Acute Myeloid Leukemia, Version 3.2019

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ABSTRACT

Acute myeloid leukemia (AML) is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths due to leukemias in the United States. Recent advances have resulted in an expansion of treatment options for AML, especially concerning targeted therapies and low-intensity regimens. This portion of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AML focuses on the management of AML and provides recommendations on the workup, diagnostic evaluation and treatment options for younger (age <60 years) and older (age ≥60 years) adult patients.

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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.

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All recommendations are category 2A unless otherwise noted.

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

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The complete NCCN Guidelines for Acute Myeloid Leukemia are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

Disclosures for the NCCN Acute Myeloid Leukemia Panel

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

Individual disclosures for the NCCN Acute Myeloid Leukemia Panel members can be found on page 749. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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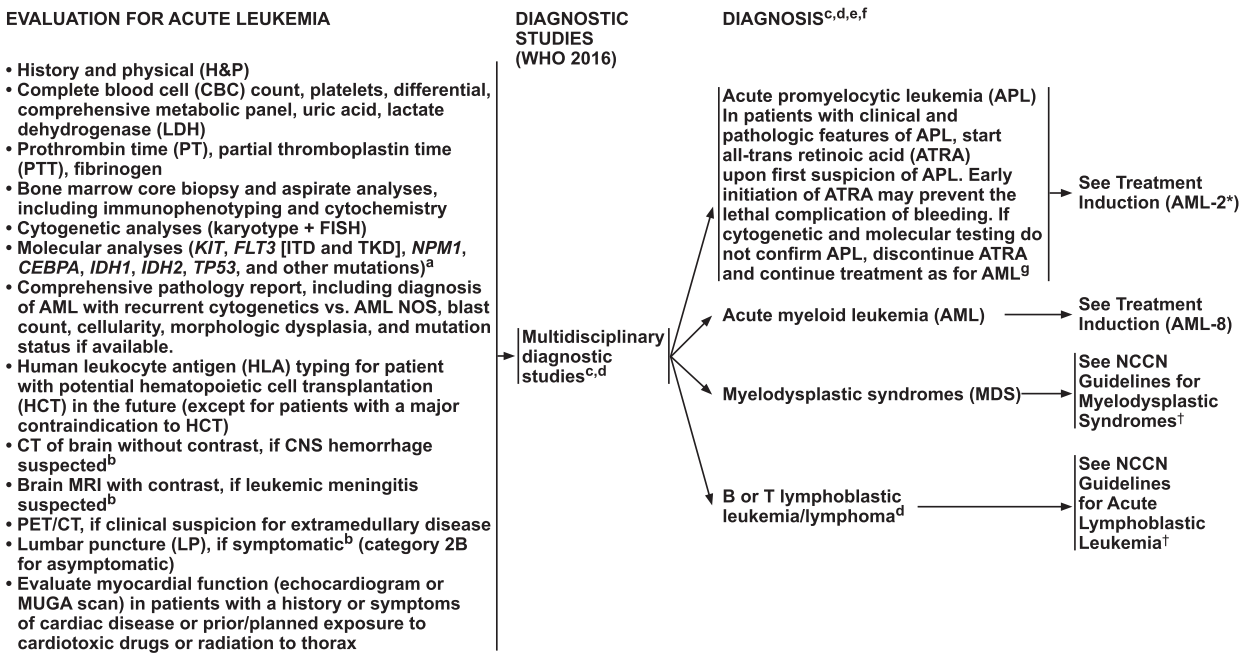

See footnotes on AML-1A*

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AML-1

Overview

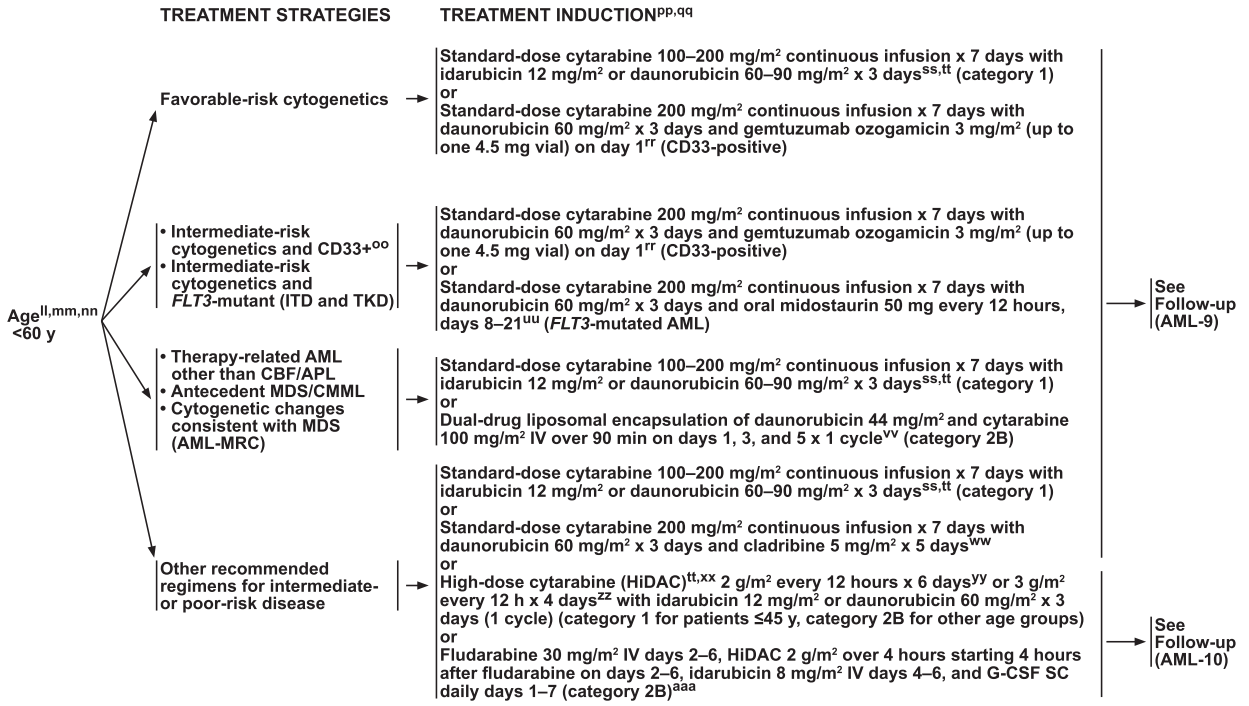
Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. It is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths from leukemias in the United States. An estimated 21,450 people will be diagnosed with AML in 2019, and 10,920 patients will die of the disease.[1] According to the SEER Cancer Statistics Review, the median age at diagnosis is 67 years[2]; other registries report 71 years,[3] with 54% of patients diagnosed at 65 years or older (and approximately a third diagnosed at ≥75 years of age).[2] Thus, as the population ages, the incidence of AML, along with myelodysplastic syndromes (MDS), seems to be rising.

Therapy-related MDS/AML (t-AML) is a well-recognized consequence of cancer treatment in a proportion of patients receiving cytotoxic therapy for solid tumors or hematologic malignancies. Reports suggest that t-AML may account for 5%–20% of patients with MDS/AML.[4–6] Two well-documented categories of cytotoxic agents associated with the development of t-AML are alkylating agents and topoisomerase inhibitors.[4,7,8] Radiotherapy, especially in the context of myeloablative therapy, given before autologous hematopoietic cell transplantation (HCT) may also increase the risk for t-AML.[9,10] The disease course of t-AML is generally progressive and may be more resistant to conventional cytotoxic therapies than de novo cases of MDS/AML.[8]

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. This portion of the guidelines discusses recommendations for the workup, diagnosis and management of AML. For the complete and most updated version of these guidelines, visit NCCN.org.

