in commercial reference laboratories and in referral centers. Therefore, it is important for physicians to submit sufficient samples to reserve aliquots of cryopreserved marrow from the time of diagnosis to allow for molecular diagnostic tests in patients with normal karyotype.

The 2 most frequent molecular lesions with prognostic impact in patients with AML are mutations of the *FLT3* gene (37%–46% of patients) encoding a receptor tyrosine kinase involved in hematopoiesis,[29,37,38] and mutations of the *NPM1* gene (28%–35%)[35,37,39] encoding a shuttling protein within the nucleolus. The *NPM1* mutation has been shown to be associated NK-AML with a reported frequency of 48% to 53%.[27,33,38] A single *NPM1* mutation, which localizes to the cytoplasm, confers a higher complete response (CR) rate and improved event-free survival (EFS) and OS compared with patients with NK-AML with wild-type *NPM1*, resulting in outcomes similar to patients with favorable cytogenetics (eg, CBF AML).[27,28,33,35,36] Two major classes of activating *FLT3* mutations have been identified in patients with AML, which include the internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations.[40–45] *FLT3*-ITD occurs in approximately 30% of cases and is more common than *FLT3*-TKD mutations, which occur in approximately 10% of patients.[25,29,38,44–48] Numerous studies have shown the negative prognostic influence of *FLT3*-ITD in patients with AML, resulting in shorter remission durations (eg, decreased disease-free survival [DFS] in patients with a CR) and poorer survival outcomes compared with patients with wild-type *FLT3*.[25,29,41,42,44,46,47,49] Among patients with *FLT3*-ITD and NK-AML, median OS from the time of diagnosis ranged from 6 to 12 months.[25,29,44,47]

Interestingly, a study in patients with NK-AML showed that prognosis was worse among patients with *FLT3*-ITD without a wild-type *FLT3*, compared with those with *FLT3*-ITD but having a wild-type *FLT3* in the second allele. The median OS among patients with *FLT3*-ITD in the absence of a wild-type *FLT3* was only 7 months compared with 46 months among both the patient subgroups with wild-type *FLT3* with or without *FLT3*-ITD.[44] The *FLT3*-TKD mutations predominantly occur independently of *FLT3*-ITD, and most frequently involve mutations in the D835 residue of a tyrosine kinase domain. Although the presence of *FLT3*-TKD mutations has been shown to be associated with shorter remission durations (eg, decreased DFS) and decreased OS outcomes in some studies,[29,41,45,48] other studies have reported no impact

of *FLT3*-TKD on prognosis[38,49,50] or even a favorable outcome on OS with *FLT3*-TKD mutations.[51] In the latter study from the UK MRC, the 5-year OS rate among patients with and without *FLT3*-TKD mutations was 53% versus 37%, respectively. Patients with a higher level of *FLT3*-TKD mutations (> 25%) had a significantly higher 5-year OS rate compared with those with lower levels of mutations, which showed an OS rate similar to that of patients without *FLT3*-TKD mutations (71% vs. 37%; adjusted *P* = .004).[51]

The discrepant findings from these studies may be a result of important differences between the studies in factors such as patient baseline characteristics, presence of concurrent genetic lesions (eg, *NPM1*, *CEBPA* mutations), or inclusion of the APL subtypes. Studies have shown that *FLT3*-TKD mutations can occur in a subgroup of patients with the prognostically favorable *NPM1* or *CEBPA* mutations.[38,50] Moreover, *FLT3*-TKD mutation as the sole genetic aberration or occurring concurrently with t(15;17)/PML-RARA (underlying lesion in the APL subtype) or with *FLT3*-ITD (*FLT3* double mutation) has been associated with poorer outcomes.[38,50]

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

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

Findings from published reports on the prognostic effects of *IDH1* mutations have been inconsistent. Although some studies showed no prognostic effect of *IDH1* mutations on OS when considering all *IDH* mutations (*IDH1* and *IDH2* combined) or in the overall patient population,[55–58] *IDH1* mutations seemed to be associated with significantly worse outcomes in the subgroup of patients with NK-AML with favorable- or intermediate-risk disease.[55,58,60] In the subgroup of patients younger than 60 years with favorable-risk AML (*NPM1* mutation without *FLT3*-ITD) in a study of patients with NK-AML, *IDH1* mutation was associated with a significantly decreased 5-year DFS rate (42% vs. 59%; *P* = .046) and trend for decreased OS rate (50% vs. 63%) compared with patients who had wild-type *IDH*.[58] In another study, *IDH* mutations (*IDH1* and *IDH2* combined) were associated with significantly inferior 5-year relapse-free survival rates (37% vs. 67%; *P* = .02) and OS rates (41% vs. 65%; *P* = .03) in the subgroup of patients with favorable-risk AML (normal karyotype with *NPM1* mutation without *FLT3*-ITD).[60] This prognostic significance was observed when *IDH1* and *IDH2* mutations were separately analyzed, although patient numbers were small for each subgroup and statistical significance was reached only for the relapse-free survival analysis.[60] *IDH1* mutation was also associated with worse EFS and OS outcomes among the subgroup of patients with intermediate-risk NK-AML (wild-type *NPM1* without *FLT3*-ITD).[55] Mutations in *IDH2* have been reported in 8% to 12% of patients with AML,[37,55,56,60,61] with a frequency of 19% reported among those with normal karyotype.[58] The presence of *IDH2* mutations was mutually exclusive with *IDH1* mutation in nearly all cases.[55,56,58] Mutations have been identified in R172 and R140 of the *IDH2* gene, with R140 mutation occurring more frequently.[58,60,61] Interestingly, the *IDH2*-R172 mutation seemed to be mutually exclusive with *NPM1* mutations and *FLT3*-ITD.[58,60,61]

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

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

The *DNMT3A* mutations have been reported in 18% to 22% of patients with AML,[37,62,63] with a frequency of 29% to 34% in those with NK-AML.[64–66] R882 is the most commonly mutated residue. This mutation has also been observed in conjunction with *NPM1* mutations and *FLT3* mutations.[63,65,66] Data concerning the prognostic significance of *DNMT3A* mutations have thus far been conflicting. Some studies in the overall AML population and in patients with intermediate risk reported no significant effect of *DNMT3A* mutations on survival outcomes,[37,65] whereas other studies have shown a negative prognostic effect in the overall population or specific subgroups.[62–64,66] Studies have shown significantly decreased OS outcomes among patients with *DNMT3A* mutations compared with those with the wild-type gene (median OS, 12–21 vs. 40–41 months).[62,63] Significantly decreased OS with *DNMT3A* mutations has also been reported in the subgroup of patients with NK-AML with wild-type *NPM1* with or without *FLT3*-ITD or *NPM1* mutation in the presence of *FLT3*-ITD, but not in the favorable subgroup with *NPM1* mutation without *FLT3*-ITD.[63] A recent study reported that in younger patients (age < 60 years) with NK-AML, presence of *DNMT3A* mutations was associated with significantly decreased OS compared with the wild-type gene (5-year OS rate, 23% vs. 45%; $P = .02$).[66] Another recent study also showed that in younger patients (age < 60 years) with NK-AML, *DNMT3A* mutation was associated with significantly decreased DFS (3-year rate, 20% vs. 49%; $P = .007$) and a trend toward decreased OS.[64] Interestingly, in this latter study, non-R882 *DNMT3A* mutations were significantly associated with poorer outcomes in patients younger than 60 years (but not R882 mutations); in contrast, in patients aged 60 years and older, *DNMT3A*-R882 mutations (but not non-R882 mutations) were associated with significantly decreased DFS (3-year rate, 3% vs. 21%; $P = .006$) and OS (3-year rate, 4% vs. 24%; $P = .01$).[64] The authors concluded that the prognostic relevance of *DNMT3A* mutations may depend on age and mutation type. Currently, the interactions of both *IDH1* or *IDH2* and *DNMT3* mutations with other molecular changes require further investigation to determine the prognostic value in patients with NK-AML. Neither of these genetic mutations is available for testing outside of the research setting. Other candidate genes currently being evaluated for prognostic importance include *TET2* and *RUNX1*.

