National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Acute Myeloid Leukemia

V.1.2006

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Acute Myeloid Leukemia

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

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

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

See NCCN Categories of Consensus

Summary of Guidelines Updates

Acute Myeloid Leukemia

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MS, References

DIAGNOSIS

Acute leukemia[a,b,c]

WORKUP

- H&P
- CBC, platelets, differential, chemistry profile
- PT, PTT, fibrinogen
- Bone marrow with cytogenetics (mandatory)
- Immunophenotyping or cytochemistry[d]
- HLA typing (in patients considered potential HSCT candidates)[e]
- Cardiac scan if prior cardiac history or prior anthracycline use or clinical scenario which would raise concern about cardiac function
- Central venous access of choice
- FLT3 mutation evaluation is recommended[f]

If clinically indicated:

- Begin alternative donor search if patient has secondary AML, an antecedent hematologic disorder, or known poor-risk cytogenetics and there is no sibling donor
- Lumbar puncture (LP), if symptomatic[g] (category 2B for asymptomatic)

CLASSIFICATION/STAIN ANALYSIS

Immunophenotyping (+) for ≥ 2 myeloid markers and (+) for typically < 2 lymphoid markers[h]
or
Myeloperoxidase (+)
or
Nonspecific esterase (+)
or
Butyrate (+)

→ Acute promyelocytic leukemia (APL) See Treatment Induction (AML-2)

→ Acute myeloid leukemia (AML) See Treatment Induction (AML-4)

Myeloperoxidase (–)
Nonspecific Esterase (–)
TdT (+)
or
Immunophenotyping (+) for ≥ 2 lymphoid markers and (+) for < 2 myeloid markers[h]
TdT (+)

→ Appropriate therapy for acute lymphoblastic leukemia (ALL)

[a] The new WHO classification defines Acute Leukemia as ≥ 20% blasts in the marrow or blood. Ongoing clinical trials for both AML and high-risk MDS may still continue to use FAB criteria at least until completion of those trials. AML evolving from MDS (AML-MDS) is often more resistant to cytotoxic chemotherapy than AML which arises without antecedent hematologic disorder and may have a more indolent course. Some clinical trials designed for high-grade MDS may allow enrollment of patients with AML-MDS.

[b] Young adults may be eligible for pediatric trials with more intensive induction regimens and transplant options.

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

[d] Samples for both techniques should be taken at the time of initial sampling. Prioritization of these two complementary diagnostic procedures will be left to the discretion of the pathology departments of the individual institutions. The role of immunophenotyping in detecting minimal residual disease remains to be validated.

[e] HLA typing for transfusion is left to the discretion of individual institutions. HSCT = hematopoietic stem cell transplantation.

[f] Testing for FLT3 mutations currently is not widely available in the community. One should consider sending marrow sample at diagnosis to a reference lab for younger patients without antecedent MDS or secondary AML.

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

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

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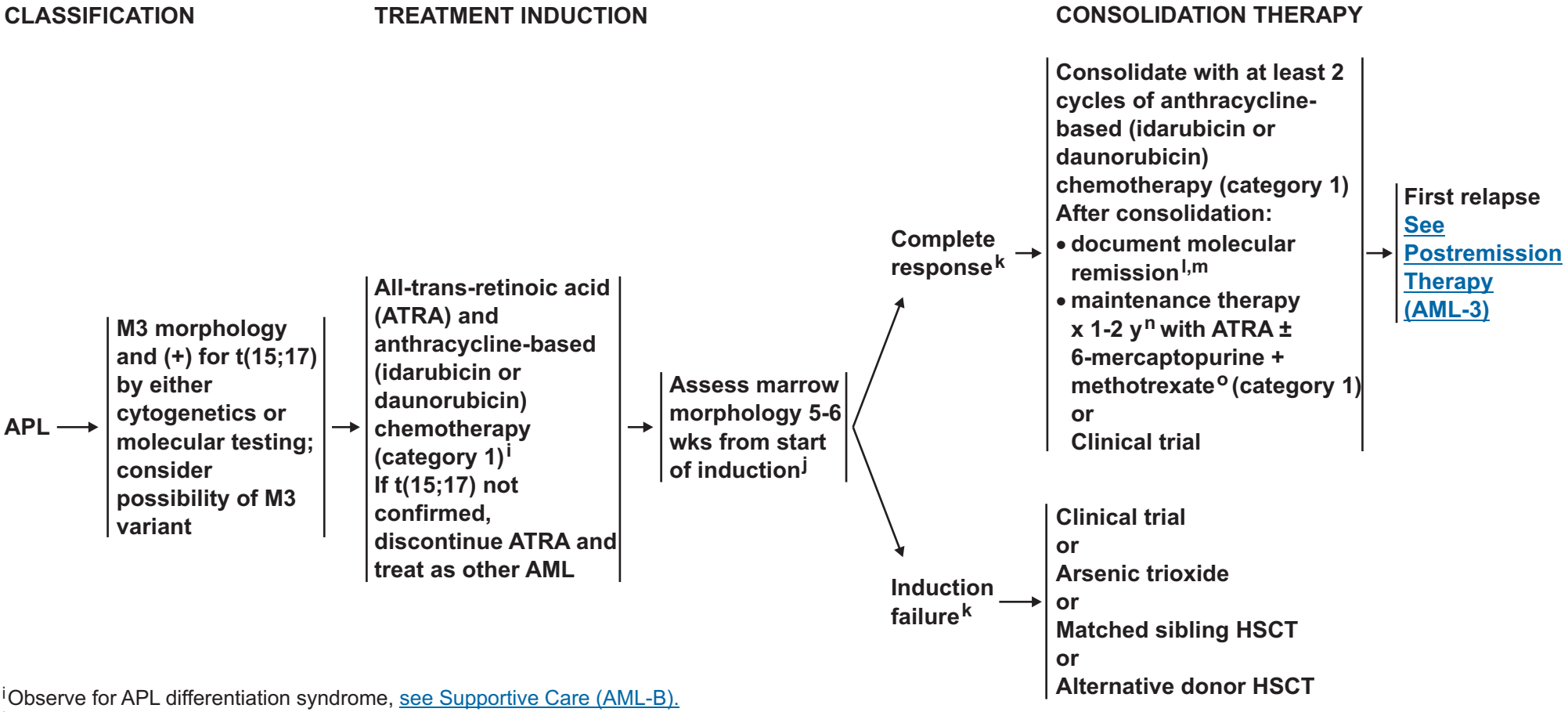
Acute Myeloid Leukemia



[i] Observe for APL differentiation syndrome, see Supportive Care (AML-B).

[j] Earlier assessment may be misleading. Patients are often still molecularly positive at the end of induction.

[k] See Response Criteria for Acute Myeloid Leukemia (AML-C).

[l] Polymerase chain reaction (PCR) should be routinely used to monitor minimal residual disease. At the current level of resolution, a change from PCR negative to positive should be confirmed in a reliable laboratory 4 wks later and if molecular relapse is confirmed by a second positive test, intervention should be strongly considered (eg, arsenic trioxide). If the second test was negative, frequent monitoring (every 3 mo for 1-2 y) is strongly suggested to confirm that the patient remains negative.

[m] If patient molecularly positive, treat as relapse (AML-3).

[n] Data suggest patients presenting with WBC > 10,000/mcL or platelets < 40,000/mcL are at a higher risk for relapse. A risk classification system is available that may influence treatment decisions. Sanz MA, Martin G, Rayon C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. Blood 1999;94:3015-3021.

[o] There are data that ATRA ± 6-mercaptopurine + methotrexate improve disease-free survival, but confirmatory studies are still in progress.