Workup

The evaluation and initial workup for suspected AML (see AML-1, above) consists of a comprehensive medical history and physical examination. Laboratory evaluations include a comprehensive metabolic panel and a complete blood count including platelets and a differential of white blood cells (WBCs). Serum uric acid and lactate dehydrogenase have prognostic relevance and should be evaluated.[11,12] Bone marrow core biopsy



See footnotes on AML-8A*

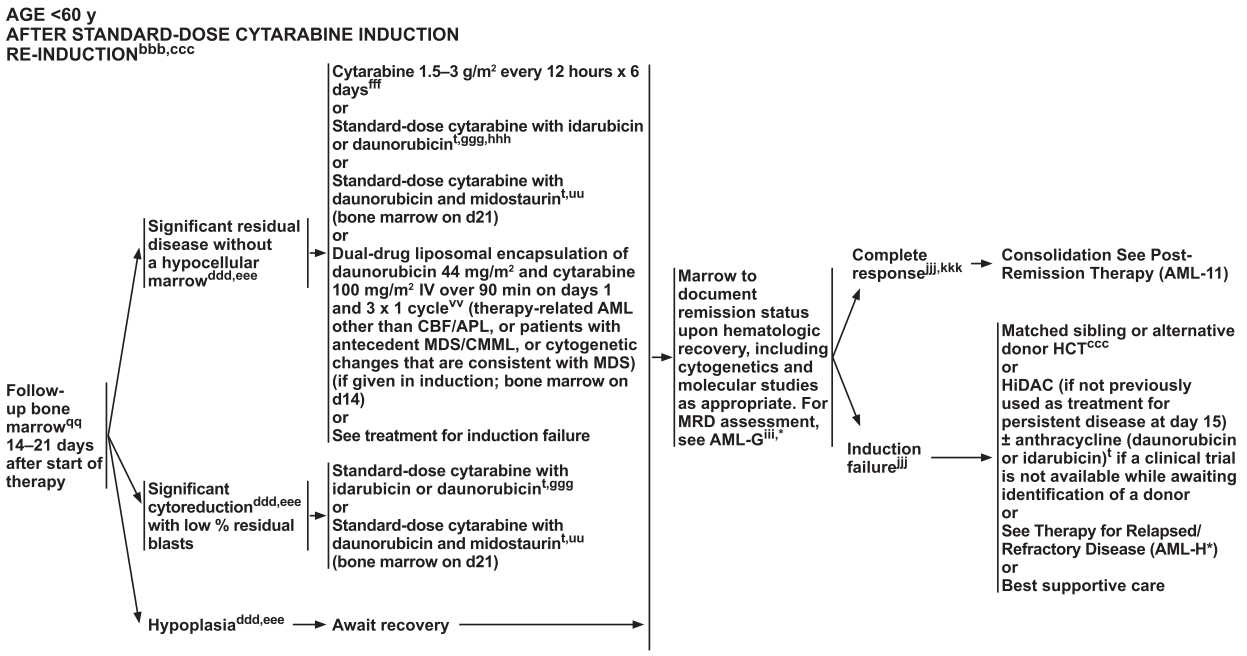
*Available online, in these guidelines, at NCCN.org.

AML-8

and aspirate analyses (including immunophenotyping and cytochemistry) and cytogenetic analyses (karyotype with fluorescence in situ hybridization) are necessary for risk stratification and to guide therapy of AML. Several gene mutations, including *KIT*, *FLT3*-ITD, *FLT3*-TKD, *NPM1*, *CEBPA*, *IDH1*/*IDH2*, *RUNX1*, *ASXL1*, and *TP53*, are associated with specific prognoses in a subset of patients and may guide treatment decisions.[13–15] All patients should be tested for mutations in these genes, and multiplex gene panels and next-generation sequencing analysis can be obtained to develop a more comprehensive prognostic assessment.[15] For instance, ideally, the mutation status of *FLT3* should be resulted rapidly to allow for the addition of an *FLT3* inhibitor, midostaurin, on day 8 of upfront intensive chemotherapy. Adequate marrow should be available at the time of diagnosis or relapse for molecular studies as per the institutional practice. Local pathologists should be consulted to discuss ways to optimize sample collection and preservation. If molecular testing is not available at the patient's treatment center, evaluation at an outside reference laboratory or transfer to another institution is recommended prior to performing the marrow evaluation. Circulating leukemic blasts from peripheral blood may alternatively be used to detect molecular abnormalities in patients.

Extramedullary presentation, including central nervous system disease, is uncommon in patients with AML. However, if extramedullary disease is suspected, a PET/CT is recommended. Patients with significant central nervous system signs or symptoms at presentation should be evaluated using appropriate imaging techniques, such as radiography, CT, or MRI for the detection of intracranial bleeding, leptomeningeal disease, or mass lesions in either the brain or spinal cord. Routine screening lumbar punctures (LPs) are not warranted at the time of diagnosis in patients with AML. However, if symptoms persist, and bleeding and mass/lesions are excluded, the patient should undergo LP for diagnostic and possible therapeutic purposes once coagulopathy has been corrected, adequate platelet support is available, and the circulating disease has been cleared through the initiation of systemic therapy. Screening LPs should be considered at first remission before first consolidation in patients with monocytic differentiation, mixed phenotype acute leukemia (MPAL), WBC count >40,000/mcL at diagnosis, high-risk acute promyelocytic leukemia (APL), or extramedullary disease, particularly in patients not receiving high-dose cytarabine (HiDAC) (ie, older patients).

Coagulopathy is common at presentation in many leukemias; it is therefore standard clinical practice to



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See footnotes on AML-9A*

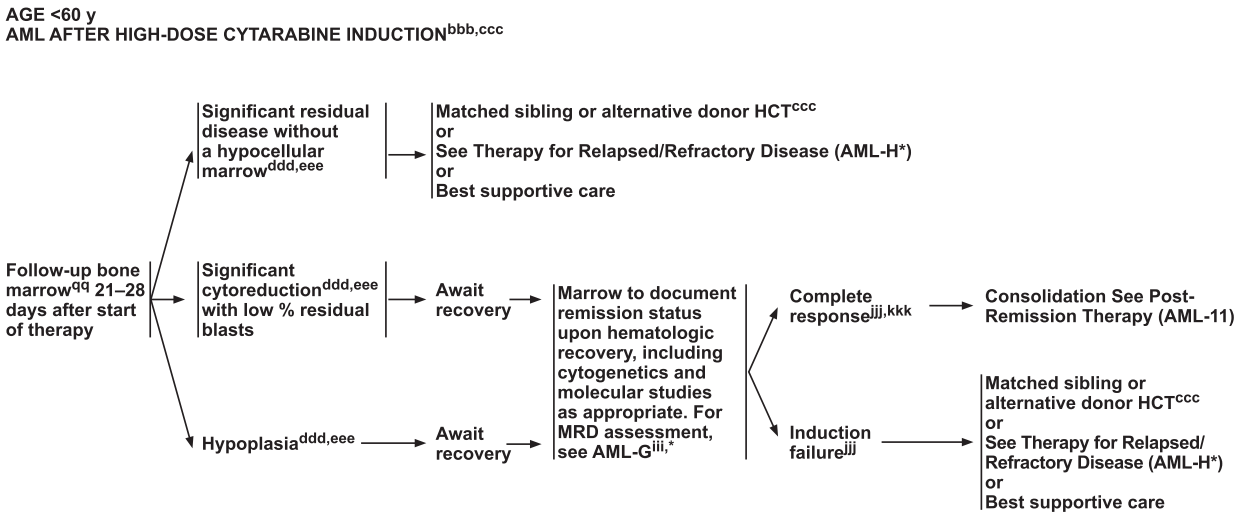
AML-9

screen for coagulopathy by evaluating prothrombin time, partial thromboplastin time, and fibrinogen activity as part of the initial evaluation and before performing any invasive procedure. The need for a cardiac evaluation (eg, echocardiogram or multigated acquisition scan) should be determined based on individual risk factors. Patients with a history or symptoms of cardiac disease, prior or planned exposure to cardiotoxic drugs or thoracic radiation, or those of an older age should have an echocardiogram. In younger patients who are otherwise asymptomatic with no history of cardiac disease, an echocardiogram can be considered. In cases of acutely ill patients, treatment should not be delayed for an echocardiogram.

Human leukocyte antigen (HLA) typing should be performed in all patients with newly diagnosed AML for whom allogeneic HCT would be considered. HLA typing of family members is recommended for patients up to age 80 years, or per institutional practice, who do not have favorable-risk cytogenetics, and tissue typing should be broadened to include alternative donor searches. In patients with any nonfavorable risk, a donor search should begin while the patient is undergoing induction chemotherapy rather than waiting for remission to be achieved. Early referral to a transplant center for patients with nonfavorable risk is recommended.

Diagnosis

In accordance with the 2016 WHO classification, a diagnosis of AML is made based on the presence of ≥20% blasts in the marrow or peripheral blood. In an appropriate clinical setting, a diagnosis of AML may be made with <20% blasts in patients with recurrent cytogenetic abnormalities including t(15;17), t(8;21), t(16;16), or inv(16) or the corresponding transcript. The accurate classification of AML requires multidisciplinary diagnostic studies using immunohistochemistry, cytochemistry, or both, in addition to molecular genetics analysis. The NCCN AML Panel suggests that complementary diagnostic techniques can be used at the discretion of the pathology department of the individual institution. Some cases may still show evidence of both myeloid and lymphoid antigen expression on the leukemic cells and are defined as acute leukemias of ambiguous lineage. This is further subgrouped into acute undifferentiated leukemia, MPAL with *BCR-ABL1* rearrangement, MPAL with rearranged *KMT2A*, MPAL with B-cell/myeloid features not otherwise specified, and MPAL with T-cell/myeloid features not otherwise specified.