As seen from the earlier discussions, patients with NK-AML may present with multiple molecular lesions. *NPM1* mutations can occur concurrently with *FLT3*-ITD, and patients who have both genetic lesions have an outcome more similar to those with isolated *FLT3*-ITD mutations.[27,33] Thus, *NPM1* mutation confers favorable prognosis only in the absence of *FLT3*-ITD.[38] Similarly, the benefit in OS outcomes seen with *CEBPA* mutations seems to be lost in the presence of concurrent *FLT3*-ITD.[53] As previously mentioned, *FLT3*-TKD in the presence of *FLT3*-ITD or occurring with t(15;17)/PML-RARA seems to be associated with poorer prognosis. In contrast, *FLT3*-TKD may be associated with an additional favorable prognosis in the presence of *NPM1* or *CEBPA* mutations.[50]

Both the NCCN and the European LeukemiaNet (ELN) classify patients with NK-AML and mutated *NPM1* or *CEBPA* (without *FLT3*-ITD) as having favorable risk.[67] In the ELN guidelines, patients with NK-AML with both mutated *NPM1* and *FLT3*, and those with wild-type *NPM1* and mutated *FLT3* or wild-type *NPM1* and *FLT3* are categorized as having intermediate-risk AML ("Intermediate I" group).[67] ELN classifies patients with t(9;11)(p22;q23), *MLLT3-MLL* and other cytogenetic abnormalities

that fall into neither the favorable or adverse category into the "Intermediate II" group. A recent analysis that evaluated the prognostic value of the ELN risk classification (based on data from the German AML96 study) showed that for patients aged 60 years and younger, median relapse-free survival was shorter for the Intermediate I than for the Intermediate II group (7.9 vs. 39.1 months, respectively). In patients older than 60 years, no major difference was observed (9.6 vs. 11.6 months, respectively).[68] In this analysis, median OS between the Intermediate I and Intermediate II groups were not as widely separated among patients aged 60 years and younger (13.6 vs. 18.7 months, respectively); in patients older than 60 years, median OS was similar between the 2 intermediate groups (9.5 vs. 9.2 months, respectively).[68] However, based on the substantial difference in relapse-free survival data between the Intermediate I and Intermediate II groups defined by ELN, the NCCN has continued to place NK-AML with *FLT3*-ITD mutations in the unfavorable risk group rather than the intermediate risk group (see "Risk Status Based on Cytogenetics and Molecular Abnormalities," on page 995). Although data are emerging on the prognostic relevance of mutations in the *IDH* and *DNMT3A* genes (see earlier discussions), the role of these molecular lesions on the risk stratification of patients with AML remains to be defined. Therefore, these molecular markers have not been incorporated into the risk categorization schema in the current guidelines.

In patients with the favorable-risk CBF AML [eg, t(8;21) or inv(16)], the presence of a mutation in *c-KIT* significantly increased the risk of relapse.[26,32,34] *c-KIT* mutations have been reported in approximately 20% of patients with CBF AML.[32,69] Studies have shown that *c-KIT* mutations are associated with decreased remission duration (eg, EFS and relapse-free survival) and decreased OS in both groups of patients with t(8;21) or inv(16).[26,32,34,69] Patients with t(8;21) or inv(16)/t(16;16) with *c-KIT* mutation are categorized as having intermediate risk AML (see "Risk Status Based on Cytogenetics and Molecular Abnormalities," on page 995).

Although none of the genetic abnormalities discussed earlier affect the initial course of AML treatment, they provide prognostic information that may influence subsequent treatment decisions. Research into basic leukemia biology using banked samples from clinical trials may provide keys to altered cellular pathways, which may lead to new treatment options. The new risk stratification incorporating molecular data along with cytogenetics is summarized in the guidelines (see "Risk Status Based on Cytogenetics and Molecular Abnormalities," on page 995).

Workup

Extramedullary presentation, including central nervous system (CNS) disease, is uncommon in patients with AML. Patients with significant CNS signs or symptoms at presentation should be evaluated using appropriate imaging techniques, such as radiography, CT, or MRI for detection of intracranial bleeding, leptomeningeal disease, or mass lesions in either the brain or spinal cord. However, if symptoms persist, and bleeding and mass/lesions are excluded, the patient should have a lumbar puncture (LP) for diagnostic and possible therapeutic purposes once coagulopathy has been corrected and adequate platelet support is available. Routine screening LPs are not warranted at the time of diagnosis in patients with AML. However, for patients at high risk for CNS disease, such as those with monocytic differentiation (M4 or M5 morphology) or high WBC count (> 100,000/mcL) at presentation, a diagnostic LP should be considered as part of the documentation of remission status. For patients who present with solitary extramedullary disease (often referred to as myeloid sarcoma, granulocytic sarcoma, or chloroma) without overt marrow disease, the initial treatment should still be based on systemic induction chemotherapy. Radiation or surgical resection may be incorporated with systemic chemotherapy in emergent situations; however, these modalities, if needed at all, should be optimally deferred until count recovery to avoid excess toxicity.

Coagulopathy is fairly common at presentation in many leukemias; it is therefore standard clinical practice to screen for coagulopathy by evaluating prothrombin time, partial thromboplastin time, and fibrinogen as part of the initial workup and before performing any invasive procedure. The need for a cardiac evaluation should be determined by individual risk factors, such as patient and family history or previous malignancy treated with cardiotoxic drugs or thoracic radiation. HLA typing should be performed in all patients with newly diagnosed AML for whom allogeneic hematopoietic stem cell transplantation (HSCT) would be considered. HLA typing of family members is recommended for patients younger than 60 years

who do not have favorable-risk cytogenetics. Tissue typing should be broadened to include unrelated donor searches in patients younger than 60 years with karyotypes or molecular abnormalities deemed high-risk. In the high-risk group, a donor search should begin while the patient is recovering from induction chemotherapy rather than waiting for remission to be achieved. Many institutions also use HLA typing to select platelet donors for allogeneic HSCT.