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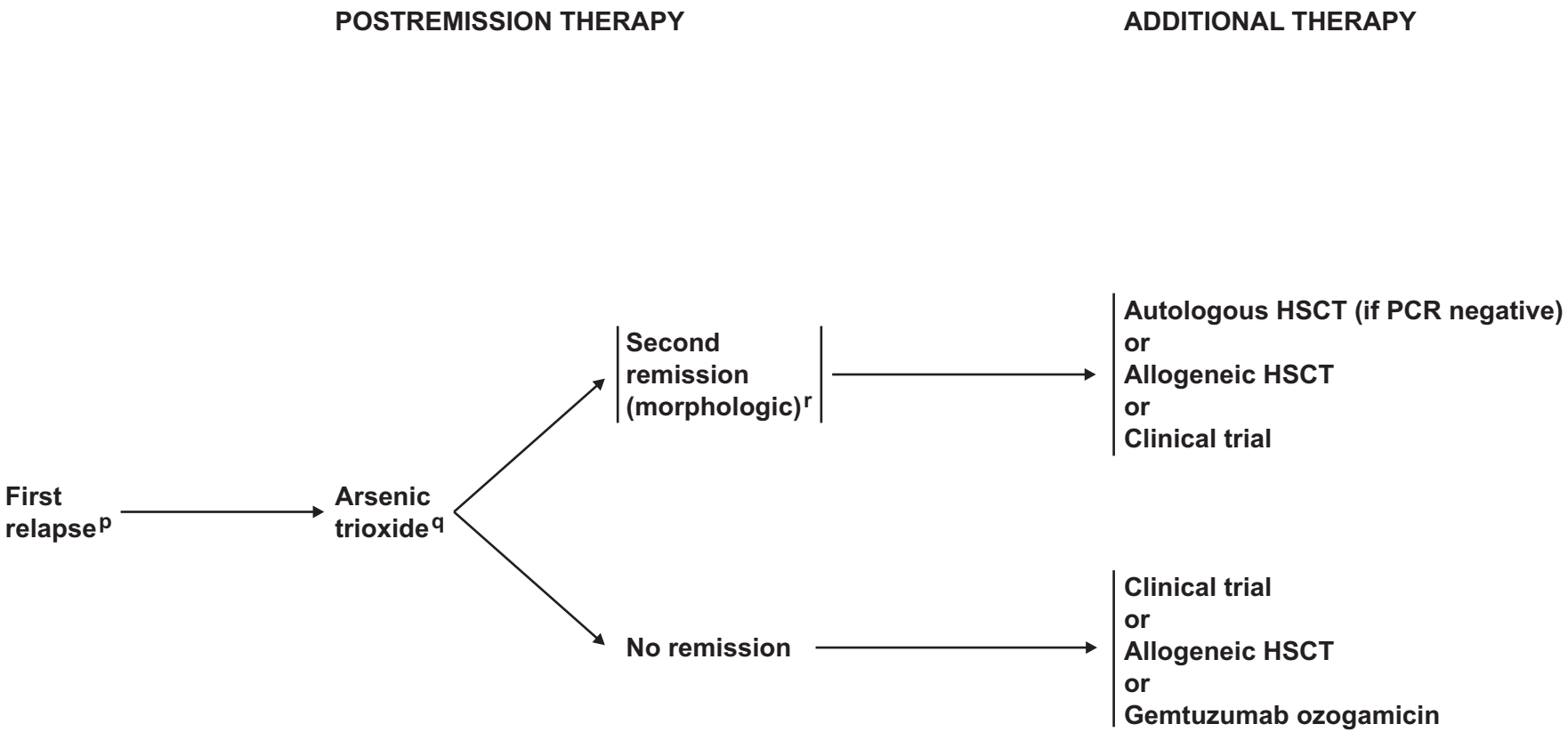
Acute Myeloid Leukemia



[p] See Supportive Care (AML-B).
[q] At the end of 2 cycles, if patient is not in molecular remission, consider allogeneic HSCT or clinical trial.
[r] Patients unable to proceed to HSCT, maintenance arsenic for up to 4 cycles is an option.

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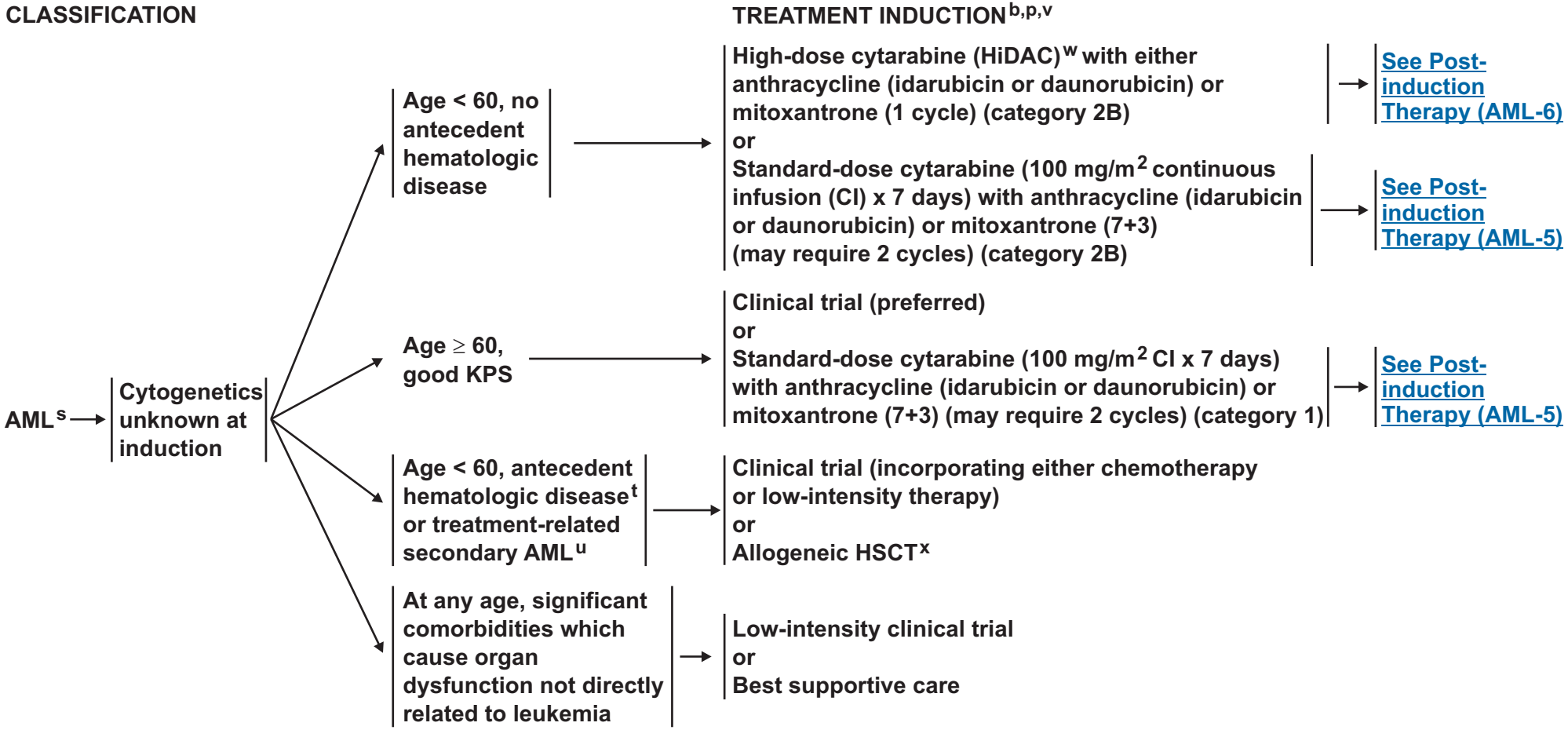
Acute Myeloid Leukemia



[b] Young adults may be eligible for pediatric trials with more intensive induction regimens and transplant options.

[p] See Supportive Care (AML-B).

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

[t] Patients known to have recognized poor-prognosis cytogenetic abnormalities prior to treatment may be treated like patients with an antecedent hematologic disorder.

[u] Rare patients with favorable karyotypes [inversion 16, t(8;21), t(16;16)] may be candidates for standard induction therapy, or APL therapy for t(15;17).

[v] See Monitoring During Therapy (AML-D).

[w] The use of high-dose cytarabine outside the setting of a clinical trial is still controversial. While the remission rates are the same for standard- and high-dose cytarabine, two studies have shown a disease-free survival advantage for patients ≤ age 50 who received the high-dose therapy (category 2B).

[x] The benefit of induction chemotherapy prior to allogeneic HSCT versus immediate HSCT is unclear in patients with high grade MDS and low blast count AML evolving from MDS. If donor is available, patient may proceed directly to HSCT.

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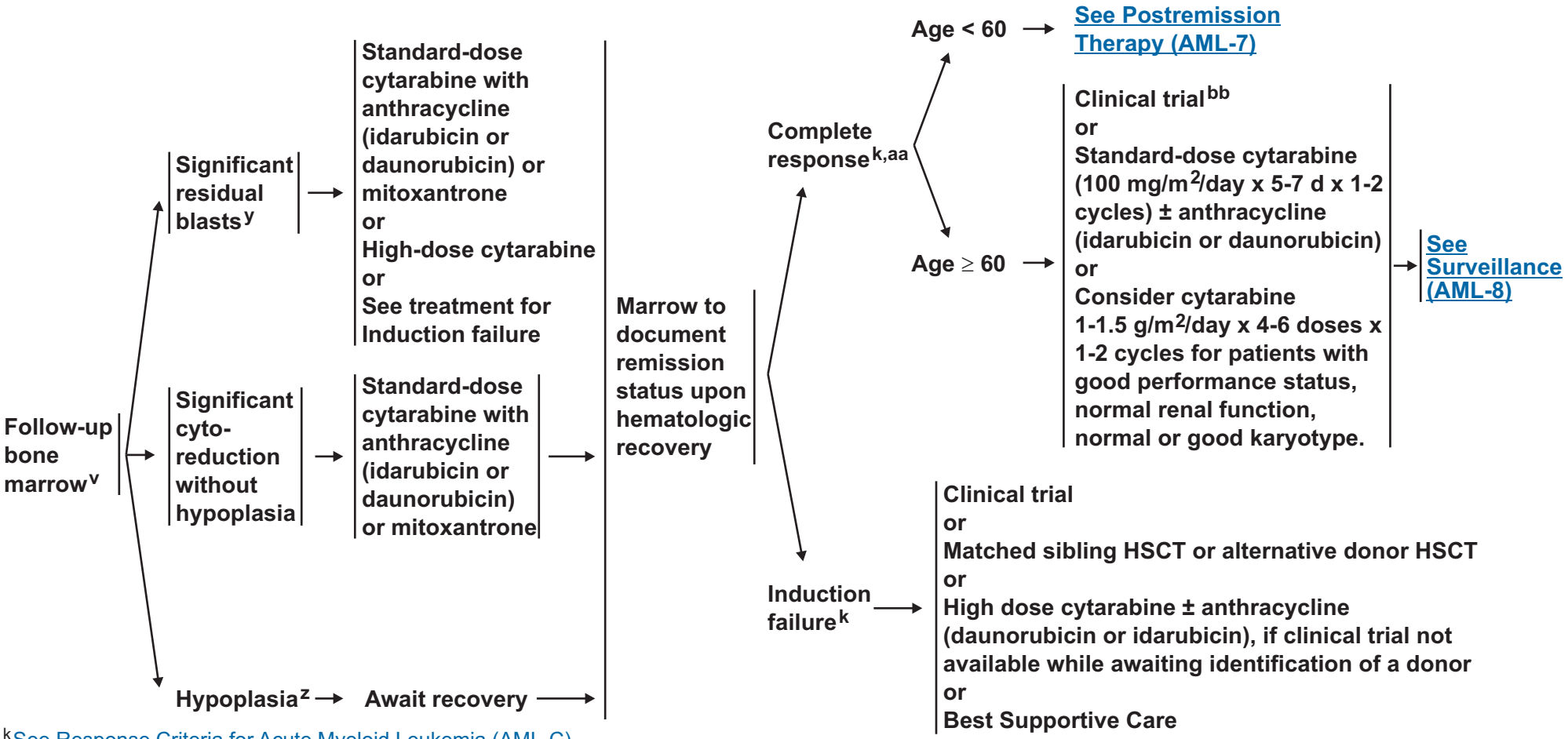
Acute Myeloid Leukemia