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[qq]See Monitoring During Therapy (AML-F*).
[bbb]Consider clinical trials for patients with targeted molecular abnormalities.
[ccc]Begin alternate donor search (haploidentical, unrelated donor or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT.
[ddd]If ambiguous, consider repeat bone marrow biopsy in 5–7 days before proceeding with therapy.
[eee]Hypoplasia is defined as cellularity less than 20% of which the residual blasts are less than 5% (ie, blast percentage of residual cellularity).
[iii]MRD testing is under investigation and may have prognostic significance. See MRD assessment (AML-G*) and Discussion for further details.
[jjj]See Response Criteria for Acute Myeloid Leukemia (AML-E*).
[kkk]Screening LP should be considered at first remission before first consolidation for patients with monocytic differentiation, mixed phenotype acute leukemia, WBC >40,000/mcL at diagnosis, extramedullary disease, or *FLT3*. See Evaluation and Treatment of CNS Leukemia (AML-B*).

AML-10

The expression of both cytochemical and/or immunophenotypic characteristics of both lineages on the same cells is defined as biphenotypic, whereas expression of lineage-specific characteristics on different populations of leukemia cells is termed bilineal. Due to the rarity of acute leukemias of ambiguous lineage (as defined by the 2016 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 measurable (also known as minimal) residual disease (MRD) in adult AML has not yet been widely incorporated into postremission monitoring strategies, except in patients with APL. However, ongoing research is moving MRD monitoring to the forefront for all patients with AML.[16]

Management of AML in Patients Younger Than 60 Years

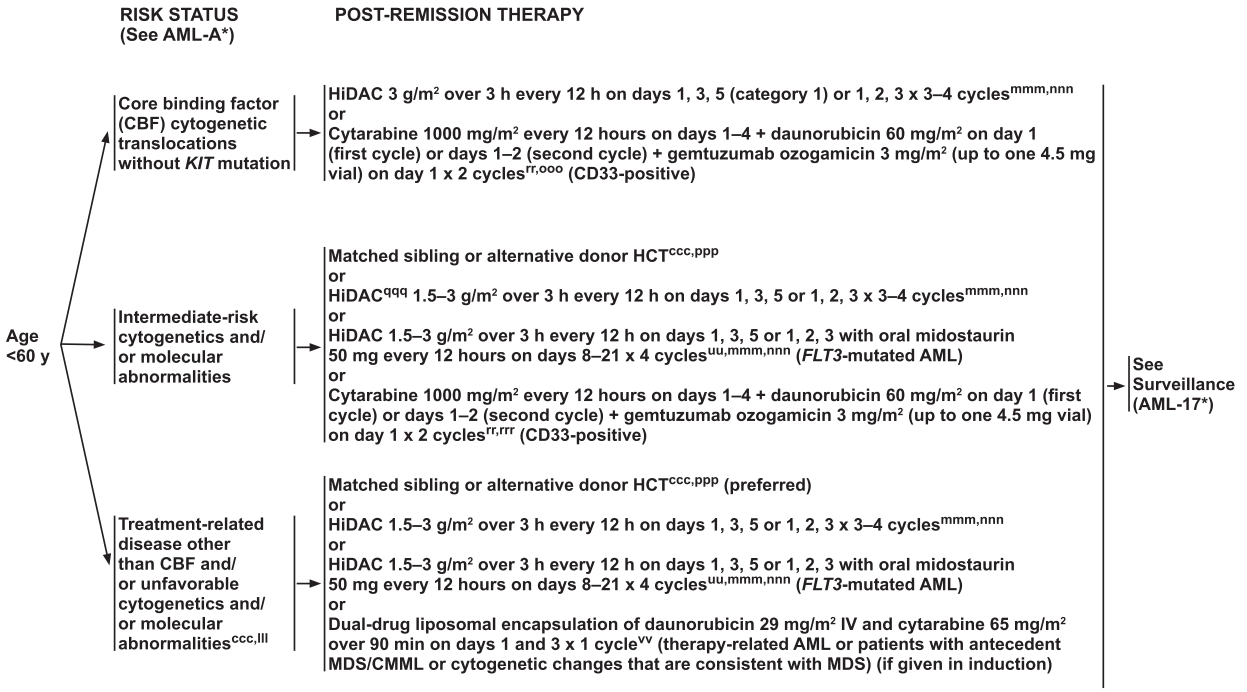
Induction Therapy

Standard induction regimens used for patients aged <60 years are based on a backbone of cytarabine plus an anthracycline. Historically, in most large cooperative group trials, daunorubicin has been the most commonly used anthracycline at doses of 45 to 60 mg/m^2 daily for 3 days. Idarubicin, which has a longer intracellular retention time, used at doses of 12 mg/m^2 daily for 3 days, has had comparable remission rates with fewer patients requiring additional therapy at day 15 to achieve remission. Complete remission (CR) rates for patients who are ≤50 years have consistently been in the range of 60%–70% in most large cooperative group trials of infusional cytarabine and anthracycline. Recent studies have incorporated targeted strategies according to cytogenetics and molecular abnormalities, and the current NCCN Guidelines for AML outline treatment strategies according to these cytogenetic risk groups (see AML-8, page 723).

Favorable-Risk Cytogenetics

Cytarabine and Anthracycline

A large randomized phase III study (E1900) from the Eastern Cooperative Oncology Group (ECOG) reported a significant increase in CR rate (71% vs 57%; $P<.001$) and median overall survival (OS; vs 16 months; $P=.003$) using daunorubicin 90 mg/m^2 daily for 3 days (n=327) versus 45 mg/m^2 daily for 3 days (n=330) in patients with



AML-11

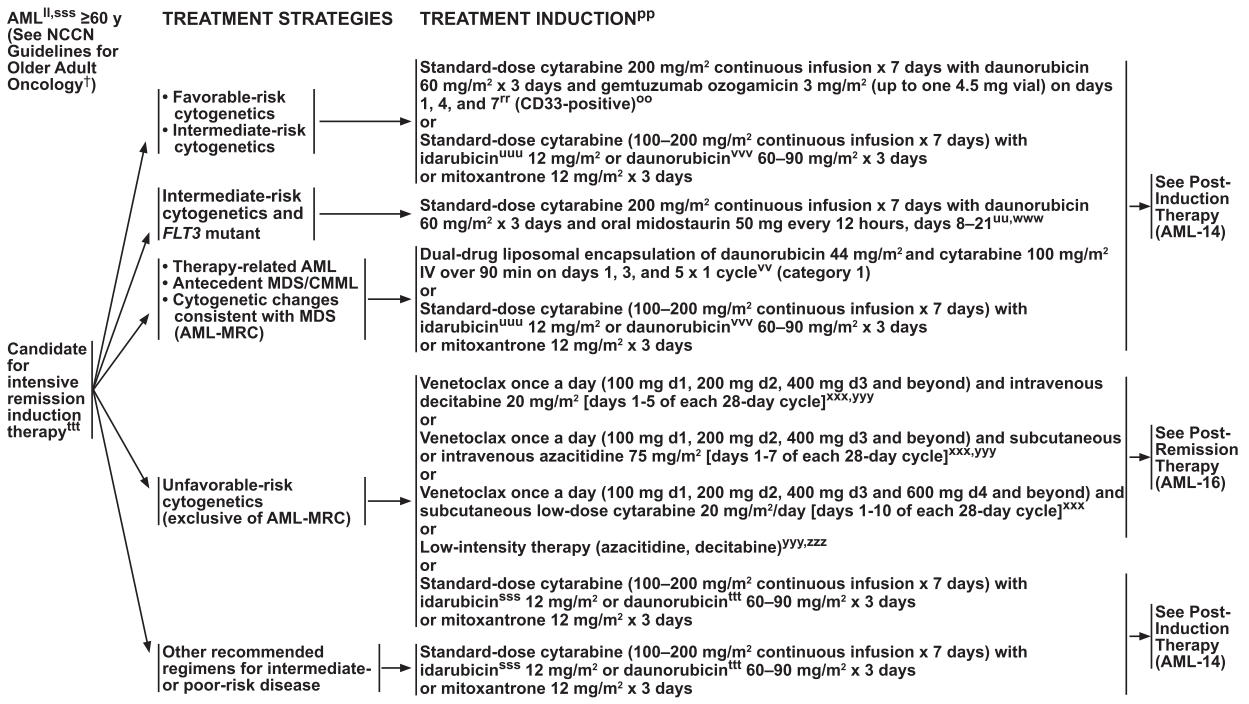
previously untreated AML aged <60 years.[17] However, based on subgroup analyses, the survival benefit with high-dose daunorubicin was shown to be restricted to patients with favorable- and intermediate-risk cytogenetic profiles (median OS, 34 vs 21 months; *P*=.004) and those <50 years of age (median OS, 34 vs 19 months; *P*=.004). The survival outcome for patients with unfavorable cytogenetics was poor, with a median OS of approximately 10 months in both treatment arms.[17] In an update of the E1900 trial, high-dose daunorubicin maintained a higher response than standard-dose daunorubicin in patients aged <50 years (hazard ratio [HR], 0.66; *P*=.002).[18] This benefit was seen regardless of risk cytogenetics. In addition, patients with *FLT3*-ITD, *DNMT3A*, and *NPM1* mutant AML had improved OS. Patients between 50 and 60 years of age with *FLT3*-ITD or *NPM1* also benefitted from high-dose daunorubicin.[18] High-dose daunorubicin was previously evaluated in a European trial that compared idarubicin 12 mg/m² daily for 3 or 4 days versus daunorubicin 80 mg/m² daily for 3 days in patients between ages 50 and 70 years; CR rates were 83%, 78%, and 70%, respectively (*P*=.04).[19] No difference was seen in relapse rate, event-free survival (EFS), or OS outcomes between the treatment arms.