Principles of AML Treatment

Treatment of acute leukemia has been divided into induction chemotherapy and postremission (or consolidation) therapy. Although obtaining a remission is the first step in controlling the disease, it is also important for patients to emerge from the induction phase in a condition to tolerate subsequent, more intensive treatments during consolidation to achieve durable disease control. Patients who do not receive postremission therapy will experience relapse, usually within 6 to 9 months. The induction strategy is influenced by individual patient characteristics such as age, presence of comorbid conditions affecting performance status, and preexisting myelodysplasia. This is particularly true of elderly patients with AML. Patients whose performance status would make them poor candidates for the standard antineoplastic regimens may still be able to participate in clinical trials using epigenetic agents designed to target this underserved patient population. If a clinical trial is not an option, then low-intensity therapy or supportive care may be the appropriate choice. In younger patients, strategies for consolidation are based on the potential risk of relapse, with higher-risk patients receiving more aggressive therapy.

Cytogenetic and molecular lesions are the most significant prognostic indicators, with failure to achieve remission after 1 cycle of induction therapy and tumor burden (WBC ≥ 100,000/mcL) included as poor-risk factors for long-term remission. At several points during the course of treatment, response is assessed based on bone marrow morphology and cytogenetic and molecular responses (see pages 997 and 998 for definitions of complete and partial response and disease relapse).

Finally, all patients require attentive supportive care related both to the underlying leukemia (ie, tumor lysis syndrome) and the adverse effects of chemotherapy (see on page 996).

Management of AML

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

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

Management of AML in Patients Younger Than 60 Years

Induction Therapy: Standard induction regimens are appropriate for patients younger than age 60 years. These regimens are based on a backbone of cytarabine and an anthracycline, and have changed little in the past 25 years. Historically, in most large cooperative group trials, daunorubicin has been the most commonly used anthracycline at doses of 45 to 60 mg/m^2 × 3 days. Idarubicin, which has a longer intracellular retention time, used at doses of 12 mg/m^2 × 3 days, has had comparable remission rates with fewer patients requiring additional therapy at day 15 to achieve remission. CR rates for patients who are 50 years or younger have consistently been in the 60% to 70% range in most large cooperative group trials of infusional cytarabine and anthracycline. A large randomized phase III ECOG study reported a significant increase in CR rate (71% vs. 57%; $P < .001$) and median OS (24 vs. 16 months; $P = .003$) using daunorubicin 90 mg/m^2 × 3 days (n = 327) versus 45 mg/m^2 × 3 days (n = 330) in patients with previously untreated AML younger than 60 years.[71] Based on subgroup analyses, however, the survival benefit with

high-dose daunorubicin was shown to be restricted to patients with favorable- and intermediate-risk cytogenetic profiles (median OS, 34 vs. 21 months; $P = .004$) and those younger than 50 years (median OS, 34 vs. 19 months; $P = .004$). The survival outcome for patients with unfavorable cytogenetics was poor, with a median OS of only 10 months in both treatment arms.[71] In a European trial that compared idarubicin 12 mg/m^2 × 3 or 4 days versus daunorubicin 80 mg/m^2 × 3 days in patients between ages 50 and 70 years, CR rates were 83% and 70%, respectively ($P = .024$).[72] No difference was seen in relapse rate, EFS, or OS outcomes between the treatment arms. According to the NCCN AML Panel, infusional cytarabine × 7 days combined with either idarubicin or escalated daunorubicin is a category 1 recommendation.

For patients with impaired cardiac function, other regimens that combine nonanthracycline agents (eg, fludarabine[73] or topotecan[74]) with cytarabine have been published.

High-dose cytarabine therapy during induction was explored previously in 2 large cooperative group trials. In an Australian Leukemia Study Group trial,[75,76] patients younger than 60 years were randomized (N = 301) to receive either high-dose cytarabine (3 g/m^2 every 12 hours on days 1, 3, 5, and 7 for a total of 24 g/m^2) or standard cytarabine therapy (100 mg/m^2/d × 7 days via continuous infusion); patients in both arms received daunorubicin (50 mg/m^2 on days 1–3) and etoposide (75 mg/m^2/d × 7 days). The CR rates were equivalent in both arms (71% and 74%, respectively), with significantly higher 5-year relapse-free survival rates with high-dose cytarabine (48% vs. 25%; $P = .007$).[76] Patients in both treatment arms received only 2 cycles of standard-dose cytarabine, daunorubicin, and etoposide for consolidation therapy. Median remission duration was 45 months for the high-dose arm, compared with 12 months for the standard treatment arm.[75] However, treatment-related morbidity and mortality were higher in the high-dose cytarabine arm; the 5-year OS rates were 33% in the high-dose arm compared with 25% with the standard dose.[76]

In a large SWOG study,[77] patients younger than 65 years (N = 665) were randomized to receive high-dose cytarabine (2 g/m^2 every 12 hours × 6 days for a total of 24 g/m^2; patients aged < 50 years were initially randomized to receive 3 g/m^2 at the above schedule before the high-dose arm was redefined to 2 g/m^2 because of toxicity concerns) or standard-dose cytarabine (200 mg/m^2/d × 7 days); patients in both treatment arms also received daunorubicin (45 mg/m^2/d × 3 days). Patients treated in the high-dose cytarabine arm received a second high-dose cycle for consolidation, whereas patients in the standard-dose arm were randomized to receive consolidation therapy with either 2 cycles of standard-dose cytarabine or 1 cycle of high-dose cytarabine plus daunorubicin. The CR rates were similar, with 55% for the high-dose arm compared with 58% for the standard-dose arm for patients younger than 50 years, and 45% for high-dose cytarabine versus 53% for standard-dose therapy for patients 50 to 65 years of age. DFS rate (for patients with a CR) and OS rate (for all patients) at 4 years was not significantly different between treatment arms. Induction therapy with high-dose cytarabine was associated with significantly higher rates of treatment-related mortality (14% vs. 5% for patients age < 50 years; 20% vs. 12% for patients age 50–64 years; $P = .003$) and grade 3 or higher neurologic toxicity (8% vs. 2% for patients < 50 years; 5% vs. 0.5% for patients age 50–64 years; $P < .0001$).[77]

For patients younger than 50 years, consolidation with high-dose cytarabine was associated with similar rates of treatment-related mortality (2% vs. 0%) and grade 3 or higher neurologic toxicity (2% vs. 0%) compared with standard dose. For patients younger than 50 years who received high-dose cytarabine at the 3-g/m^2 dose schedule for induction, the rates of treatment-related deaths (10% vs. 5%) and grade 3 or greater neurologic toxicity (16% vs. 2%) were higher than for those who received the standard dose. Similarly, for patients younger than 50 years who received high-dose cytarabine at the 3-g/m^2 dose schedule for consolidation, the rates of treatment-related deaths (4% vs. 0%) and grade 3 or greater neurologic toxicity (16% vs. 0%) were higher than for those who received the standard dose.[77]