AML POST-INDUCTION THERAPY[p,v] AFTER STANDARD-DOSE CYTARABINE

POSTREMISSION THERAPY



[k] See Response Criteria for Acute Myeloid Leukemia (AML-C).
[p] See Supportive Care (AML-B).
[v] See Monitoring During Therapy (AML-D).
[y] Begin matched unrelated donor search if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.
[z] Hypoplasia is defined as cellularity < 10-20% and residual blasts < 5-10%.
[aa] Patients in remission may be screened with LP if initial WBC > 100,000/mcL or monocytic histology. See Evaluation and Treatment of CNS leukemia (AML-A).
[bb] May include a reduced-intensity nonmyeloablative allogeneic HSCT.

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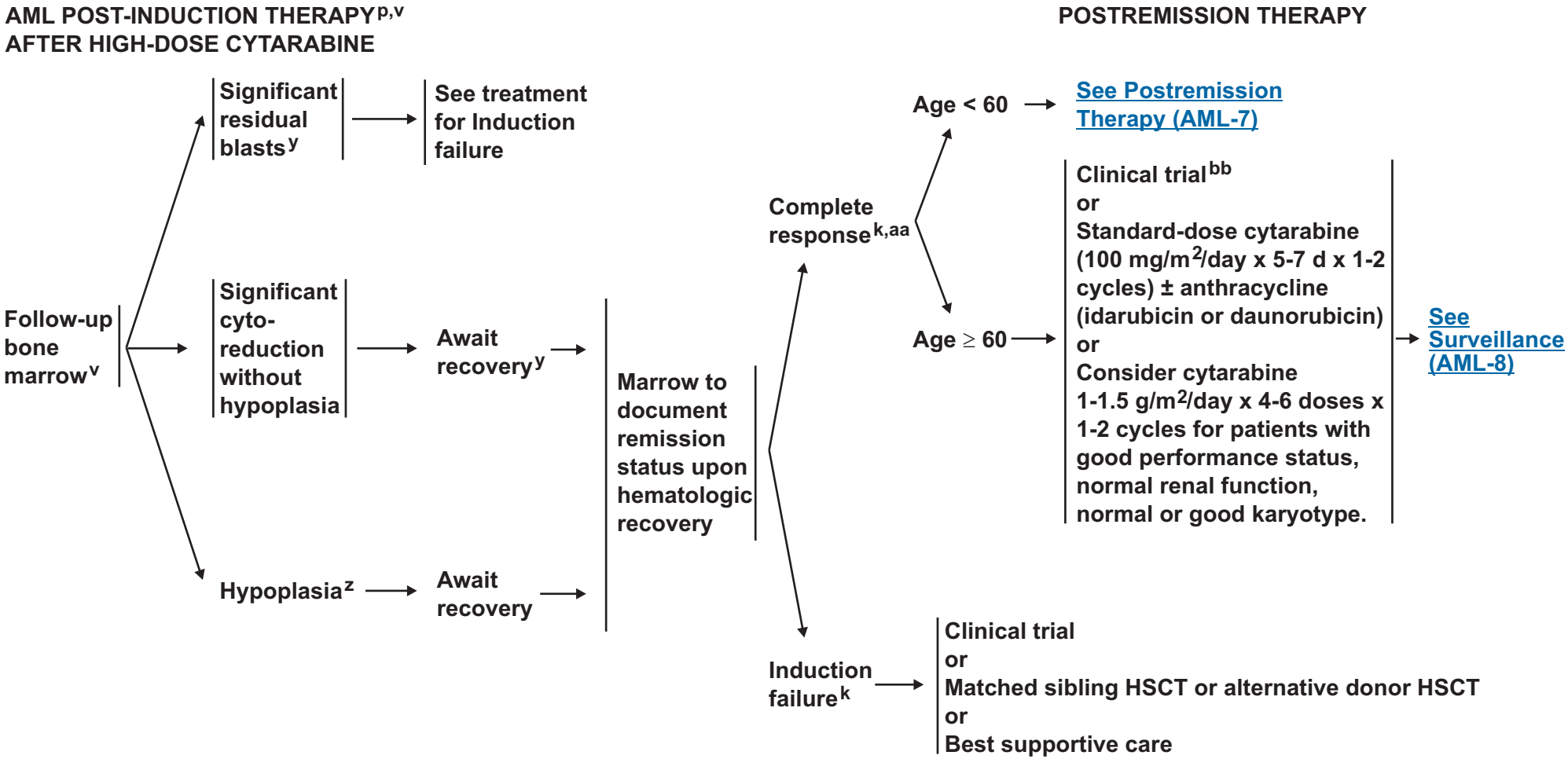

[k] See Response Criteria for Acute Myeloid Leukemia (AML-C).
[p] See Supportive Care (AML-B).
[v] See Monitoring During Therapy (AML-D).
[y] Begin matched unrelated donor search if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.
[z] Hypoplasia is defined as cellularity < 10-20% and residual blasts < 5-10%.
[aa] Patients in remission may be screened with LP if initial WBC > 100,000/mcL or monocytic histology. See Evaluation and Treatment of CNS leukemia (AML-A).
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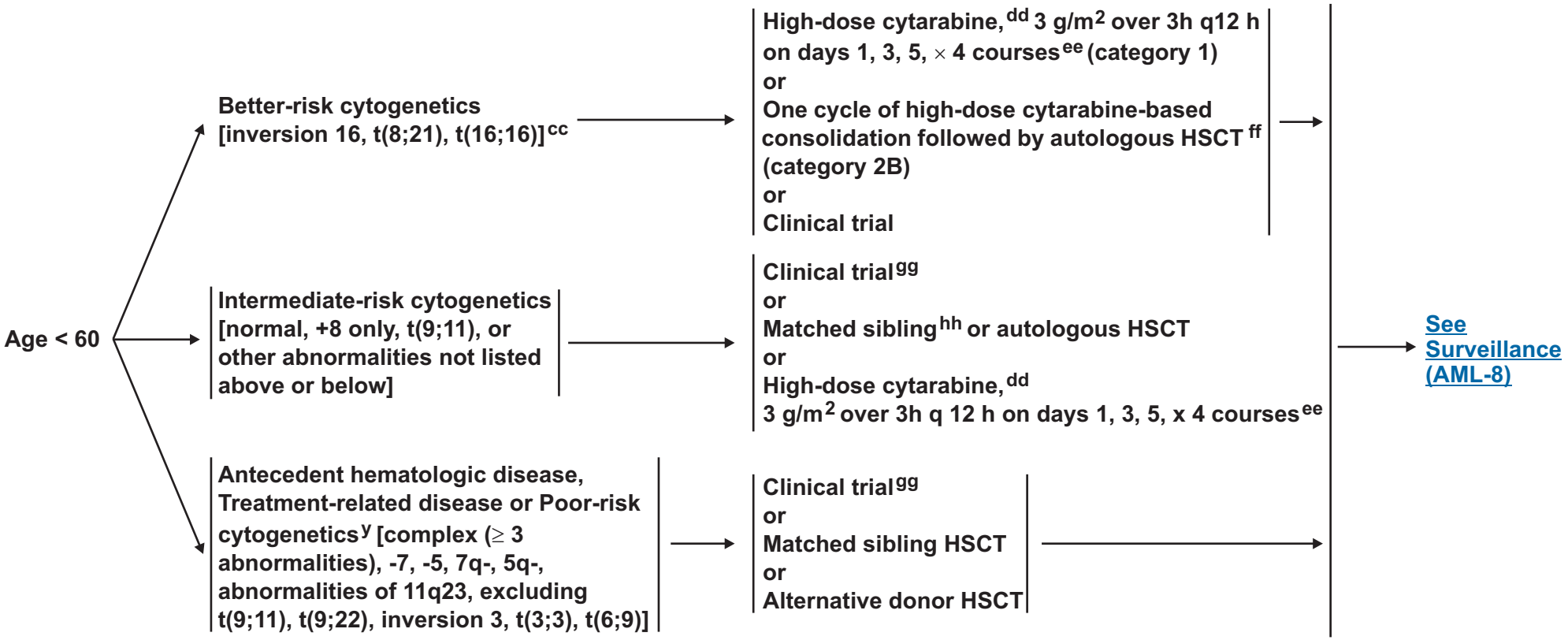
Acute Myeloid Leukemia

POSTREMISSION THERAPY



[y] Begin matched unrelated donor search if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.