In a systematic review and meta-analysis of 29 randomized controlled trials (RCTs) comparing idarubicin to daunorubicin,[20] idarubicin had a lower remission failure rate compared with daunorubicin (relative risk [RR], 0.81; 95% CI, 0.66–0.99; *P*=.04), but no difference was observed in early death or overall mortality.[20]

It has been suggested that a dose of 60 mg/m² daunorubicin may be equally as effective as 90 mg/m² and have a lower toxicity. A study from Burnett et al[21] compared these 2 doses in 1,206 patients who were predominately aged <60 years. There was no difference in CR (73% vs 75%; odds ratio [OR], 1.07; 95% CI, 0.83–1.39; *P*=.60). The 60-day mortality was higher in patients receiving 90 mg/m² (10% vs 5%; HR, 1.98; 95% CI, 1.30–3.02; *P*=.001), though the 2-year OS was similar (59% vs 60%; HR, 1.16; 95% CI, 0.95–1.43; *P*=.15).[20] It is worth noting that all patients received a second course of chemotherapy that included additional daunorubicin (50 mg/m²) on days 1, 3, and 5, which may potentially have mitigated the effects of a 90 mg/m² daunorubicin dose.

CD33-Positive AML

Gemtuzumab ozogamicin (GO), a humanized anti-CD33 monoclonal antibody conjugated with the cytotoxic



agent calicheamicin,[22] was initially approved in 2000 as a monotherapy for AML based on data from single-arm phase II trials for older adult patients in first relapse.[23] The voluntary withdrawal of the drug in 2010 was based on interim data from a randomized trial in adult patients aged <60 years with AML comparing induction regimens of cytarabine and daunorubicin with or without GO, in which there was no improvement in outcomes and a small but significant increase in early mortality in the GO arm.[24] Subsequent results of this trial eventually showed no difference in overall mortality between the 2 arms.[25] Since its withdrawal from the market, studies have demonstrated a significant benefit for GO in specific patient populations. In the MRC AML 15 trial, the efficacy and safety of adding GO (3 mg/m^2 on day 1 of induction) to 3 induction regimens, including daunorubicin (50 mg/m^2 on days 1, 3, and 5) and cytarabine (100 mg/m^2 on days 1–10 every 12 hours), was evaluated in patients ≤60 years of age with previously untreated AML (n=1,113).[26] The addition of GO was well tolerated, and no differences in relapse-free survival (RFS) or OS rates were seen between arms that received or did not receive GO. The patients predicted to derive significant benefit with GO addition to chemotherapy included those with favorable-risk cytogenetics, with a trend toward benefit for those with intermediate-risk cytogenetics.[26] A meta-analysis of 5 randomized trials (including adult patients aged ≥60 years) showed that adding GO (including alternative dosing schedules) to conventional induction therapy also provides survival benefit.[27] A review of these and other studies (see "Management of AML in Patients Older than 60 Years," page 736) led to the approval of GO in September 2017 for the treatment of adults with newly diagnosed CD33-positive AML.

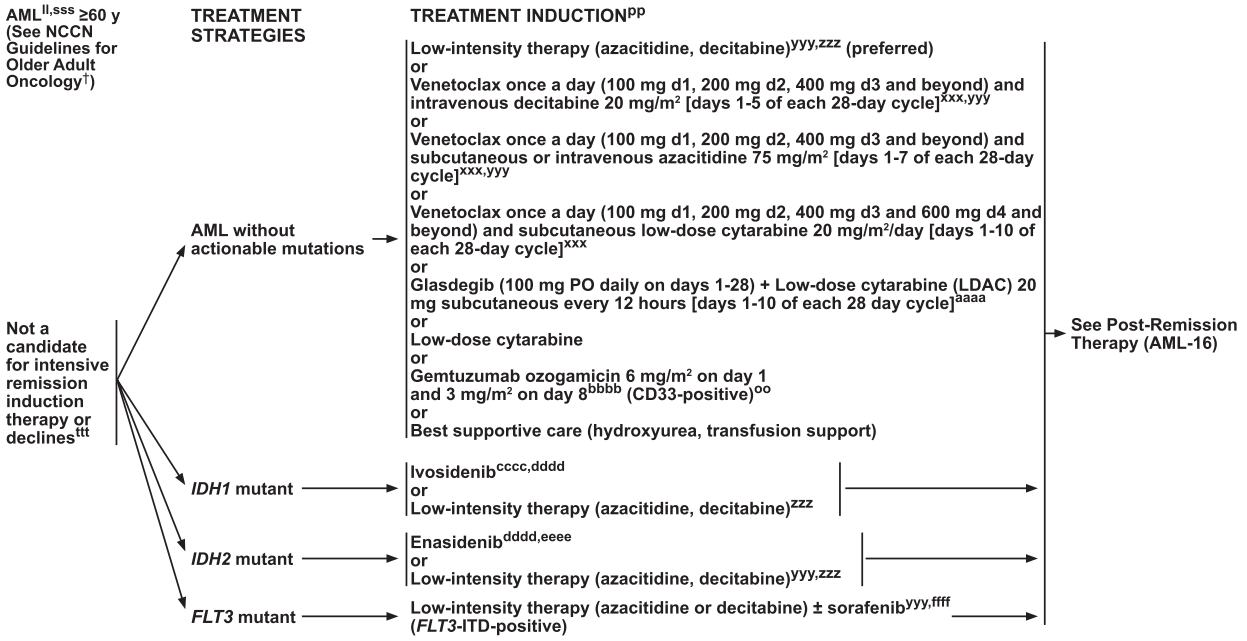
KIT Mutated AML

Emerging studies are evaluating the impact of adding dasatinib, a tyrosine kinase inhibitor, to AML therapy in core binding factor (CBF) AML with *KIT* mutations.[28,29]

Intermediate-Risk Cytogenetics

FLT3-Positive AML

Most *FLT3*-mutated AML cases occur in patients with intermediate-risk cytogenetics. Data have demonstrated improved survival for patients with newly diagnosed *FLT3*-mutation–positive AML when midostaurin is added to standard chemotherapy as part of frontline treatment.[30–32] This led to its breakthrough designation and approval by the FDA in 2017. In the CALGB 10603/RATIFY Alliance trial, patients aged 18 to 59 years, with