Younger patients (age < 50 years) who received high-dose cytarabine induction and consolidation in the SWOG trial had the best OS and DFS rates at 4 years(52% and 34%, respectively) compared with those who received standard-dose induction and consolidation (34% and 24%, respectively) or standard induction with high-dose consolidation (23% and 14%, respectively).[77] However, the percentage of patients achieving a CR who did not proceed to

consolidation was twice as high in the high-dose cytarabine induction arm.[77] The risks for neurotoxicity and renal insufficiency are increased with high-dose cytarabine; therefore, both renal and neurologic function should be closely monitored in patients receiving this treatment. In a CALGB trial,[78] the subgroup of patients aged 60 years or younger (n = 156) who received standard-dose cytarabine-daunorubicin induction therapy and 4 courses of high-dose cytarabine consolidation (3 g/m^2 every 12 hours on days 1, 3, and 5, per course) experienced a 4-year DFS rate of 44%. Among all patients who received consolidation with high-dose cytarabine, the rates of treatment-related deaths and serious neurotoxicity were 5% and 12%, respectively.[78]

Because the OS outcomes for the high-dose arm in the SWOG trial (high-dose cytarabine induction and 2 cycles of high-dose cytarabine consolidation; 4-year OS rate of 52% for patients age < 50 years) is comparable to those of the CALGB trial with standard-dose infusional cytarabine induction and 4 cycles of high-dose cytarabine consolidation (4-year OS rate of 52% for patients age ≤ 60 years), the use of high-dose cytarabine in the induction phase outside of a clinical trial remains controversial. The decision to use high- versus standard-dose cytarabine for induction might be influenced by consolidation strategies; fewer high-dose consolidation cycles may be needed for patients induced with high-dose cytarabine or for those who will undergo early autologous HSCT. Although the remission rates are similar for high- and standard-dose cytarabine, 2 studies have shown more rapid marrow blast clearance after 1 cycle of high-dose therapy and a DFS advantage for patients aged 50 years or younger who received the high-dose therapy.[79] No data are available using more than 60 mg/m^2 of daunorubicin or 12 mg/m^2 of idarubicin with high-dose cytarabine. High-dose cytarabine plus an anthracycline as induction therapy is considered a category 2B recommendation for patients younger than 60 years.

With either high- or standard-dose cytarabine-based induction for younger patients, between 20% and 45% of these patients will not enter remission. In a recent report of 122 patients treated with high-dose cytarabine and daunorubicin, the remission rates were strongly influenced by cytogenetics, with CR rates of 87%, 79%, and 62% for favorable-, intermediate-, and poor-risk groups, respectively.[80]

Patients with antecedent hematologic disease or treatment-related secondary leukemia are considered poor-risk, unless they have favorable cytogenetics, such as t(8;21), inv(16), t(16;16), or t(15;17). In addition, patients with unfavorable karyotypes, such as -7, -5, 11q23 abnormalities or complex cytogenetic abnormalities, are also considered poor-risk. Although all patients with AML are best managed within the context of an appropriate clinical trial, this poor-risk group of patients, in particular, should be entered into a clinical trial (incorporating either chemotherapy or low-intensity therapy), if available, because only 40% to 50% of these patients experience a CR with standard induction therapy. In addition, HLA testing should be performed promptly in those who may be candidates for either fully ablative or reduced-intensity allogeneic HSCT from a matched sibling or an unrelated donor, which constitutes the best option for long-term disease control.

Because of the decreased probability of achieving remission through induction chemotherapy, transplantation without induction chemotherapy may be considered for patients with antecedent myelodysplasia or treatment-related leukemia who have an available sibling donor and who have a relatively low percentage of marrow involvement. In a European Group for Blood and Marrow Transplantation (EBMT) trial,[81] patients with high-risk myelodysplasia or AML evolving from myelodysplasia who received allogeneic HSCT without prior cytarabine-based chemotherapy had a 3-year DFS rate of 34%. Patients who received initial chemotherapy and experienced a CR had a 45% DFS rate, compared with 10% for patients who did not experience response to chemotherapy before transplantation.[81] An alternative strategy for patients with antecedent myelodysplasia who have not received a hypomethylating agent would be a trial of either decitabine or azacytidine while a rapid donor search is initiated.

Postinduction Therapy : To judge the efficacy of the induction therapy, a bone marrow aspirate and biopsy should be performed 7 to 10 days after completion of induction therapy. In patients who have received standard-dose cytarabine induction and have residual blasts without hypoplasia, additional therapy with standard-dose cytarabine and anthracycline should be considered. For those with significant residual blasts or clear-cut induction failure, escalation to high-dose cytarabine with or without an anthra-

cycline is the most common salvage strategy. Other options include an allogeneic HSCT if a matched sibling or alternative donor has been identified, or participation in a clinical trial. For patients whose clinical condition has deteriorated such that active treatment is no longer appropriate, best supportive care should be continued. If the marrow is hypoplastic (defined as cellularity < 10%–20% and residual blasts < 5%–10%), additional treatment selection may be deferred until marrow recovery, when the remission status can be assessed.

Patients initially treated with high-dose cytarabine and who have significant residual blasts 7 to 10 days after completion of induction chemotherapy are considered to have experienced induction failure. These patients should be considered for a clinical trial, allogeneic HSCT with matched sibling or matched unrelated donor, or best supportive care. Additional high-dose cytarabine at this time is unlikely to induce remission in these cases. If an HLA-matched sibling or matched unrelated donor has been identified, an allogeneic HSCT may salvage 25% to 30% of patients with induction failure. If no donor is immediately available, patients should be considered for a clinical trial. Again, if the patient's clinical condition has deteriorated to a point at which active therapy would be detrimental, best supportive care may be the most appropriate option.

Occasionally, patients with both myeloid and lymphoid markers at diagnosis (biphenotypic leukemia) may experience response to ALL therapy if an AML induction regimen failed.[3] Treatment decisions for patients with significant reduction without hypoplasia or those with hypoplasia are deferred until the blood counts recover and a repeat marrow is performed to document remission status. Response is then categorized as complete response or induction failure.