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

[dd] Alternative regimens incorporating intermediate doses are acceptable.

[ee] While the original study design incorporated maintenance chemotherapy following a planned 4 cycles of consolidation, only a small fraction of the patients who received HiDAC, also received maintenance therapy.

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

[gg] Clinical trials when available are strongly recommended in the treatment of patients with poor prognostic features (eg, high WBC, CD56+, FLT3 mutation or two cycles of induction needed to achieve CR).

[hh] "Matched sibling" refers to a complete match or one antigen mismatch.

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Acute Myeloid Leukemia

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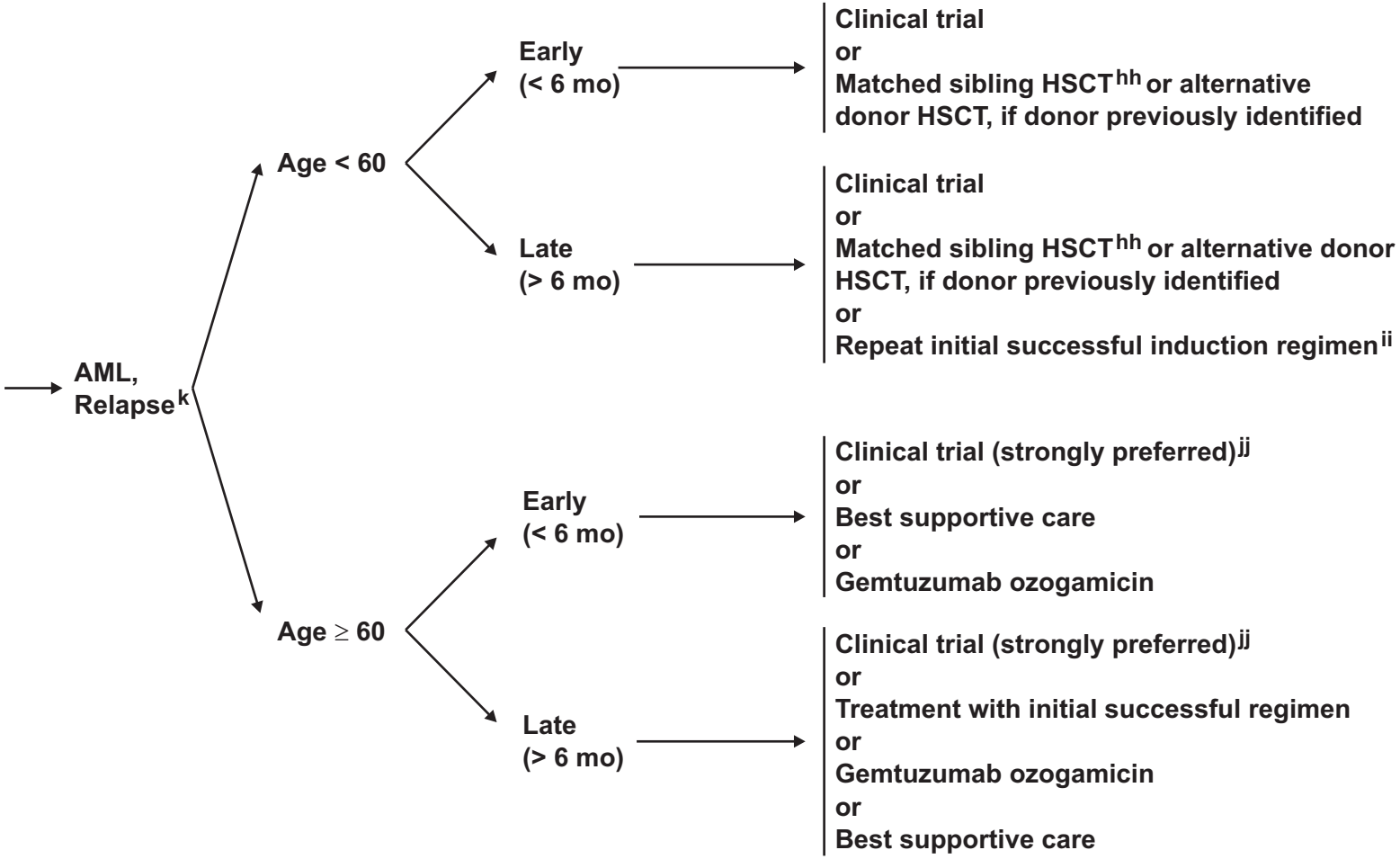
SURVEILLANCE (POST COMPLETION OF CONSOLIDATION)

- CBC, platelets every 1-3 mo for 2 y, then every 3-6 mo up to 5 y
- Bone marrow aspirate only if peripheral smear abnormal or cytopenias develop
- Matched unrelated donor search should be initiated at first relapse in appropriate patients concomitant with institution of other therapy

→ AML, Relapse[k]

SALVAGE THERAPY



[k] See Response Criteria for Acute Myeloid Leukemia (AML-C).

[hh] "Matched sibling" refers to a complete match or one antigen mismatch.

[ii] Reinduction therapy may be appropriate in certain circumstances, such as patients with long first remission. If a second CR is achieved, then consolidation with autologous or allogeneic HSCT should be considered.

[jj] May include trials of reduced intensity/nonmyeloablative HSCT.

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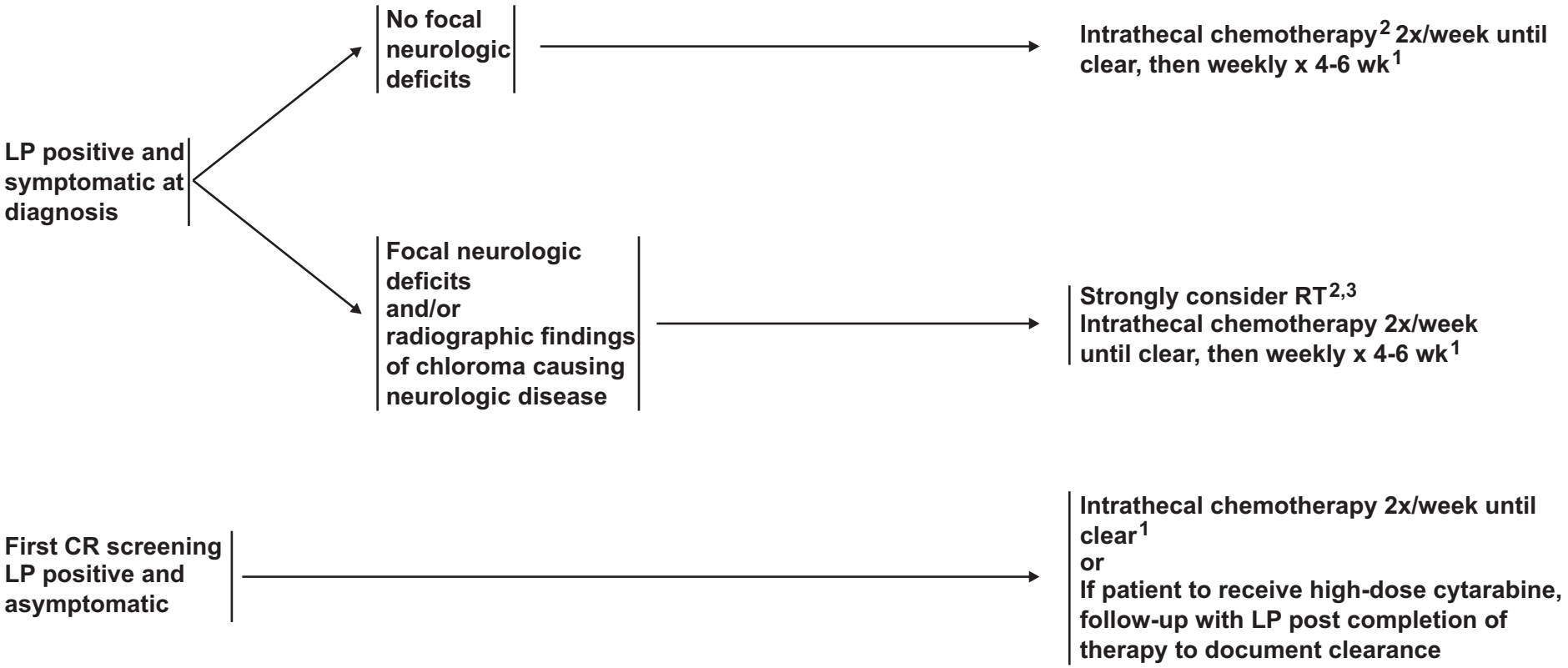
Acute Myeloid Leukemia

EVALUATION AND TREATMENT OF CNS LEUKEMIA[1]



[1] Further CNS surveillance per institutional practice.
[2] Induction chemotherapy should be started concurrently.
[3] Concurrent use of CNS RT with high-dose cytarabine or IT methotrexate may increase risk of neurotoxicity.