See footnotes on AML-13A*

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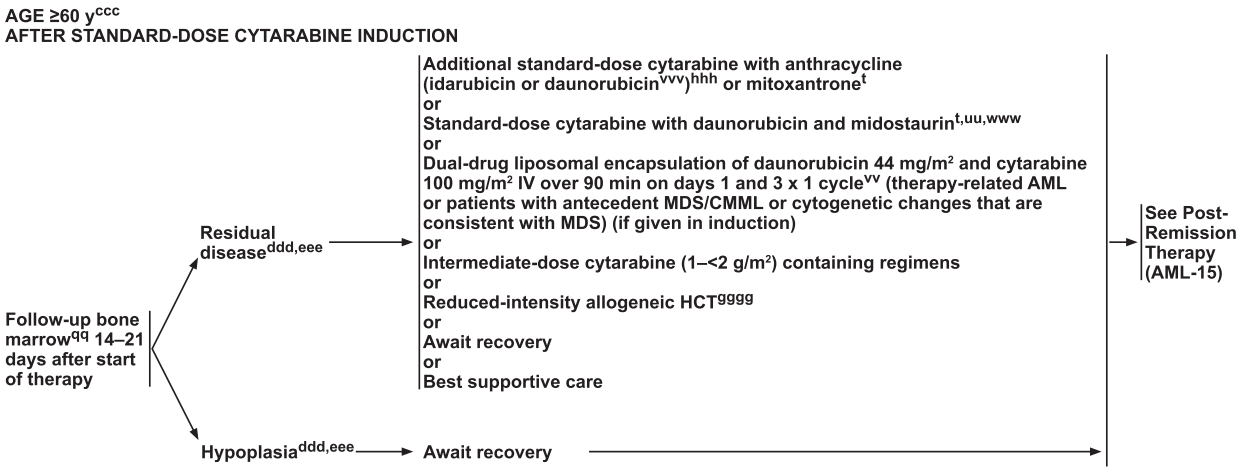
AML-13

newly diagnosed *FLT3*-mutation–positive AML (ITD or TKD) were randomized (n=717) to receive standard cytarabine therapy (200 mg/m² daily for 7 days via continuous infusion) and daunorubicin (60 mg/m² on days 1–3) with placebo or midostaurin (50 mg, twice daily on days 8–21).[32] If residual disease in the bone marrow was observed on day 21, patients were treated with a second blinded course. Patients who experienced CR received 4 28-day cycles of HiDAC (3 g/m² every 12 hours on days 1, 3, and 5) with placebo or midostaurin (50 mg, twice a day on days 8–21) followed by a year of maintenance therapy with placebo or midostaurin (50 mg twice a day).[32] The median OS was 74.7 months (95% CI, 31.5–not reached [NR]) in the midostaurin group compared with 25.6 months (95% CI, 18.6–42.9) in the placebo group (*P*=.009).[32] Patients who received midostaurin with standard induction and consolidation therapy experienced significant improvement in OS (HR for death, 0.78; *P*=.009) and EFS (HR for event or death, 0.78; *P*=.002) compared with those on the placebo arm.[32]

Some studies suggest that a higher dose of daunorubicin (90 mg/m²), compared with lower doses of either 45 or 60 mg/m², is significantly associated with increased CR and survival rates in patients with intermediate-risk cytogenetics and those who have *FLT3*-ITD mutation–positive AML.[33,34] A phase III study compared idarubicin (12 mg/m² for 3 days) and high-dose daunorubicin (90 mg/m² for 3 days) with standard cytarabine therapy during induction in young adults with newly diagnosed AML (age range, 15–65 years). It was determined that high-dose daunorubicin was associated with higher OS and EFS rates in patients with *FLT3*-ITD mutation–positive AML.[35] However, these studies did not include midostaurin.

Therapy-Related AML or Antecedent MDS/Chronic Myelomonocytic Leukemia or AML-MRC

Although most cases of AML are de novo, secondary AML and t-AML account for approximately 25% of all AML cases and are associated with poor outcomes.[36,37] Emerging data have demonstrated improved survival in older patients with secondary AML when a dual-drug liposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio (CPX-351) is used as frontline therapy.[38–40] In a phase II trial, newly diagnosed older patients (age ≥60 years) with AML (n=126), were randomized 2:1 to first-line CPX-351 or the conventional administration of cytarabine and daunorubicin (7+3 regimen).[39] Compared with the standard 7+3 regimen, CPX-351 produced higher response rates (CPX-351, 66.7% vs 7+3, 51.2%; *P*=.07), however differences in



[t]For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course.
[qq]See Monitoring During Therapy (AML-F*).
[uu]This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 2017;377:454-464.
[vv]Lancet JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. J Clin Oncol 2018;36:2684-2692.
[ccc]Begin alternate donor search (haploidentical, unrelated donor or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT.
[ddd]If ambiguous, consider repeat bone marrow biopsy in 5–7 days before proceeding with therapy.
[eee]Hypoplasia is defined as cellularity less than 20% of which the residual blasts are less than 5% (ie, blast percentage of residual cellularity).
[hhh]If daunorubicin 90 mg/m² was used in induction, the recommended dose for daunorubicin for reinduction prior to count recovery is 45 mg/m² for no more than 2 doses. Analogously, if idarubicin 12 mg/m² was used for induction, the early reinduction dose should be limited to 10 mg/m² for 1 or 2 doses.
[vvv]The complete response rate and 2-year overall survival in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m² are also comparable to the outcome for idarubicin 12 mg/m²; the higher dose daunorubicin did not benefit patients > age 65 (Lowenberg B, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 2009;361:1235-1248).
[www]The RATIFY trial studied patients age 18–60 y. An extrapolation of the data suggests that older patients who are fit to receive 7+3 should be offered midostaurin since it seems to provide a survival benefit without undue toxicity.
[gggg]Reduced-intensity transplant is a reasonable option in patients with identified donors available to start conditioning within 4–6 weeks from start of induction therapy. Patients without an identified donor would most likely need some additional therapy as a bridge to transplant. Reduced-intensity HCT may be appropriate for patients with a low level of residual disease post-induction (eg, patients with prior MDS who reverted back to MDS with <10% blasts). It is preferred that this approach be given in the context of a clinical trial.

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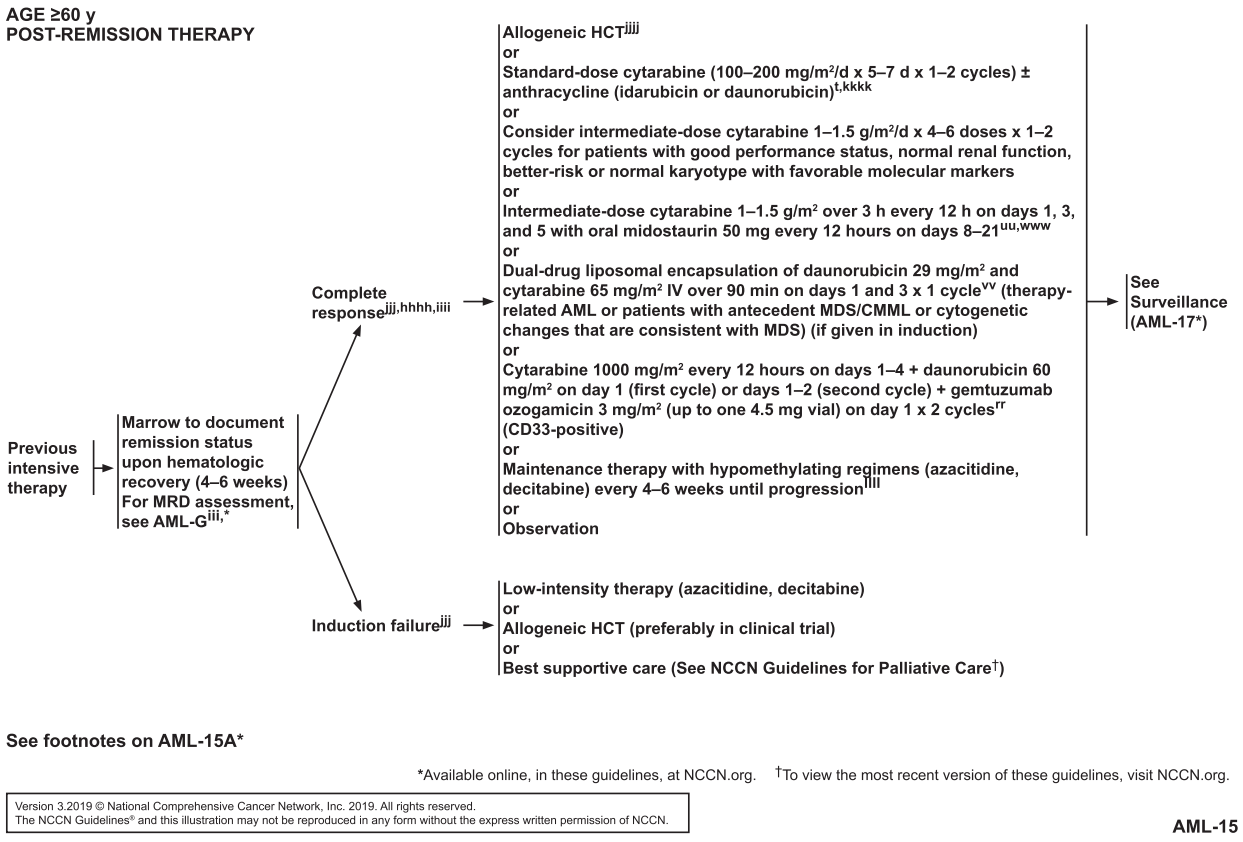
AML-14