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

Since 1994, multiple (3–4) cycles of high-dose cytarabine therapy have been the standard consolidation regimen for patients younger than 60 years with either good- or intermediate-risk cytogenetics. This consolidation therapy is based on a CALGB trial comparing 100 mg/m^2, 400 mg/m^2, and 3 g/m^2 doses of cytarabine.[78] The 4-year DFS rate for patients receiving consolidation with 3 g/m^2 of high-dose cytarabine was 44%, with a 5% treatment-related mortality rate and a 12% incidence of severe neurologic toxicity. Although the initial report did not break down remission duration by cytogenetic groups, subsequent analysis showed a 5-year relapse-free survival (continuous CR measured from time of randomization) rate of 50% for CBF AML, 32% for patients with normal karyotype, and 15% for patients in other cytogenetic categories, overall (P < .001). Among the patients who received high-dose cytarabine consolidation, the 5-year relapse-free survival rate was 78% for CBF AML, 40% for normal karyotype, and 21% for other cytogenetic categories.[80] Notably, however, in patients with CBF AML who were treated with postremission therapy with high-dose cytarabine, the presence of *c-KIT* mutations resulted in poorer outcomes.[32] In an analysis of patients with CBF AML treated on CALGB trials (n = 110), *c-KIT* mutations among patients with inv(16) were associated with a higher cumulative incidence of relapse at 5 years (56% vs. 29%; P = .05) and decreased 5-year OS rate (48% vs. 68%) compared with wild-type *c-KIT*; in multivariate analysis, the presence of *c-KIT* mutations remained a significant predictor of decreased OS in the subgroup with inv(16). In patients with t(8;21), *c-KIT* mutations were also associated with a higher incidence of relapse at 5 years (70% vs. 36%: P = .017), but no differences were observed in 5-year OS (42% vs. 48%).[32] The CALGB trial also included maintenance chemotherapy following the consolidation phase; however, not all patients in remission received maintenance (55% of patients in CR) following high-dose cytarabine consolidation.[78] Subsequent clinical trials have not included maintenance as postremission therapy.

The recent shortages of several chemotherapy agents have raised the question of how best to use cytarabine. The HOVON/SAKK study compared a double-induction concept using intermediate- or high-dose cytarabine as part of an induction/consolidation regimen in a phase III randomized study in patients (age 18–60 years) with newly diagnosed AML (N = 860).[82] Patients were randomized to treatment with an "intermediate-dose" cytarabine regimen (cycle 1: cytarabine, 200 mg/m^2 × 7 days + idarubicin, 12 mg/m^2 × 3 days; cycle 2: cytarabine, 1 g/m^2 every

12 hours × 6 days + amsacrine, 120 mg/m^2 × 3 days) [12 g/m^2 cytarabine] or a "high-dose" cytarabine regimen (cycle 1: cytarabine, 1 g/m^2 every 12 hours × 5 days + idarubicin, 12 mg/m^2 × 3 days; cycle 2: cytarabine, 2 g/m^2 every 12 hours × 4 days + amsacrine, 120 mg/m^2 × 3 days) [26 g/m^2 cytarabine]. Patients who experienced a CR after both treatment cycles were eligible to receive consolidation with a third cycle of chemotherapy or autologous or allogeneic HSCT.[82] A similar proportion of patients in each treatment arm received consolidation with a third chemotherapy cycle (26%–27%), autologous HSCT (10%–11%), and allogeneic HSCT (27%–29%). No significant differences were observed between the intermediate- and high-dose arms in rates of CR (80% vs. 82%), 5-year EFS (34% vs. 35%), or 5-year OS (40% vs. 42%),[82] results that seem comparable to those from the CALGB study with high-dose cytarabine.[78] 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).[82] Outcomes were poor for patients with monosomal karyotype at baseline (n = 83), although the high-dose regimen was associated with significantly improved rates of 5-year EFS (13% vs. 0%; P = .02) and OS (16% vs. 0%; P = .02) compared with those of the intermediate-dose in this subgroup. The incidence of grade 3 or 4 toxicities after cycle 1 was higher in the high-dose arm than in the intermediate-dose arm (61% vs. 51%: P = .005), but the incidence of 30-day mortality was the same in both arms (10%).[82] This study suggests that 2 cycles of intermediate-dose cytarabine (1 g/m^2 every 12 hours × 6 days; total dose 12 g/m^2 per cycle) for each consolidation cycle may be a feasible alternative to the current NCCN recommendations of 3 cycles of high-dose cytarabine (3 g/m^2 for 6 doses; total dose of 18 g/m^2 per cycle). However, what importance amsacrine may have served in the outcomes of the HOVON/SAKK study is currently not known.

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

Previous version of these guidelines have used cytogenetics as the major defining criteria for risk of relapse. In the latest versions of these guidelines, the panel has endeavored to incorporate emerging data on the influence of mutations in specific genes such as *c-KIT*, *FLT3*, *CEBPA*, and *NPM1* on subsets of patients within a cytogenetic category (see "Risk Status Based on Cytogenetics and Molecular Abnormalities," on page 995).

In the EORTC/GIMEMA trial comparing outcomes between patients aged 45 or younger in no-donor (patients in CR planned for autologous HSCT) versus donor groups (patients in CR with matched sibling donor planned for allogeneic HSCT) on an intent-to-treat basis, the 4-year DFS rate for the subgroup with good-risk cytogenetics [eg, t(8;21) or inv(16)] was 66% for the no-donor group (n = 73; 63% underwent HSCT) and 62% for the donor group (n = 50; 72% underwent HSCT).[83] Treatment-related mortality rates were 6% and 17%, respectively.

Outcomes from the earlier phase III SWOG/ECOG study in younger patients (age ≤ 55 years) also suggested similar outcomes in those with favorable cytogenetics undergoing HSCT; based on intent-to-treat analysis, the 5-year survival rate (from time of CR) was 71% for the autologous HSCT group (n = 26; 65% underwent HSCT) and 63% for the allogeneic HSCT group (n = 19; 84% underwent HSCT).[21] The UK MRC study (AML 10) also reported no DFS or OS advantage with allogeneic HSCT among patients (age < 55 years) with favorable-risk cytogenetics.[84] These data suggest that in the favorable-risk subgroup of patients with AML, the potential

advantage with allogeneic HSCT in preventing relapse may be offset by high rates of transplant-related deaths. Outcomes from multiple cycles of high-dose cytarabine consolidation are comparable to results with autologous HSCT. Thus, for this subgroup of patients, high-dose cytarabine followed by autologous HSCT should be the preferred HSCT option, and allogeneic HSCT may be better reserved as salvage therapy or for those with *c-KIT* mutations.

The panel has provided the following options for consolidation therapy for patients with better risk cytogenetics (those with CBF leukemia, without *c-KIT* mutations): 1) 3 to 4 cycles of high-dose cytarabine (category 1); or 2) 1 to 2 cycles of high-dose cytarabine followed by autologous HSCT (category 2B). However, outcomes in favorable-risk patients who have *c-KIT* mutations are more similar to those of patients with intermediate-risk karyotype, and these patients should be considered for either clinical trials targeted toward the molecular abnormality or consolidation strategies similar to those used in the intermediate-risk group. A well-thought-out plan for salvage therapy with either a matched sibling or unrelated donor HSCT should be an important part of the treatment decision for these patients.