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Acute Myeloid Leukemia

SUPPORTIVE CARE (1 of 2)

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

General

- **Prophylactic antibiotics, including antifungals, are left to the discretion of the individual institutions.**
- **Growth factors may be considered in the elderly after chemotherapy is complete under certain circumstances. Note that such use may confound interpretation of the bone marrow. Patient should be off G-CSF for a minimum of 7 days before obtaining bone marrow to document remission.**
- **Blood products:**
  - **Leukocyte-depleted products used for transfusion**
  - **Irradiated blood products for patients receiving immunosuppressive therapy (fludarabine, HSCT).**
  - **Transfusion thresholds-- RBCs for Hgb ≤ 8 g/dL or symptoms of anemia; platelets for patients with platelets < 10,000/mcL or with any signs of bleeding.**
  - **CMV screening for potential HSCT candidates may be considered.[1]**
- **Tumor lysis prophylaxis: hydration with diuresis, and urine alkalinization and allopurinol.**
- **Clinical evidence of tumor lysis syndrome and problematic hyperuricemia or inability to tolerate oral medication: consider rasburicase.**
- **Saline or steroid eye drops to both eyes daily for all patients undergoing high-dose cytarabine therapy until 24 h post completion of cytarabine.**
- **Patients in remission may be screened by LP, if initial WBC > 100,000/mcL or monocytic histology.**
- **Patients receiving high dose cytarabine therapy (particularly those with impaired renal function or patients > 60 years), are at risk for cerebellar toxicity. Neurologic assessments including tests for nystagmus, slurred speech, and dysmetria should be performed before each dose of cytarabine.**
  - **In patients exhibiting rapidly rising creatinine due to tumor lysis or who develop cerebellar toxicity, high-dose cytarabine should be discontinued.**
  - **Patients with abnormal assessments must have a cytarabine dose reduction and should not receive high-dose cytarabine as part of any subsequent therapy. (Smith GA, Damon LE, Rugo HS, et al. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. J Clin Oncol 1997;15(2):833-839).**

[1] Patients who are allo-immunized should receive HLA-specific blood products.

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

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Acute Myeloid Leukemia

SUPPORTIVE CARE (2 of 2)

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

APL

- **If there is a high index of suspicion of APL differentiation syndrome (fever, increasing WBC > 10,000/mcL, shortness of breath, hypoxemia, pleural or pericardial effusions), close monitoring of pulmonary status is indicated, as is monitoring for fluid overload. If the patient develops pulmonary infiltrates or hypoxemia, initiate dexamethasone for 15 days (10 mg BID for 3-5 days with a taper) and consider interrupting ATRA therapy until hypoxemia resolves.**
- **Patients with relapsed APL or with hyperleukocytosis after ATRA may be at increased risk of CNS disease. Prophylactic intrathecal therapy (IT) is being evaluated in this group.**
- **Management of clinical coagulopathy and overt bleeding: Aggressive platelet transfusion support to maintain platelets $\geq$ 50,000/mcL,fibrinogen replacement with cryoprecipitate and fresh frozen plasma to replace clotting factors.**
- **Leukapheresis is not recommended in the routine management of patients with a high WBC count in APL because of the difference in leukemia biology; however, in life threatening cases with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution.**

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Acute Myeloid Leukemia

RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA[1]

- **Morphologic leukemia-free state**
  - **Bone marrow < 5% blasts in an aspirate with spicules**
  - **No blasts with Auer rods or persistence of extramedullary disease**
- **If there is a question of residual leukemia, a bone marrow aspirate/biopsy should be repeated in one week.**
- **A bone marrow biopsy should be performed if spicules are absent from the aspirate sample.**
- **Complete remission[2]**
  - **Patient achieves a morphologic leukemia-free state and**
    - **Absolute neutrophil count > 1000/mcL**
    - **Platelets ≥ 100,000/mcL**
    - **No residual evidence of extramedullary disease**
    - **Morphologic CR - patient independent of transfusions**
    - **Cytogenetic CR - cytogenetics normal (in those with previously abnormal cytogenetics)**
    - **Molecular CR - molecular studies negative[3]**
- **Partial remission[4]**
  - **Decrease of at least 50% in the percentage of blasts to 5 to 25% in the bone marrow aspirate.**
- **Patients failing to achieve a complete response are considered treatment failures.**
- **Relapse following complete response is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause (eg, bone marrow regeneration after consolidation therapy).**

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

[2] There are some clinical trials, particularly in the elderly or those with antecedent myelodysplasia, who are reporting a variant of CR referred to as CRp. This has been loosely defined as < 5% marrow blasts and transfusion independence but with persistence of cytopenia (usually thrombocytopenia).

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

[4] PR's are only useful in assessing responsiveness to new agents and should not be considered a therapy goal for standard therapy.

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Acute Myeloid Leukemia

MONITORING DURING THERAPY

Induction:

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

Post–remission therapy:

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

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Summary of the Guidelines updates

Highlights of major changes in the 2006 version of the Acute Myeloid Leukemia guidelines from the 2.2005 version include:

- In the workup of a patient with acute myeloid leukemia, the criteria for the recommendation of a cardiac scan was expanded to include a clinical scenario which would raise concern about cardiac function (AML-1).
- Text and a reference was added to footnote "n", regarding the use of risk classification systems to determine treatment strategies for APL (AML-2).
- The recommendation for maintenance therapy in patients with a complete response to induction therapy was changed to the following options: ATRA ± 6-mercaptopurine + methotrexate (category 1) (AML-2).
- Gemtuzumab ozogamicin was added as a treatment option for patients who do not achieve a remission after treatment with arsenic trioxide after their first relapse (AML-3).
- For patients who have induction failure after treatment with high-dose cytarabine, the treatment recommendation of "HiDAC ± anthracycline, if clinical trial not available while awaiting identification of a donor" was deleted (AML-6).
- Best supportive care was added as a treatment recommendation for patients with a late relapse (> 6 mo) over the age of 60 y (AML-8).
- In the attachment "Evaluation and Treatment of CNS Leukemia", a footnote was added stating "Further CNS surveillance per institutional practice (AML-A).
- There were 2 additions to the Supportive care section of the guidelines (AML-B 1 of 2):
  - Irradiated blood products should be used for patients receiving immunosuppressive therapy (eg, fludarabine, transplant).
  - Rasburicase may be considered for patients with clinical evidence of tumor lysis syndrome and problematic hyperuricemia or cannot tolerate oral medication.
- Leukapheresis was clarified in the APL supportive care section (AML-B 2 of 2), "Leukapheresis is not recommended in the routine management of patients with a high WBC count with APL because of the difference in leukemia biology, however in life threatening cases with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution."

Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Approximately 11,960 people will be diagnosed with acute myeloid leukemia (AML) in 2005, and 9,000 patients will die from the disease.[1] As the population ages, the incidence of AML, along with myelodysplasia, appears to be rising. Equally disturbing is the increasing incidence of treatment-related myelodysplasia and leukemia in survivors of tumors of childhood and young adulthood such as Hodgkin's disease, sarcomas, breast and testicular cancers, and lymphomas. Ionizing radiation and occupational exposure to benzene and petrochemicals are also associated with AML.[2]

The clinicians comprising the AML panel convene annually to update guidelines for the diagnosis and treatment of AML in adults. Clinical trials have led to significant improvements in treatment in some areas, primarily in acute promyelocytic leukemia (APL). However, recent large clinical trials have highlighted the need for new, innovative strategies since outcomes for AML patients, particularly the older patients, have not substantially changed in the last three decades.

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

Initial Evaluation

The initial evaluation has two objectives. The first is to identify the pathology causing the disease including factors such as prior toxic exposure or myelodysplasia, cytogenetics and molecular markers that may have an impact on chemoresponsiveness and propensity for relapse which may guide choice of treatment. The second objective focuses on patient-specific factors including comorbid conditions that may affect an individual's ability to tolerate chemotherapy.

Currently, there are two systems used by pathologists to define hematopoietic malignancies. The French-American-British (FAB) classification relies on morphology; traditionally using cytochemical stains, but more recently incorporating immunophenotyping using flow cytometry to differentiate myeloid from lymphoid blasts. Acute myeloid leukemia is then subcategorized into eight entities based on degree of differentiation. At the time the FAB classification was

described (1976), pathologists chose to use 30% blasts as the threshold between high-grade myelodysplasia (MDS) and AML.

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

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

The International Working Group revised diagnostic and response criteria for AML in 2001 to reflect current understanding of acute myeloid leukemia [4] (AML-C). Although roughly 75% of patients with acute leukemia can be categorized as myeloid or lymphoid lineage based on routine cytochemistries, immunophenotyping is necessary for proper diagnosis in a subset of patients, particularly those with undifferentiated morphology. In many large institutions, immunophenotyping is more rapidly available than cytochemistry, thus facilitating earlier initiation of therapy. In keeping with the recommendations adopted by the International Working Group, the panel endorses the use of flow cytometry as the preferred technique to differentiate AML from acute lymphoblastic leukemia (ALL). Some cases may still show evidence of both myeloid and lymphoid antigen expression on the leukemic cells. These cases will require consultation with an experienced hematopathologist. Aberrant expression of differentiation antigens present at diagnosis may allow tracking of residual abnormal cells by flow cytometry in follow-up samples that may appear normal by conventional morphology. However, the role of immunophenotyping and molecular markers to monitor minimal residual disease in adult AML remains an area of research interest at present.