EFS and OS were not statistically significant.[39] A planned analysis of the secondary AML subgroup demonstrated that CPX-351 was associated with a higher complete response rate (57.6% vs 31.6%; *P*=.06).[39] These results led to the development of a randomized phase III study comparing the efficacy and safety of CPX-351 to the conventional administration of cytarabine and daunorubicin (control arm) in patients 60–75 years of age with newly diagnosed secondary AML (n=309).[40] With a median follow-up of 20.7 months, CPX-351 significantly improved OS compared with the control arm (median, 9.56 vs 5.95 months; HR, 0.69; 95% CI, 0.52-0.90; *P*=.003).[40] CPX-351 was also associated with significantly higher overall remission (47.7% vs 33.3%; *P*=.016) and CR (37.3% vs 25.6%; *P*=.04) rates. The most frequently reported grade 3 to 5 adverse events in the CPX-351 and control groups were febrile neutropenia (68.0% vs 70.9%), pneumonia (19.6% vs 14.6%), and hypoxia (13.1% vs 15.2%).[40]

Other Regimens for Intermediate- or Poor-Risk Cytogenetics

Standard-Dose Cytarabine, Anthracycline, and Cladribine

A phase III randomized trial from the Polish Adult Leukemia Group evaluated the efficacy and safety of adding a purine analog to an induction regimen comprising daunorubicin and cytarabine in patients ≤60 years of age with previously untreated AML (n=652).[41] In this study, patients were randomized to the following treatment arms: daunorubicin and cytarabine (daunorubicin 60 mg/m² daily for 3 days and cytarabine 200 mg/m² continuous infusion for 7 days; DA arm); DA with addition of cladribine (5 mg/m² daily for 5 days; DAC arm); and DA with addition of fludarabine (25 mg/m² daily for 5 days; DAF arm). Patients with a partial response after induction could receive a second cycle of the assigned induction regimen. Postremission treatment was the same in the 3 arms. Patients with a CR after induction received consolidation with a course of intermediate-dose cytarabine (1.5 g/m² on days 1–3) and mitoxantrone (10 mg/m² on days 3–5), followed by a course of HiDAC (2 g/m² every 12 hours on days 1, 3, and 5).[41] A similar proportion of patients in the 3 arms proceeded to allogeneic HCT. The DAC regimen resulted in a significantly higher CR rate after induction (67.5% vs 56%; *P*=.01) and improved OS outcomes (median, 24 vs 14 months; 3-year OS, 45% vs 33%; *P*=.02) compared with the DA arm. Based on subgroup analysis, significant improvements in OS with DAC compared with DA were observed for patients ≥50 years of age, those with initial WBC count 50×10^9/L or greater,



See footnotes on AML-15A*

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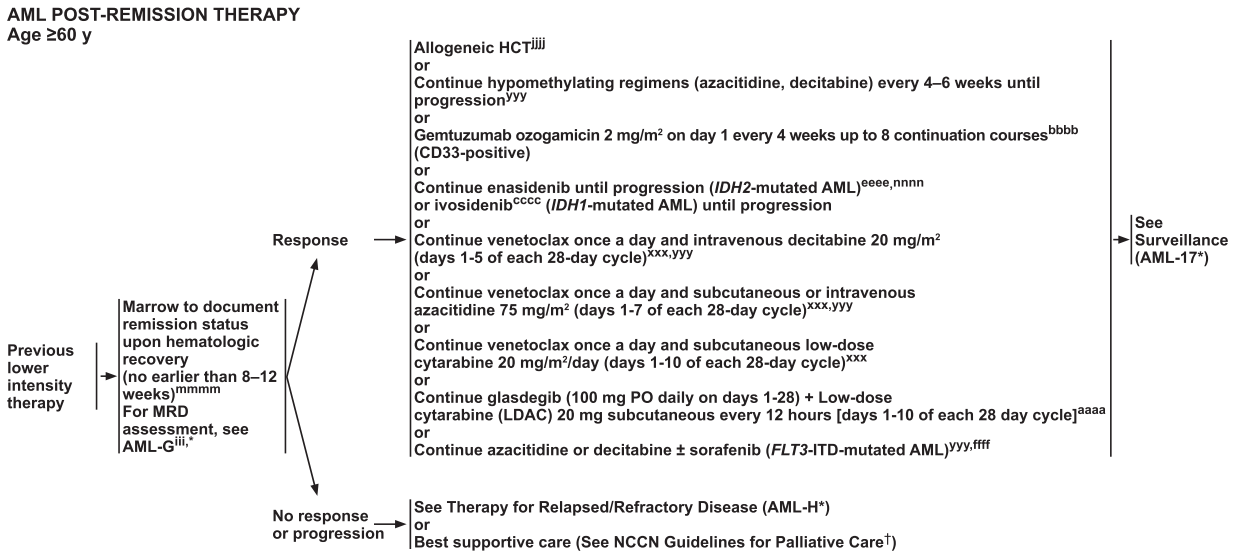
AML-15

and patients with high-risk karyotype.[41] No significant improvements in efficacy were observed in the overall DAF arm with regard to CR rate (59%) or OS (median, 16 months; 3-year OS rate, 35%); however, in subgroup analysis, significant improvements with DAF compared with DA were observed among patients with high-risk karyotype. The incidence of hematologic toxicities and other adverse events were similar among treatment arms.[41] Although this randomized trial showed an advantage for the addition of cladribine to a standard induction regimen, bone marrow aspirates were not performed after the first cycle of induction until either counts recovered or blasts reappeared in the peripheral blood, which would delay administration of a second cycle of induction compared with standard practice in the United States.

High-Dose Cytarabine-Containing Regimens

The use of HiDAC as induction therapy continues to be a controversial approach. The most recent study from the EORTC-GIMEMA AML-12 trial suggests that HiDAC (3 g/m² every 12 hours on days 1, 2, 5, and 7) improves outcome in patients who are <46 years of age.[42] This study randomized 1,900 patients between the ages of 15 and 60 years into 2 treatment groups, HiDAC and standard-dose cytarabine (SDAC; 100 mg/m²/d by continuous infusion for 10 days). Both groups were also given daunorubicin (50 mg/m²/d on days 1, 3, and 5) and etoposide (50 mg/m²/d on days 1–5). Data from a median 6-year follow-up indicate an OS near statistical significance (HiDAC, 42.5% vs SDAC, 38.7%; P=.06), and when separated by age with a cutoff of 46 years, the benefit was relegated to the younger patient cohort (HiDAC, 51.9% vs SDAC, 43.3%; P=.009) compared with patients ≥46 years of age (HiDAC, 32.9% vs SDAC, 33.9%; P=.91). Other populations that benefited from HiDAC were high-risk patients including patients with very poor-risk cytogenetic abnormalities and/or *FLT3*-ITD mutation or with secondary AML. There was no significant increase in grade 3 or 4 toxicities except for an increase in conjunctivitis (grade 2–3) with HiDAC (12.4%) versus SDAC (0.5%). Incidence of adverse events was equivalent (SDAC, 67.6% vs HiDAC, 66.2%). Patients in CR received a single consolidation cycle of daunorubicin and cytarabine (500 mg/m² every 12 hours for 6 days) and subsequent HCT.[42]

HiDAC therapy during induction was initially explored 2 decades ago in 2 large cooperative group trials. In an Australian Leukemia Study Group trial,[43,44] patients <60 years of age were randomized (n=301) to receive either HiDAC (3 g/m² every 12 hours on days 1, 3, 5, and 7 for a total of 24 g/m²) or standard cytarabine



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See footnotes on AML-16A*

therapy (100 mg/m² daily for 7 days via continuous infusion); patients in both arms received daunorubicin (50 mg/m² on days 1–3) and etoposide (75 mg/m² daily for 7 days). The CR rates were equivalent in both arms (71% and 74%, respectively), and a significantly higher 5-year RFS rate was observed in the HiDAC arm (48% vs 25%; P=.007).[44] 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.[43] However, treatment-related morbidity and mortality were higher in the HiDAC arm; the 5-year OS rates were 33% in the high-dose arm compared with 25% in the standard-dose arm.[44]