The panel members agreed that transplant-based options (either matched sibling or alternate donor allogeneic HSCT, or 1–2 cycles of dose-intensive cytarabine followed by autologous HSCT) afforded a lower risk of relapse and a somewhat higher DFS as consolidation for most patients with intermediate-risk cytogenetics. In the previously discussed SWOG/ECOG trial, the 5-year survival rates (from time of CR) for patients with intermediate-risk cytogenetics were 36% for the autologous HSCT group (n = 37; 59% underwent HSCT) and 52% for the allogeneic HSCT group (n = 47; 66% underwent HSCT).[21] In the UK MRC AML 10 trial, significant benefit with allogeneic HSCT was observed for the subgroup of patients with intermediate-risk cytogenetics (but not for those with favorable or high-risk cytogenetics); in this subgroup, the DFS (50% vs. 39%; P = .004) and OS rates (55% vs. 44%; P = .02) were significantly higher among the donor groups than the no-donor groups.[84] In the aforementioned EORTC/GIMEMA trial, the 4-year DFS rate among patients with intermediate-risk AML was 48.5% for the no-donor group (n = 104; 62.5% underwent HSCT) and 45% for the donor group (n = 61; 75% underwent HSCT).[83] The incidence of relapse was 47% and 35%, respectively, and the incidence of deaths in CRs was 5% and 20%, respectively. The 4-year OS rate among intermediate-risk patients was 54% for the no-donor group and 53% for the donor group.[83] Other options for this group include clinical trials or multiple courses (3–4) of high-dose cytarabine consolidation.[85] Alternative regimens incorporating intermediate doses of cytarabine (1.5–2 g/m^2) may also be reasonable in this group. Comparable 5-year DFS rates were reported in patients younger than 60 years with normal karyotype after either 4 cycles of intermediate- or high-dose cytarabine (41%) or autologous HSCT (45%).[85]

During the past 3 to 5 years, "normal" cytogenetics have been shown to encompass several molecular lesions with divergent risk behaviors. A large German trial has revealed additional molecular prognostic markers for patients with NK-AML.[27] The presence of an isolated *NPM1* or *CEBPA* mutation improves prognosis only slightly less than for patients with CBF translocations (see "Initial Evaluation" on page 999). For this subset of patients, therapy with multiple cycles of high-dose cytarabine is a category 1 option, and allogeneic HSCT should be reserved until relapse. Another option for this group is 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT (category 2B). In contrast, patients with an isolated *FLT3*-ITD mutation and normal karyotype have an outlook similar to those with poor-risk cytogenetics[34] and should be considered for a clinical trial or early allogeneic HSCT. In a recent report that evaluated the ELN risk classification in a large cohort of patients, those in the "Intermediate I" risk group (which includes all patients with NK-AML with *FLT3* abnormalities and those lacking both *FLT3* and *NPM1* mutations), relapse-free survival was more favorable with allogeneic HSCT (94 vs. 7.9 months without allogeneic HSCT).[68] Preliminary trials incorporating *FLT3* inhibitors either as part of induction or postremission therapy (including post-HSCT) continue; however, the agents currently under investigation have shown only minimal impact. The panel strongly recommends clinical trials as standard therapy for patients with poor prognostic features, which include *FLT3* abnormalities in the setting of otherwise normal karyotype, high WBC (> 50,000/mcL) at diagnosis, or 2 cycles of induction therapy needed to achieve CR.

In the aforementioned EORTC/GIMEMA trial, a 43% 4-year DFS rate was reported in the donor group of patients with poor-risk cytogenetics (n = 64; 73% underwent HSCT); this was significantly higher than the 4-year DFS rate (18%; P = .008) among the no-donor group (n = 94; 46% underwent HSCT), although only approximately half of the patients were able to proceed with the planned HSCT in the no-donor group.[83] The SWOG/ECOG trial reported a 5-year survival rate (from time of CR) of 44% with allogeneic HSCT (n = 18; 61% underwent HSCT) and 13% with autologous HSCT (n = 20; 50% underwent HSCT) among the subgroup of patients with unfavorable cytogenetics; moreover, the 5-year survival rate was similar between those allocated to autologous HSCT and those intended for chemotherapy consolidation alone (13% and 15%, respectively).[21]

The panel uniformly endorsed allogeneic HSCT with matched sibling or matched unrelated donor (including cord blood) or clinical trial as consolidation therapy for patients with poor-risk cytogenetics or molecular abnormalities. Another option for this group is 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT, if allogeneic transplant is not an available option.

Management of AML in Patients Older Than 60 Years

Induction Therapy: The creation of separate guidelines for patients older than 60 years recognizes the poor outcomes in this group treated with standard cytarabine and an anthracycline. In patients older than 60 years, the proportion of those with favorable CBF translocations decreases, as does the number with isolated *NPM1* mutations, whereas the number of those with unfavorable karyotypes and mutations increases. Secondary AML, either related to prior myelodysplasia or prior chemotherapy, also increases, along with a higher rate of multidrug resistance protein expression. Although studies in the Swedish Leukemia Registry documented improvement in outcomes for patients younger than 60 years over the past 3 decades, no similar improvement was observed for the older population.[70,74] Treatment-related mortality frequently exceeds any expected transient response in this group, particularly in patients older than 75 years or in those who have significant comorbid conditions or ECOG performance status greater than 2.

For older patients (age > 60 years) with AML, the panel recommends using patient performance status, in addition to adverse features (eg, unfavorable cytogenetics and therapy-related AML or prior MDS) and comorbid conditions, to select treatment options rather than relying on a patient's chronologic age alone. A treatment decision-making algorithm for previously untreated, medically fit, elderly patients (age ≥ 60 years) with AML was recently developed by the German AML cooperative group. Based on data from a large study in elderly patients (N = 1406), patient and disease factors significantly associated with CR and/or early death were identified and risk scores were developed based on multivariate regression analysis.[86] 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 intensive treatments.[86] The factors included in the algorithm are the following: body temperature (≤ 38°C, > 38°C), hemoglobin levels (≤ 10.3, > 10.3 g/dL), platelet counts (≤ 28K, > 28K–≤ 53K, > 53K–≤ 10K, > 10K counts/mcL), fibrinogen levels (≤ 150, > 150 mg/dL), age at diagnosis (60–64, > 64–67, > 67–72, > 72 years), and type of leukemia (de novo, secondary). The algorithm can be accessed online at http://www.aml-score.org/.