Although cytogenetic information is usually unknown when treatment is initiated in patients with de novo AML, karyotype represents the single most important prognostic factor for predicting remission rate, relapse, and overall survival. Therefore, the importance of obtaining sufficient

samples of marrow or peripheral blood blasts at diagnosis for this analysis cannot be overemphasized. In a recent update, of 1,213 AML patients treated on CALGB protocols, the 5-year survival rate was 55% for patients with favorable cytogenetics, 24% for patients with intermediate risk, and 5% for those with poor risk cytogenetics.[5]

A molecular abnormality, internal tandem duplication or mutation of the FLT3 gene, encoding a growth factor receptor, has also been reported to confer a worse prognosis. Several recent large series have studied the impact of partial tandem duplications or mutations of FLT3 as an independent predictor of relapse-free survival. In the most recent series,[6] patients with a normal karyotype and a FLT3 partial tandem duplication or mutation had a 5-year survival of 20% versus 42% for patients with no FLT3 abnormality. At the present time, screening for FLT3 mutations is not widely available in the community, but may be available through the hematopathology divisions of referral centers. Although the information regarding FLT3 is unlikely to affect initial therapy, it may influence decisions about post-remission treatment, particularly in patients with normal karyotypes. Internal tandem duplication of the MLL gene has also been associated with a poor prognosis in patients with normal karyotypes. The information gained from research into basic leukemia biology in areas such as this using samples banked from clinical trials may provide keys to new therapeutic options.

Because disseminated intravascular coagulation (DIC) is fairly common at presentation in many leukemias, good clinical practice includes performing coagulation screening before placement of a central vascular access device. Cardiac evaluation is not routinely required except for patients with cardiac risk factors based on patient history, family history, or a previous malignancy for which they may have been treated with anthracyclines.

Human lymphocyte antigen (HLA) typing should be performed in all newly diagnosed AML patients for whom allogeneic hematopoietic stem cell transplantation (HSCT) would be considered. This group usually includes patients under ages 50 to 55 who do not have favorable cytogenetics or who have a history of antecedent myelodysplasia. In patients with antecedent myelodysplasia or unfavorable karyotypes who do not have a sibling donor, an unrelated donor search should be initiated at this point. Many institutions also use HLA typing to help select platelet donors for patients who become alloimmunized. Decisions regarding HLA typing for transfusion support are left to individual institutions.

Extramedullary presentations including CNS disease are uncommon events in AML. In 2004, the NCCN updated the guidelines to cover CNS involvement as well as solid organ infiltration. Patients with significant CNS signs or symptoms at presentation should be evaluated radiographically for intracranial bleeding, leptomeningeal disease or mass lesions in either brain or spinal cord. If symptoms persist and bleeding and mass lesions are excluded, the patient should have a lumbar puncture (LP) for diagnostic and possible therapeutic purposes once coagulopathy has been corrected and adequate platelet support is available. Routine screening LP's are not warranted in AML at diagnosis. However, patients with high risk of CNS disease such as those with monocytic differentiation (M4 or M5) or high WBC (>100,000/mcL) at diagnosis are recommended to have a diagnostic LP as part of the documentation of remission status.

For patients who present with solitary extramedullary disease (often referred to as granulocytic sarcoma or chloroma) without overt marrow disease, the initial treatment approach is systemic chemotherapy; radiation or surgical resection may be incorporated

at time of systemic chemotherapy in emergent situations, but these modalities, if needed at all, should optimally be deferred until count recovery to avoid excess toxicity.

Initial Induction Treatment

The initial treatment of acute leukemia has been divided into induction chemotherapy and post-remission (or consolidation) therapy. Although obtaining an initial remission is the first step in controlling the disease, it is also important that the patient emerge from the induction phase in condition to tolerate subsequent more intensive treatments during consolidation to achieve a durable remission. Patients who do not receive post-remission therapy will relapse, usually within 6 to 9 months. The induction strategy will be influenced by individual patient characteristics, such as age, presence of comorbid conditions affecting performance status, and pre-existing myelodysplasia. Patients with poor performance status who cannot tolerate chemotherapy should receive supportive care or a low-intensity clinical trial that would not produce the toxicities characteristic of current AML antineoplastic regimens.

Acute Promyelocytic Leukemia (APL)

The identification of fusion of the promyelocytic leukemia (PML) gene on chromosome 15 with the retinoic acid receptor (RAR) alpha gene on chromosome 17 as the molecular hallmark of APL, as well as earlier empiric observations on efficacy of retinoic acid in inducing differentiation of APL cells, led to treatment strategies which differ significantly from other subclasses of AML. In trials from Shanghai, CR rates of 85% were reported with all-trans-retinoic acid (ATRA) as a single agent. The first US Intergroup trial which compared ATRA to conventional Ara-C and daunorubicin (7+3) confirmed similar CR rates of 70% for both treatments.[7, 8] The French APL91 trial comparing ATRA followed by Ara-C and DNR versus combining ATRA with the chemotherapy showed comparable CR rates of 92% with either regimen but a lower relapse rate at 2 years for concomitant chemotherapy+ATRA, with a 6% versus 16% relapse rate in those receiving sequential therapy.[9]

Therapy for APL is often associated with a constellation of symptoms and physiologic abnormalities, including fluid retention, dyspnea, episodic hypotension, pulmonary infiltrates, and pulmonary or pericardial effusions now referred to as “retinoic acid syndrome”. The panel has provided management recommendations (see AML-B) in the supportive care section.

The Italian GIMEMA 93 trial and the Spanish PETHEMA trial reduced the induction regimen to ATRA combined with idarubicin, yielding a 95% CR rate, which has raised speculation as to the need for Ara-C. The trials differed in that in the PETHEMA trial, consolidation consisted of 3 cycles of idarubicin alternating with mitoxanthrone while the GIMEMA consolidation used these same agents, but paired them with either Ara-C, VP-16, or Ara-C+6TG. Disease-free survivals were 86% and 90% respectively. When the data from the two trials were combined, a prognostic model for relapse-free survival was constructed using initial WBC < 10,000/mcL and platelets >40,000/mcL. Low risk patients defined by WBC <10,000/mcL + platelets > 40,000/mcL had a DFS of 97%; intermediate risk patients, defined by WBC <10,000/mcL + platelets <40,000/mcL, had a DFS of 82% and those with WBC >10,000/mcL had a DFS of 66%.[10]

Based on these trials, the panel has made the recommendation that initial induction outside of a protocol setting consist of at least concomitant anthracycline and ATRA. Treatment with at least ATRA should commence as soon as the diagnosis is suspected and before genetic confirmation. Because of the risk of early mortality due to

coagulopathy in patients with presumptive APL based on morphology and DIC screen, the panel suggests starting ATRA+chemotherapy as initial therapy. If the initial clinical diagnosis of APL is not confirmed by cytogenetic findings, ATRA is stopped. Because the differentiating action of ATRA occurs over a longer time period than the cytoreduction of conventional chemotherapy, we do not recommend a marrow evaluation earlier than day 35 from start of treatment as persistence of promyelocytes at earlier points may lead to overtreatment. By day 35, one should expect a cytogenetic remission, but many patients do not achieve molecular remission until completion of 1-2 cycles of consolidation. The committee has included additional information regarding response criteria and post-remission monitoring in the guidelines.

For patients who achieve a CR, the current non-protocol recommendations are for treatment with 2 cycles of anthracycline-based chemotherapy followed by maintenance with ATRA every 3 months either alone or combined with weekly methotrexate and daily 6MP. A maintenance regimen of ATRA 1 week on and 1 week off is currently under investigation. The consolidation recommendations are based on the data from the combined GIMEMA/PETHEMA studies which showed no difference in disease-free or overall survival in single drug anthracycline consolidation versus combinations containing Ara-C as well as an anthracycline. The current trials, which are attempting to refine consolidation, have two purposes. One is to address the relatively high rate of relapse (30-35%) in high-risk patients and the second is to minimize the acute and long-term toxicities of the treatment program. There are several ongoing trials that have intensified consolidation by (1) including ATRA with anthracycline during consolidation (PETHEMA) or (2) administering two cycles of conventional dose daunorubicin consolidation followed by a randomization to receive or not receive 2 cycles of arsenic trioxide (US Intergroup Trial) or (3) adding Ara-C to consolidation, with higher Ara-C doses given for high-risk patients (French APL Trial). The most recent data from the PETHEMA trial did show a significant reduction of relapse rate at 3 years from 17% overall to 7.5% when ATRA was given for 15 days of each of 3 cycles of consolidation. At the present time, the panel has not incorporated this information into the guidelines as we are awaiting maturation of these data along with the outcomes of the two other large national trials.

The recommendations for maintenance ATRA are derived from several trials which showed superior relapse-free survivals for patients receiving ATRA as maintenance. The French APL91 trial showed decreased relapse rates at 2 years for ATRA (21%), 6MP+methotrexate (13%), and ATRA, 6MP+methotrexate (8%), versus no maintenance (35%). The US Intergroup trial showed superiority of disease-free survival for patients receiving maintenance ATRA versus no maintenance. Patients should be monitored with RT-PCR for PML/RARα fusion transcript at the end of consolidation and at a minimum of every 3 months for 2 years and then every 6 months (as a minimum) for 2-3 years. Patients who are not in molecular remission at completion of consolidation should be considered in the same category as patients with induction failure. Patients who have confirmed molecular relapse (2 consecutive positive PCR studies within 1 month) should also be treated with salvage therapy.