In a large SWOG study,[45] patients aged <65 years (n=665) with de novo or secondary AML were randomized to receive HiDAC (2 g/m² every 12 hours for 6 days for a total of 24 g/m²; patients aged <50 years were initially randomized to receive 3 g/m² at that schedule before the high-dose arm was redefined to 2 g/m² because of toxicity concerns) or standard-dose cytarabine (200 mg/m² daily for 7 days); patients in both treatment arms also received daunorubicin (45 mg/m² daily for 3 days). Patients treated in the HiDAC 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 HiDAC plus daunorubicin. The CR rates were similar, with 55% for the high-dose arm compared with 58% for the standard-dose arm for patients aged <50 years, and 45% for HiDAC versus 53% for standard-dose therapy for patients 50 to 65 years of age. Disease-free survival (DFS) rate (for patients with a CR) and OS rate (for all patients) at 4 years were not significantly different among treatment arms. Induction therapy with HiDAC was associated with significantly higher rates of treatment-related mortality (14% vs 5% for patients aged <50 years; 20% vs 12% for patients aged 50–64 years; P=.003) and grade 3 or higher neurologic toxicity (8% vs 2% for patients aged <50 years; 5% vs 0.5% for patients aged 50–64 years; P<.0001).[45] For patients aged <50 years, consolidation with HiDAC was associated with similar rates of treatment-related mortality (2% vs 0%) and grade ≥3 neurologic toxicity (2% vs 0%) compared with the standard dose. For the original cohort of patients aged <50 years who received 3 g/m² HiDAC for induction, the rates of treatment-related deaths (10% vs 5%) and grade ≥3 neurologic toxicity (16% vs 2%) were higher than for those who received the standard

dose. Similarly, for patients aged <50 years who received 3 g/m² HiDAC for consolidation, the rates of treatment-related deaths (4% vs 0%) and grade ≥3 neurologic toxicity (16% vs 0%) were higher than for those who received the standard dose.[45]

Younger patients (aged <50 years) who received HiDAC induction and consolidation in the SWOG trial had the highest OS and DFS rates at 4 years (52% and 34%, respectively) compared with those who received standard-dose induction and consolidation (34% and 24%, respectively) or standard induction with high-dose consolidation (23% and 14%, respectively).[45] However, the percentage of patients achieving a CR who did not proceed to consolidation was twice as high in the HiDAC induction arm.[45] The risks for neurotoxicity and renal insufficiency are increased with HiDAC; therefore, both renal and neurologic function should be closely monitored in patients receiving this treatment. In a CALGB trial,[46] the subgroup of patients aged ≤60 years (n=156) who received standard-dose cytarabine-daunorubicin induction therapy and 4 courses of HiDAC consolidation (3 g/m² every 12 hours on days 1, 3, and 5, per course) experienced a 4-year DFS rate of 44%. Among all patients who received consolidation with HiDAC, the rates of treatment-related deaths and serious neurotoxicity were 5% and 12%, respectively.[46]

Because the OS outcomes for the high-dose arm in the SWOG trial consisting of HiDAC induction and 2 cycles of HiDAC consolidation (4-year OS rate of 52% for patients aged <50 years) were comparable to those of the CALGB trial with standard-dose infusional cytarabine induction and 4 cycles of HiDAC consolidation (4-year OS rate of 52% for patients aged ≤60 years), the use of HiDAC in the induction phase outside of a clinical trial remains controversial. A meta-analysis including 22 trials and 5,945 patients with de novo AML younger than 60 years of age showed improved RFS and reduced risk of relapse, particularly in the favorable-risk cytogenetics, for patients receiving HiDAC versus standard chemotherapy.[47] However, toxicity was a limiting factor and emphasis was placed on the importance of future studies to define the populations that would most benefit from HiDAC and to optimize dosing recommendations. 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 HiDAC or for those who will undergo early autologous HCT. Although the remission rates are similar for high- and standard-dose cytarabine, 2 studies have shown more rapid marrow blast clearance after 1 cycle of high-dose therapy and a DFS advantage for patients aged 50 years or younger who received the high-dose therapy.[48] No data are available using more than 60 mg/m² of daunorubicin or 12 mg/m² of idarubicin with HiDAC. With either high- or standard-dose cytarabine-based induction for younger patients, between 20% and 45% of these patients will not enter remission. In a report of 122 patients treated with HiDAC and daunorubicin, the remission rates were strongly influenced by cytogenetics, with CR rates of 87%, 79%, and 62% for favorable-, intermediate-, and poor-risk groups, respectively.[49]

In the MRC AML 15 trial, younger patients with untreated AML (median age, 49 years), were randomized to 2 induction courses of (1) daunorubicin and cytarabine with or without etoposide (ADE; n=1,983), or (2) ADE versus fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida; n=1,268).[50] In consolidation, patients were randomized to amsacrine, cytarabine, etoposide, and then mitoxantrone/cytarabine, or HiDAC (3 g/m²; n=1,445).[50] Patients in the HiDAC arm received 1.5 g/m² in consolidation and were treated with or without a fifth course of cytarabine (n=227). There were no significant differences in the rate of CR between ADE and FLAG-Ida (81% vs 84%, respectively), but FLAG-Ida significantly decreased relapse rates (FLAG-Ida, 38% vs ADE, 55%; $P<.001$).[50] A recent randomized phase III study from the HOVON/SAKK groups compared standard cytarabine/idarubicin induction with or without clofarabine (10 mg/m² on days 1–5) for patients with AML between the ages of 18 to 65 years.[51] Although no difference was seen in the OS and EFS in the group as a whole, there was a decrease in relapse rate counterbalanced by an increased rate of death in remission for the clofarabine arm. A subset analysis showed a significant improvement in OS and EFS for the European LeukemiaNet (ELN) intermediate I group, primarily in patients in the *NPM1* wild-type/*FLT3*-ITD–negative subgroup, with a 4-year EFS of 40% for the clofarabine arm versus 18% for the control arm.[51]

NCCN Recommendations

The NCCN AML Panel strongly encourages enrollment in a clinical trial for treatment induction of patients aged <60 years with AML. For patients not enrolled in a clinical trial, cytogenetics and the risk status of the disease guide treatment strategies (see AML-8, page 723). For patients with favorable-, intermediate- and poor-risk cytogenetics, infusional standard-dose cytarabine (100–200 mg/m² continuous infusion) for 7 days combined with either idarubicin (12 mg/m² for 3 days) or daunorubicin (60–90 mg/m² for 3 days) is a category 1 recommendation.[17] For patients with intermediate-risk AML, midostaurin and GO are added to standard-dose cytarabine (200 mg/m² continuous infusion) for 7 days combined with daunorubicin (60 mg/m² for 3 days) for patients with *FLT3*- and CD33-positive AML, respectively, as category 2A recommendations.[26,32]

Patients with antecedent hematologic disease or t-AML are considered poor-risk, unless they have favorable cytogenetics such as t(8;21), inv(16), or t(16;16).

In addition, patients with unfavorable karyotypes, such as 11q23 abnormalities, monosomy -5 or -7, monosomal karyotype, or complex cytogenetic abnormalities and mutations including *RUNX1*, *ASXL1*, and *TP53*, are also considered to have poor risk. Although all patients with AML are best managed within the context of an appropriate clinical trial, it is particularly important that this poor-risk group of patients should be entered into a clinical trial (incorporating either chemotherapy or novel agents), if available, given that only 40%–50% of these patients experience a CR (approximately 25% in older adult patients with poor-risk cytogenetics) with standard induction therapy. In addition, HLA testing should be performed promptly in those who may be candidates for either fully ablative or reduced-intensity conditioning (RIC) allogeneic HCT from a matched sibling or an alternative donor, which constitutes the best option for long-term disease control.[52] For younger patients (aged <60 years) with t-AML other than CBF/APL, antecedent MDS/ chronic myelomonocytic leukemia (CMML), and cytogenetic changes consistent with MDS (AML-MRC), CPX-351 [daunorubicin (44 mg/m^2) and cytarabine (100 mg/m^2)] as an intravenous infusion over 90 minutes on days 1, 3, and 5 of 1 cycle is a category 2B recommendation (see AML-8, page 723), because the trial did not include this patient population.[40]

Other recommended regimens for intermediate- or poor-risk disease include standard-dose cytarabine (200 mg/m^2 continuous infusion for 7 days) combined with daunorubicin (60 mg/m^2 for 3 days) and cladribine (5 mg/m^2 for 5 days) as a category 2A recommendation.[41] HiDAC plus an anthracycline as induction therapy is a category 1 recommendation for patients 45 years of age or younger, though it remains a category 2B recommendation for other age groups.[42,43,45,48] The study from Willemze et al[42] that demonstrated improved OS for patients between the ages of 15 and 45 years treated on this regimen was integral in the change of the recommendation to category 1 for this age group. Fludarabine (30 mg/m^2 IV for days 2–6) plus HiDAC (2 g/m^2) over 4 hours starting 4 hours after fludarabine in combination with idarubicin (8 mg/m^2 IV days 4–6) and granulocyte colony-stimulating factor (SC daily on days 1–7) is a category 2B recommendation.[50] For patients with impaired cardiac function, other cytarabine-based regimens combined with noncardiotoxic agents can be considered.