Older adults with intact functional status (ie, ECOG score 0–2), minimal comorbidity, and favorable cytogenetic or molecular mutations, may benefit from standard therapies regardless of chronologic age. A reasonable treatment regimen for these patients includes standard-dose cytarabine (100–200 mg/m^2 by continuous infusion per day × 7 days) along with 3 days of anthracycline. Although patients older than 75 years with significant comorbidities generally do not benefit from conventional chemotherapy treatment, the rare patient with favorable or normal karyotype and no significant comorbidities might be the exception to this dogma. For patients with NK-AML, the remission rates are 40% to 50% with cytarabine combined with idarubicin, daunorubicin or mitoxantrone. The randomized French ALFA-9801 study (N = 468) showed that idarubicin induction

(the standard 12 mg/m^2 × 3 days or intensified with 12 mg/m^2 × 4 days) compared with high-dose daunorubicin (up to 80 mg/m^2) yielded a significantly higher CR rate in patients aged 50 to 70 years (80% vs. 70%, respectively; P = .03).[72] The median OS for all patients was 17 months. The estimated 2-year EFS and OS rates were 23.5% and 38%, respectively, and estimated 4-year EFS and OS rates were 18% and 26.5%, respectively; no differences were observed between treatment arms with regard to EFS, OS, and cumulative relapse rates.[72] In the HOVON trial, which randomized patients aged 60 years and older to induction therapy with standard-dose cytarabine combined with either standard-dose daunorubicin (45 mg/m^2 × 3 days; n = 411) or dose-escalated daunorubicin (90 mg/m^2 × 3 days; n = 402), the CR rate was 54% and 64%, respectively (P = .002).[87] No significant differences were observed in EFS, DFS, or OS outcomes between treatment arms. Among the subgroup of patients aged 60 to 65 years (n = 299), an advantage with dose-escalated compared with standard-dose daunorubicin was observed with regard to rates of CR (73% vs. 51%), 2-year EFS (29% vs. 14%), and 2-year OS (38% vs. 23%). These outcomes with dose-escalated daunorubicin seemed similar to those with idarubicin (12 mg/m^2 × 3 days) from the ALFA-9801 study, in which the 3-year EFS and OS rates were 30% and 40%, respectively.[88] In the HOVON trial, the benefit in OS outcomes for the dose-escalated daunorubicin group was observed only in patients aged 65 years and younger or in those with CBF translocations.[87]

Another option for patients who are medically fit is the purine nucleoside analogue clofarabine (currently FDA-approved only for the treatment of relapsed or refractory pediatric ALL). In a large phase II study from the MD Anderson Cancer Center, 112 patients (age > 60 years; median age, 71 years), most of whom had additional risk factors, received clofarabine, 30 mg/m^2 intravenously for 5 days.[89] CR/complete response with incomplete platelet recovery (CRp) was achieved in 46% of patients, with a 30-day mortality rate of 10%. Patients who experienced a remission continued to receive therapy every 4 to 6 weeks to maintain remission for up to 6 additional treatment cycles. For the entire patient cohort, the median DFS and OS were 37 and 41 weeks, respectively; patients experiencing a CR had a median OS of 72 weeks.[89] An ECOG-led phase III trial is currently in progress, which will compare induction therapy with single-agent clofarabine versus cytarabine/daunorubicin in patients older than 60 years. Consolidation therapy in this trial would be either continuation of clofarabine or intermediate-dose cytarabine.

For patients who are deemed unfit for standard induction or intermediate-intensity therapy such as clofarabine, recent options have focused on epigenetic agents, including hypomethylating drugs such as 5-azacytadine and decitabine, alone or in combination with histone deacetylase inhibitors.

An international randomized phase III study by Fenaux et al.[90] compared the hypomethylating agent 5-azacytidine with conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy) in patients with MDS (N = 358). Although this study was designed for evaluation of treatment in patients with high-risk MDS (based on FAB criteria), 113 study patients (32%) fulfilled criteria for AML using the 2008 WHO classification, with marrow-blast percentage between 20% and 30%.[90,91] In the subgroup of these patients with AML, a significant survival benefit was found with 5-azacytidine compared with conventional care regimens, with a median OS of 24.5 versus 16 months (hazard ratio [HR], 0.47; 95% CI, 0.28–0.79; P = .005).[91] The 2-year OS rate was 50% and 16%, respectively (P = .001).

Another hypomethylating agent, decitabine, has also been evaluated as remission induction therapy for older patients with AML.[92] In a phase II study in patients aged 60 years and older (N = 55; median age, 74 years), the CR rate with this agent (20 mg/m^2/d for 5 days) was 24% (including 6/24 patients [24%] with poor-risk cytogenetics), and the median EFS and OS were 6 and 8 months, respectively.[92] In an open-label randomized phase III study, decitabine was compared with physician's choice (either low-dose cytarabine or supportive care) in older patients (age ≥ 65 years) with newly diagnosed AML.[93] 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 = .10). 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 = .03). The CR (including CRp) rate was significantly higher with decitabine (18% vs. 8%; P = .001).[93] Both azacytidine and decitabine are approved by the FDA as treatment for patients with MDS.

The United Kingdom National Cancer Research Institute AML 14 trial randomized 217 older patients (primarily age > 60 years; de novo AML, n = 129; secondary AML, n = 58; high-risk MDS, n = 30) unfit for chemotherapy to receive either low-dose cytarabine subcutaneously (20 mg twice daily for 10 consecutive days, every 4–6 weeks) or hydroxyurea (given to maintain target WBC counts < 10,000/mcL).[94] Patients were also randomized to receive all-trans retinoic acid (ATRA) or no ATRA. Low-dose cytarabine resulted in a CR rate of 18% (vs. 1% with hydroxyurea) and a survival benefit compared with hydroxyurea in patients with favorable or normal karyotype. No advantage was observed with the addition of ATRA. The median DFS in patients who achieved a CR with low-dose cytarabine was 8 months.[94] 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.

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

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

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

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

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

Postremission Therapy: Patients who achieve a CR (including CRi) with standard induction chemotherapy may receive further consolidation with these agents. The French ALFA 98 trial randomized patients aged 65 years and older who achieved remission (n = 164 randomized for postremission therapy), to consolidation with either 1 additional course of standard-dose cytarabine (200 mg/m^2 × 7 days) plus the anthracycline to which they had been randomized for induction (idarubicin, 9 mg/m^2 × 4 days or daunorubicin, 45 mg/m^2 × 4 days) or 6 monthly

courses of anthracycline (1 day only) at the above doses and 60 mg/m^2 of cytarabine every 12 hours as a subcutaneous infusion at home for 5 days each month.[95] Based on intent-to-treat analysis, patients randomized to the ambulatory arm had a significantly higher 2-year DFS rate (28% vs. 17%; P = .04) and OS rate (from time of CR; 56% vs. 37%; P = .04) compared with the single course of intense chemotherapy consolidation. In addition, the 2-year death rate in CR was significantly lower in the ambulatory arm (0% vs. 5%; P = .04) and no differences were observed in the cumulative relapse rate between arms.[95] Although the CALGB trial did not show an overall benefit for higher doses of cytarabine consolidation in older patients, a subset of patients with a good performance status, normal renal function, and a normal or low risk karyotype might be considered for a single cycle of cytarabine (1.0–1.5 g/m^2/d × 4–6 doses) without an anthracycline.

The role of myeloablative allogeneic HSCT is limited in older patients because of significant comorbidities; however, ongoing interest has been shown in reduced-intensity conditioning (RIC) allogeneic HSCT as consolidation therapy.[96,97] 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.[96,97] In a retrospective analysis comparing outcomes with RIC allogeneic HSCT and autologous HSCT in patients aged 50 years and older based on large registry data, allogeneic HSCT was associated with lower risk for relapse and superior DFS and OS relative to autologous HSCT.[96] The authors also noted that a survival benefit was not observed in the subgroup of patients undergoing allogeneic HSCT in first CR because of an increased incidence of nonrelapse mortality.