Arsenic trioxide is the recommended current non-protocol salvage therapy for patients with persistent or relapsed APL. Molecular remissions have been achieved in 80% of patients treated for either clinical or molecular relapse in several studies from China, US, and Europe.[11] Patients who achieve a molecular remission with arsenic

trioxide as second line therapy should be considered for autologous HSCT, if they do not have contraindications to high-dose therapy. Patients who received a PCR-negative autograft had a 75% 7-year overall survival in a recent retrospective study published by the European APL Group, compared to a 52% overall survival for patients receiving allogeneic HSCT.[12] The differences in survival are accounted for by high treatment-related mortality in the allogeneic group, which influences our recommendations to reserve allogeneic transplant for those who have persistent disease despite salvage therapy. For patients in second CR who have contraindications to HSCT, maintenance therapy with arsenic trioxide is an option in the absence of an appropriate clinical trial. For patients with persistent disease following arsenic trioxide who are not allogeneic transplant candidates, options include clinical trial or gemtuzumab ozogamicin. Gemtuzumab ozogamicin has shown significant activity in relapsed APL.[13]

Acute Myeloid Leukemia

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

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

Standard induction regimens based on a backbone of cytarabine (cytosine arabinoside, Ara-C) and an anthracycline (or anthracenedione) have changed little in the last 25 years. Historically, in most large cooperative group trials, daunorubicin has been the most common anthracycline. However, idarubicin, which has a longer intracellular retention time, has also been used.

The merits of dose-intensive cytarabine therapy during induction have been explored in two large cooperative clinical trials. In an Australian Leukemia Study Group trial,[14] 301 patients under age 60 years were randomized to receive either high-dose cytarabine (HiDAC) (3 g/m^2 q12h on days 1, 3, 5, and 7 for a total of 24 g/m^2) or standard cytarabine therapy (100 mg/m^2/d x 7 days via continuous infusion); both arms received daunorubicin (50 mg/m^2 on days 1 to 3) and etoposide (75 mg/m^2/d x 7 days). The CR rates were equivalent in both arms (71% and 74%, respectively), although treatment-related morbidity and mortality were higher in the high-dose arm. However, with patients in both arms of the study received only two cycles of standard-dose cytarabine, daunorubicin, and etoposide for consolidation, median remission duration was 45 months for the dose-intensive arm, compared with 12 months for the standard treatment arm.

In a Southwestern Oncology Group (SWOG) study,[15] patients were randomized to receive HiDAC (2 g/m^2 every 12 hours x 6 days for a total of 24 g/m^2) or standard-dose cytarabine (200 mg/m^2/d x 7 days); patients in both treatment arms also received daunorubicin

(45 mg/m^2/d x 3 days). Patients receiving HiDAC induction therapy received a second high-dose cycle for consolidation, and patients in the standard-dose treatment arm were randomized to receive either two cycles of standard-dose cytarabine consolidation or one cycle of HiDAC plus daunorubicin consolidation. The complete response rates were again equivalent: 55% for the HiDAC treatment arm compared with 58% for the standard-dose arm for patients under 50 years, and 45% for HiDAC versus 53% for standard-dose therapy for patients 50 to 65 years of age. Patients in the HiDAC arm experienced higher treatment-related mortality (12% vs. 5%) and neurologic toxicity.

Younger patients who received both HiDAC induction and consolidation in the SWOG trial had the best survival (52%) and disease-free survival (34%) rates at 4 years, when compared with standard induction and consolidation (34% survival and 24% disease-free survival) or standard induction with high-dose consolidation (23% survival and 14% disease-free survival). However, the percentage of patients achieving a CR who did not proceed to consolidation was twice as high in the HiDAC induction arm. The use of HiDAC induction outside a clinical trial remains controversial. The risks for neurotoxicity and renal insufficiency are increased with high-dose cytarabine and both renal and neurologic function should be closely monitored in patients receiving such treatment (AML-B, 1 of 2)

In a Cancer and Leukemia Group B (CALGB) trial,[16] patients who received standard-dose cytarabine-daunorubicin induction therapy and three to four courses of HiDAC consolidation also achieved a 4-year disease-free interval of 44% with similar rates of neurotoxicity and treatment-related mortality. Because the remission rates are comparable, the decision to use HiDAC versus standard-dose cytarabine for induction will be influenced by consolidation strategies; fewer HiDAC consolidation cycles may be needed for patients induced with HiDAC or for patients who will undergo early autologous stem cell transplantation, versus standard-dose induction and 3 to 4 cycles of HiDAC consolidation.

With either high- or standard-dose cytarabine-based induction for younger patients, it should be remembered that between 20% and 45% of these patients will not enter remission. In a recent report of 122 patients treated with HiDAC and daunorubicin, the remission rates were strongly influenced by cytogenetics, with complete remission rates of 87%, 79%, and 62% for favorable, intermediate, and poor risk groups, respectively.[17]

Many factors, including a higher incidence of multi-drug resistance markers, contribute to lower CR rates in older patients; clinical trials are of the utmost importance in this age group. However, in the absence of a clinical trial, standard-dose cytarabine and an anthracycline is acceptable induction therapy for patients over 60 years of age with adequate organ function and performance status (category 1) (AML-4). The SWOG trial comparing standard-dose cytarabine-daunorubicin induction to mitoxantrone and etoposide in patients over 55 years of age showed no improvement in CR rate (43% for cytarabine plus daunorubicin vs. 34% for mitoxantrone and etoposide) or decrease in regimen-related toxicity (16% vs. 22%, respectively) in the mitoxantrone and etoposide arm.[18]

Patients who are known to have unfavorable karyotypes defined by findings such as -7, -5, 11q23 abnormalities or complex cytogenetic abnormalities, or those who have antecedent myelodysplasia or secondary AML should be entered into a clinical trial (incorporating either chemotherapy or low-intensity therapy), if available, since only 40% to 50% of these patients achieve CR with standard

induction therapy, and response durations are short. In addition, HLA testing should be done promptly in those who may be candidates for either a fully ablative or a reduced intensity allogeneic HSCT as a transplant from a sibling or an unrelated donor constitutes the best option for long-term disease control. Due to the decreased probability of achieving remission through induction chemotherapy, transplantation without induction chemotherapy may be considered for patients with antecedent myelodysplasia or treatment-related leukemia who have an available sibling donor. In an EBMT trial, patients with high-risk myelodysplasia or AML evolving from myelodysplasia who received allogeneic transplantation without prior chemotherapy had a 25% 3-year disease-free survival. Patients who received antecedent chemotherapy and achieved a CR had a 45% disease-free survival, compared with 10% for patients who did not respond to chemotherapy before transplantation.

To evaluate the efficacy of the induction regimen, the panel recommends repeating a bone marrow test 7 to 10 days after completion of induction (AML-D). In patients who have received standard-dose Ara-C induction and still have residual blasts, additional therapy with either standard-dose Ara-C and anthracycline (or anthracenedione) or with high-dose Ara-C if the amount of persistent disease is substantial, should be considered. If the marrow is hypoplastic, await recovery and document remission with a repeat marrow (including cytogenetics if the original karyotype was abnormal) at time of hematopoietic recovery (AML-5).

For patients who are initially treated with high-dose Ara-C and who have resistant disease, additional high-dose Ara-C is unlikely to induce remission. If a sibling donor has been identified, an allogeneic HSCT may salvage 25% to 30% of patients with induction failure. If no donor is immediately available, patients should be considered for a clinical trial. Occasionally, patients with both myeloid and lymphoid markers at diagnosis (biphenotypic leukemia) may respond to acute lymphoblastic leukemia (ALL) therapy if they failed an AML induction regimen.

Post-remission Therapy

Since 1994, multiple (3-4) cycles of HiDAC therapy have been the non-protocol standard consolidation regimen for patients under 60 years of age with either good- or intermediate-risk cytogenetics. This therapy is based on a CALGB trial comparing 100 mg/m^2, 400 mg/m^2, and 3 g/m^2 doses.[16] The 4-year disease-free survival rate (irrespective of cytogenetic risk group) for patients receiving 3 g/m^2 was 44%, with a 5% treatment-related mortality rate and a 12% incidence of severe neurologic toxicity. Although the initial report did not break down disease-free survival rates by cytogenetic subgroups, subsequent analysis showed a disease-free survival rate of 60% for patients with good-risk cytogenetics, 30% for intermediate-risk cytogenetics, and 12% for poor-risk cytogenetics in patients receiving HiDAC consolidation; these outcomes are similar to those on the high-dose treatment arm in the SWOG trial.[19]

Choices for consolidation strategies currently are: 1) multiple cycles of high-dose cytarabine, 2) one or more cycles of high-dose cytarabine followed by autologous HSCT or 3) allogeneic stem cell transplantation from sibling or unrelated donors. The decisions regarding autologous and allogeneic HSCT are strongly influenced by the (1) expected relapse rate with standard chemotherapy, (2) the additional morbidity and mortality associated with the transplant procedure, which in turn are strongly influenced by patient-specific comorbidity, and (3) salvage options. The most recent comparison of autologous versus allogeneic HSCT was a combined EORTC/GIMEMA trial for

patients less than age 46 with results stratified by cytogenetic risks: good [t(8;21) or inv 16)]; normal, and poor (all other abnormalities). In the good risk group disease-free survival was 66% for autologous HSCT and 62% for allogeneic HSCT, with a 6% treatment related mortality (TRM) for autologous HSCT and 17% for allogeneic HSCT. The autologous results are comparable to the CALGB data on multiple cycles of high-dose cytarabine both for relapse-free survival and mortality.[20]

The NCCN AML panel members did not reach a consensus on a single preferred post-remission strategy for patients with good-risk cytogenetics. Either multiple cycles of dose-intensive consolidation (category 1) or one cycle of dose-intensive (HiDAC) consolidation followed by autologous transplantation (category 2B) can produce good survival rates (60-65%) in this group (AML-7). Factors such as patient age, comorbid conditions, and features of the disease at diagnosis, including elevated leukocyte counts (50,000/mcL) or number of cycles of induction to achieve remission, should play a role in choosing a consolidation strategy, as should issues regarding fertility and salvage options. Patients who require two cycles of chemotherapy to achieve a remission are at very high risk for relapse and should be considered for either clinical trial or allogeneic transplant as initial consolidation whenever possible. The long-term toxicities of allogeneic HSCT are considered prohibitive for patients with good risk cytogenetics; the panel would reserve this option for patients who experience relapse.

Panel members achieved more consensus that transplant-based options using either sibling or autologous stem cell sources were an appropriate strategy for patients with intermediate-risk cytogenetics. In the EORTC/GIMEMA trial, the 4-year DFS was 48.5% for allogeneic and 45% for autologous HCT in patients with normal cytogenetics. Other options for this group include clinical trials or high-dose cytarabine consolidation. Alternative regimens incorporating intermediate doses of cytarabine are also acceptable in this group (AML-7). Comparable 5-year DFS were reported this year in AML patients <60 years with normal karyotype after either four cycles of intermediate or high-dose cytarabine (41%) or autologous HSCT (45%).[21]

The panel uniformly endorsed allogeneic HSCT with sibling or unrelated donors or clinical trial as consolidation therapy for patients with poor-risk cytogenetics or patients with therapy-related AML or prior myelodysplasia. Sibling allogeneic HSCT produced a 43% DFS rate in this group of patients in the EORTC/GIMEMA trial, with similar outcomes for unrelated donor recipients reported by the International Bone Marrow Transplant Registry (IBMTR). The outcome for autologous HSCT was comparable to chemotherapy, with 18% DFS (AML-7). The NCCN AML panel members strongly recommend clinical trials as standard therapy for patients with poor prognostic features, which also include high WBC, CD56+, FLT3 abnormalities or two cycles needed to achieve CR.

For patients older than age 60, regardless of cytogenetics, enrollment in a clinical trial designed to assess new strategies to maintain remission is recommended. Several institutions are exploring the use of reduced intensity allogeneic HSCT as consolidation therapy for older patients in the context of a clinical trial. If a clinical trial is not available, the alternative is one to two cycles of standard-dose cytarabine with or without an anthracycline. For the older patient with good performance status, normal renal function and a favorable or intermediate-risk karyotype, several panel members would consider using somewhat higher doses of Ara-C (1-1.5 g/m^2/d x 4-6 doses) without an anthracycline (AML-6).

Induction Failure

Patients under age 60 who fail to achieve remission with one cycle of HiDAC or two cycles of standard-dose Ara-C should be considered for allogeneic HSCT using either a sibling or an unrelated donor source. Long-term disease-free survival of 25% to 30% has been reported for sibling donor HSCT as salvage therapy for induction failures. In the absence of a transplant option, clinical trial and best supportive care are acceptable alternatives.

Salvage Therapy

Acute Myeloid Leukemia

For patients younger than 60 years with AML who have experienced an early (<6 months) relapse after induction chemotherapy, Phase I or II trials are considered an appropriate strategy. If the relapse is detected when the tumor burden is low and the patient has a previously identified sibling or unrelated donor, allogeneic HSCT can be considered as primary therapy.

In patients younger than 60 who have relapsed after a "long" (≥6 months) remission, re-induction therapy using either the initial regimen or new agents in the setting of a clinical trial is appropriate (AML-8). After achieving a second remission, these patients would also be candidates for transplantation using either an allogeneic graft of family or registry origin or autologous stem cells if no donor is available.

Patients older than 60 years old with relapse beyond 6 months who are robust and wish to continue treatment after relapse may be offered salvage therapy with: 1) clinical trial (strongly preferred), 2) gemtuzumab ozogamicin (Mylotarg™, Wyeth Laboratories, Philadelphia, PA) or 3) repetition of the initial induction therapy, if they had a long initial remission. Best supportive care is always an option for those who do not wish to pursue intensive treatment.

Mylotarg™ (gemtuzumab ozogamicin), calicheamicin conjugated with an anti-CD33 monoclonal antibody, was approved for the treatment of relapsed AML in older patients. Mylotarg as a single agent produced clearance of marrow and peripheral blood blasts and transfusion independence in 26% of patients over age 60 with blasts expressing CD33. Therapy-related toxicity was low, with infusional side effects of fever, chills and hypotension as the main acute reactions. Some patients continued to have persistently low platelet counts without evidence of persistent leukemia. Liver function abnormalities were seen in 24% of patients, particularly when this agent was combined with hepatotoxic agents.[22] Exposure to Mylotarg™ within 3-4 months of HSCT has been reported to increase the risk of veno-occlusive disease-like syndrome.

Evaluation and Treatment of CNS Leukemia

The panel added a section on the treatment of leptomeningeal involvement by AML. Although this complication is much less frequent with AML than with ALL, we believed that this topic should be included. The panel does not recommend routine screening lumbar punctures at diagnosis in asymptomatic patients (AML-A). Patients with headache, confusion, or altered sensorium without focal neurologic signs should have appropriate radiographic studies to exclude CNS bleeding or infection. These symptoms may also be caused by leukostasis, which may resolve with measures such as leukapheresis to reduce the white cell count. If symptoms do not clear and no evidence of intracranial bleeding is found, a lumbar puncture should be performed after coagulopathy is corrected and platelet support is given. If the cytology is positive, the patient should receive intrathecal therapy with either Ara-C or methotrexate

twice weekly until the CSF is clear of blasts and then weekly for 4 to 6 weeks. Systemic chemotherapy should be initiated at the same time. High-dose Ara-C induction therapy may substitute for intrathecal chemotherapy since it crosses the blood-brain barrier; the CSF must then be reassessed after induction and further therapy given as appropriate.

For patients who have focal neurologic deficits such as cranial nerve palsies or motor weakness, magnetic resonance imaging should also be performed to identify infiltrative or mass lesions (chloromas), which would benefit from radiation therapy. One should, however, bear in mind that high-dose Ara-C and cranial radiation used concomitantly may carry increased risks of neurotoxicity.

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

Monitoring and Supportive Care (AML-B)

The supportive care factors brought up for discussion have also been updated. Growth-factor support may be considered for older patients during induction therapy, once they have achieved hypoplasia. This recommendation is based on an Eastern Cooperative Oncology Group (ECOG) study.[23] Recommendations on the use of cytokines for infection or for slow marrow recovery are left to institutional policy. G-CSF should have been discontinued for a minimum 7 days before obtaining a bone marrow to document response because of effects on marrow morphology.

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

The standard tumor lysis prophylaxis is hydration with alkalinization of the urine and allopurinol administration. Rasburicase (genetically engineered recombinant form of urate oxidase enzyme) therapy should be considered if the patient is unable to tolerate oral medication, has clinical evidence of tumor lysis syndrome or problematic hyperuricemia.

Patients who receive HiDAC need to be closely monitored for changes in renal function. Renal dysfunction is highly correlated with increased risk of cerebellar toxicity. Patients need to be monitored for nystagmus, dysmetria, and ataxia before each dose of HiDAC; patients exhibiting any neurologic signs should have the HiDAC discontinued, and all subsequent Ara-C therapy must be standard-dose, rather than high-dose. HiDAC should also be discontinued in patients with rapidly rising creatinine caused by tumor lysis.

Specific supportive care issues should be considered when treating patients with APL. The first is the development of the “retinoic acid syndrome” of which the initial signs and symptoms are fever, increasing WBC over 10,000/mcL, and fluid retention. Patients with these findings should be closely monitored for hypoxia, the development of pulmonary infiltrates or pleural effusion. If any of

these findings occur, the patients should be started on dexamethasone 10 mg twice a day for 3 to 5 days, the dose is then tapered over a week. ATRA may need to be held during the initial acute symptomatic period but may be restarted when symptoms improve (AML-B, 2 of 2). Arsenic trioxide may induce a similar syndrome called the “APL differentiation syndrome” which also responds to dexamethasone.

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

Another issue centers on the occurrence of cardiac arrhythmias in patients receiving arsenic trioxide. The compound is known to prolong the QT interval, making patients susceptible to ventricular arrhythmias. Careful monitoring to maintain electrolytes (Ca 9.0, K 4.0, Mg 2.0) in the upper normal range and avoidance of other drugs that prolong the QT interval will lessen the risk of cardiac arrhythmias.

Post-remission Surveillance

Recommendations for post-remission surveillance are detailed on AML-8. Complete blood counts including platelets should be monitored every 1-3 months for the first 2 years after patients have completed consolidation, then every 3-6 months for a total of 5 years. Bone marrow evaluation is recommended only if the hemogram becomes abnormal, rather than as part of routine surveillance of the bone marrow at fixed intervals, unless this is being done as part of a research protocol. Finally, a matched unrelated donor search may be considered at first relapse in appropriate patients concomitant with initiation of therapy.

Disclosures for the NCCN AML Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Berlex, Inc.,Celgene, Cell Genesys, Inc.,Cell Therapeutics, Inc., Genentech, Genzyme, Millennium, Novartis, Ortho Biotech, and Tibotec.

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