Estey et al.[98] prospectively evaluated a protocol in which patients aged 50 years and older with unfavorable cytogenetics would be evaluated for a RIC allogeneic HSCT. Of the 259 initial patients, 99 experienced a CR and were therefore eligible for HSCT evaluation; of these patients, only 14 ultimately underwent transplantation because of illness, lack of donor, refusal, or unspecified reasons. The authors compared the results of RIC allogeneic HSCT with those from matched subjects receiving conventional-dose chemotherapy. This analysis suggested that RIC allogeneic HSCT was associated with improved relapse-free survival, and the authors concluded that this approach remains of interest.[98] In an analysis of outcomes between 2 different strategies for matched sibling allogeneic HSCT, outcomes in younger patients (age ≤ 50 years; n = 35) receiving conventional myeloablative allogeneic HSCT were compared with those in older patients (age > 50 years; n = 39) receiving RIC allogeneic HSCT.[99] This study showed similar rates of 4-year nonrelapse mortality (19% and 20%, respectively), and no difference was seen in relapse and OS rates.[99]

A recent retrospective study based on data in older patients (age 50–70 years) with AML compared outcomes in patients who underwent allogeneic HSCT (either myeloablative conditioning or RIC; n = 152) and those who did not receive HSCT in first CR (chemotherapy only; n = 884).[100] Allogeneic HSCT in first CR was associated with a significantly lower 3-year cumulative relapse rate (22% vs. 62%; P < .001) and higher 3-year relapse-free survival rate (56% vs. 29%; P < .001) compared with the non-HSCT group. Although HSCT was associated with a significantly higher rate of nonrelapse mortality (21% vs. 3%; P < .001), the 3-year OS rate showed a survival benefit with HSCT (62% vs. 51%; P = .012).[100] Among the patients who underwent allogeneic HSCT, myeloablative conditioning was used in 37% of patients, whereas RIC was used in 61%. Survival outcomes between these groups were similar, with a 3-year OS rates of 63% and 61%, respectively.[100]

Another recent study evaluating treatment in older patients (age 60–70 years) compared outcomes between RIC allogeneic HSCT (reported to the Center for International Blood and Marrow Transplant Research; n = 94) and standard chemotherapy induction and postremission therapy from the CALGB studies (n = 96).[101] Allogeneic HSCT in first CR was associated with significantly lower 3-year relapse (32% vs. 81%; P < .001) and higher 3-year leukemia-free survival rates (32% vs. 15%; P < .001) compared with the chemotherapy-only group. As would be expected, allogeneic HSCT was associated with a significantly higher rate of nonrelapse mortality (36% vs. 4%; P < .001) at 3 years; the 3-year OS rate was not significantly different between the groups (37% vs. 25%; P = .08), although a trend was seen favoring allogeneic HSCT.[101]

Collectively, these studies suggest that RIC allogeneic HSCT is a feasible treatment option for patients aged 60 years and older, particularly those in

first CR with minimal comorbidities and who have an available donor. For this strategy to be better used, potential transplant options should be considered during induction therapy, and unrelated donor options/searches explored earlier in the disease management.

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

Postremission Surveillance and Salvage Therapy for AML

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

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

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

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

The guidelines provide a list of several commonly used salvage regimens (see page 998). The regimens represent purine analog (eg, fludarabine, cladribine, clofarabine)–containing regimens, which have shown remission rates of 30% to 45% in several clinical trials, and those that have been used as the comparator arms in U.S. cooperative group trials in the past decade. The representative regimens included are: 1) cladribine, cytarabine, and granulocyte colony-stimulating factor (G-CSF), with or without mitoxantrone or idarubicin[102,103]; 2) fludarabine, cytarabine, and G-CSF (FLAG regimen) with or without idarubicin[104,105]; 3) etoposide and cytarabine, with or without mitoxantrone[106]; or 4) clofarabine, cytarabine and G-CSF.[107] In addition, high-dose cytarabine, if not previously used as treatment for persistent disease at day 15, with or without anthracycline may also be considered in the salvage setting. Notably, these salvage treatment options are aggressive regimens intended for appropriate patients who can tolerate such therapies; for other patents, less aggressive treatment options may include low-dose cytarabine[94,108] or hypomethylating agents.[91–93,109–111]

Supportive Care for AML

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

When transfusion support is required, leukocyte-depleted blood products should be used for transfusion. Radiation of all blood products is advised in all patients receiving immunosuppressive therapy, particularly for patients receiving fludarabine-based regimens and those undergoing HSCT. Cytomegalovirus (CMV) screening for potential HSCT candidates

is left to institutional policies regarding provision of CMV-negative blood products to patients who are CMV-negative at time of diagnosis.

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

Patients who receive high-dose cytarabine should be closely monitored for changes in renal function, because renal dysfunction is highly correlated with increased risk of cerebellar toxicity. Patients should be monitored and assessed for nystagmus, dysmetria, slurred speech, and ataxia before each dose of high-dose cytarabine; patients exhibiting any neurologic signs should discontinue high-dose cytarabine, and all subsequent cytarabine therapy must be administered as standard dose. Patients who develop cerebellar toxicity should not be rechallenged with high-dose cytarabine in future treatment cycles.[112] High-dose cytarabine should also be discontinued in patients with rapidly rising creatinine caused by tumor lysis.

Decisions regarding the use and choice of antibiotics to prevent and treat infections should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns. A randomized phase III study has shown that in patients with neutropenia undergoing induction chemotherapy for AML or MDS, posaconazole was significantly more effective in preventing invasive fungal infections than fluconazole or itraconazole, and was associated with improved OS outcomes.[113] However, azoles should not be given during anthracycline chemotherapy because they impair drug metabolism and can increase toxicity.

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

Evaluation and Treatment of CNS Leukemia

Leptomeningeal involvement is much less frequent (< 3%) in patients with AML than in those with ALL; therefore, the panel does not recommend LP as part of the routine diagnostic workup. However, if neurologic symptoms (eg, headache, confusion, altered sensory input) are present at diagnosis, an initial CT/MRI should be performed to rule out the possibility of intracranial hemorrhage or presence of mass/lesion. If no mass effect is seen, cerebrospinal fluid (CSF) cytology should be sampled by LP. If the LP is negative, the patient can be followed with a repeat LP if symptoms persist. If the LP is positive, intrathecal chemotherapy with cytarabine or methotrexate is recommended, given concurrently with systemic induction therapy. Initially, the intrathecal therapy should be given twice weekly until the cytology shows no blasts, and then weekly for 4 to 6 weeks. High-dose cytarabine, when used as part of induction therapy, may substitute for intrathecal chemotherapy because it crosses the blood-brain barrier; the CSF must then be reassessed after completion of induction therapy, and further therapy should be given as appropriate. The use of liposomal cytarabine, which has a longer half-life, for intrathecal use offers the benefit of less frequent (once weekly) administration.

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The NCCN guidelines staff have no conflicts to disclose.