Postinduction Therapy

After Standard-Dose Cytarabine Induction

To judge the efficacy of the induction therapy, a bone marrow aspirate and biopsy should be performed 14 to 21 days after start of therapy (see AML-9, page 724). In patients who have received standard-dose cytarabine induction and have significant residual disease without hypoplasia (defined as cellularity less than 20% of which the residual blasts are less than 5% [ie, blast percentage of residual cellularity]), additional therapy with standard-dose cytarabine and anthracycline or escalation to HiDAC (1.5–3 g/m^2 every 12 hours for 6 days) may be considered for reinduction; no data are available to determine superiority of standard-dose cytarabine or HiDAC. After a bone marrow biopsy on day 21, standard-dose cytarabine with anthracycline and midostaurin should be considered for patients with *FLT3*-mutation–positive AML.[32] If dual-drug liposomal encapsulation of daunorubicin and cytarabine was given during induction, after a bone marrow biopsy on day 14, reinduction with CPX-351 [daunorubicin (44 mg/m^2) and cytarabine (100 mg/m^2)] as an intravenous infusion over 90 minutes on days 1 and 3 is recommended for patients with t-AML other than CBF/APL, antecedent MDS/CMML, or AML-MRC.[40] Treatments for induction failure may also be considered.

For patients with significant (>50%) cytoreduction and a low percentage of residual blasts (as defined previously; see AML-9, page 724), standard-dose cytarabine with idarubicin or daunorubicin, or standard-dose cytarabine with daunorubicin and midostaurin for patients with *FLT3* mutant AML is recommended. For patients who have residual blasts after induction with standard-dose cytarabine combined with daunorubicin and cladribine, a second cycle of the same induction regimen may be administered if >50% cytoreduction is observed. If daunorubicin (90 mg/m^2) was used in induction, the recommended dose for reinduction of daunorubicin prior to count recovery is 45 mg/m^2 for no more than 2 doses. Similarly, if idarubicin (12 mg/m^2) was used for induction, the early reinduction dose should be limited to 10 mg/m^2 for 1 or 2 doses. If the marrow is hypoplastic, additional treatment selection is deferred until the remission status can be assessed.

If hypoplasia status is unclear, a repeat bone marrow biopsy should be considered 5 to 7 days before proceeding with post induction therapy. For patients who achieve CR with the additional postinduction therapy, consolidation therapy can be started on count recovery. Screening LP should be considered at first remission before first consolidation for patients with monocytic differentiation, MPAL, WBC count >40,000/mcL at diagnosis, or extramedullary disease.

Patients who have persistent disease after 2 courses of therapy (including a reinduction attempt based on midcycle marrow) are considered to have primary induction failure. Treatment options include clinical trial or use of salvage chemotherapy regimens used for relapsed/refractory (R/R) disease. However, the likelihood of achieving a CR with a third chemotherapy regimen is low, at approximately 20%. If the patient did not receive HiDAC for persistent disease at day 15,

HiDAC with or without anthracycline may be used if a clinical trial is not available and a donor is not yet identified. If the patient has an identified sibling or alternative donor available, a transplant option should be explored. For patients whose clinical condition has deteriorated such that active treatment is not an option, best supportive care should be continued.

After High-Dose Cytarabine Induction

Patients initially treated with HiDAC and who have significant residual disease without a hypocellular marrow 21 to 28 days after start of therapy are considered to have experienced induction failure (see AML-10, page 725). In the ELN Guidelines, primary induction failure is defined as failure to achieve CR after 2 courses of intensive induction chemotherapy.[14] Additional HiDAC therapy at this time is unlikely to induce remission in these cases. These patients should be considered for a clinical trial or salvage regimens used for R/R disease. If an HLA-matched sibling or alternative donor has been identified, an allogeneic HCT may be effective in 25%–30% of patients with induction failure. If no donor is immediately available, patients should be considered for a clinical trial. If the patient's clinical condition has deteriorated to a point at which active therapy would be detrimental, best supportive care may be the most appropriate option. If the patient has a significant cytoreduction after HiDAC, with a small quantity of residual blasts or hypoplasia, additional therapy should be delayed for an additional 10 to 14 days and the marrow status may be reassessed.

Occasionally, patients with both myeloid and lymphoid markers at diagnosis may experience response to acute lymphoblastic leukemia therapy if an AML induction regimen failed.[53] 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 a CR or primary induction failure.

Postremission or Consolidation Therapy

Although successful induction therapy clears the visible signs of leukemia in the marrow and restores normal hematopoiesis in patients with de novo AML, additional postremission therapy (ie, consolidation) may be needed to reduce the residual abnormal cells to a level that can be contained by immune surveillance. For patients <60 years of age, postremission therapy is also based on risk status defined by cytogenetics and molecular abnormalities (see AML-11, page 726).

High-Dose Cytarabine

Since 1994, multiple (3–4) cycles of HiDAC 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.[46] The 4-year DFS rate for patients receiving consolidation with 3 g/m^2 of HiDAC was 44%, with a 5% treatment-related mortality rate and a 12% incidence of severe neurologic toxicity. Although the initial report did not break down remission duration by cytogenetic groups, subsequent analysis showed a 5-year RFS (continuous CR measured from time of randomization) rate of 50% for CBF AML, 32% for patients with normal karyotype AML (NK-AML), and 15% for patients in other cytogenetic categories (overall $P<.001$). Among the patients who received HiDAC consolidation, the 5-year RFS rate was 78% for CBF AML, 40% for NK-AML, and 21% for other cytogenetic categories.[49]

In some studies, in patients with CBF AML who received postremission therapy with HiDAC, the presence of *KIT* mutations resulted in poorer outcomes, particularly in t(8;21).[54,55] In a multicenter study, patients with CBF AML (n=67) were enrolled in intensive chemotherapy protocols that involved HiDAC postremission therapy.[54] At 24 months, a *KIT* mutation in the TKD at codon 816 (TKD^{816}) in patients with t(8;21) was associated with a significantly higher incidence of relapse (90% vs 35.3%, $P=.002$) and lower OS (25% vs 76.5%, $P=.006$) compared with patients with wild-type KIT.[54] In CBF AML with inv(16), TKD^{816} did not result in a significant difference in relapse incidence and OS.[54] The prognostic influence of other KIT mutations on CBF AML, including mutations on exon 17 (mut*KIT17*) and exon 8 (mut*KIT8*), have been investigated.[55,56] In an analysis of patients with CBF AML treated on CALGB trials (n=110), *KIT* mutations (mut*KIT17* and mut*KIT8*) among patients with inv(16) were associated with a higher cumulative incidence of relapse at 5 years (56% vs 29%; $P=.05$) and a decreased 5-year OS rate (48% vs 68%) compared with wild-type *KIT*; in multivariate analysis, the presence of *KIT* mutations remained a significant predictor of decreased OS in the subgroup with inv(16). In patients with t(8;21), *KIT* mutations were associated with a higher incidence of relapse at 5 years (70% vs 36%: $P=.017$), but no difference was observed in 5-year OS (42% vs 48%).[55] The CALGB trial also included 4 courses of intensive maintenance chemotherapy after the consolidation phase; however, not all patients in remission received maintenance (55% of patients in CR) after HiDAC consolidation.[46] Subsequent clinical trials have eliminated maintenance during postremission therapy. However, the impact of *KIT* mutations in CBF AML is unclear. A meta-analysis of 11 studies examining the effect of *KIT* mutations on CR, OS, and relapse rates of CBF AML determined that

KIT mutations did not affect CR rates.[57] In patients with t(8;21) AML, *KIT* mutations were associated with an increased risk of relapse and shorter OS rates compared with inv(16) AML.[57]

A prospective study analyzed the effect of a condensed HiDAC consolidation therapy schedule given on days 1, 2, and 3 versus the commonly used schedule of days 1, 3, and 5 in adult patients (aged 18–60 years) with AML (n=176), and found that there was no cumulative hematologic toxicity and no change in survival.[58]

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 HiDAC as part of an induction/consolidation regimen in a phase III randomized study in patients (aged 18–60 years) with newly diagnosed AML (n=860).[59] Patients were randomized to treatment with an "intermediate-dose" cytarabine regimen (12 g/m^2 cytarabine; cycle 1: cytarabine, 200 mg/m^2 daily for 7 days + idarubicin, 12 mg/m^2 daily for 3 days; cycle 2: cytarabine, 1 g/m^2 every 12 hours for 6 days + amsacrine, 120 mg/m^2 daily for 3 days) or a "high-dose" cytarabine regimen (26 g/m^2 cytarabine; cycle 1: cytarabine, 1 g/m^2 every 12 hours for 5 days + idarubicin, 12 mg/m^2 daily for 3 days; cycle 2: cytarabine, 2 g/m^2 every 12 hours for 4 days + amsacrine, 120 mg/m^2 daily for 3 days). Patients who experienced a CR after both treatment cycles were eligible to receive consolidation with a third cycle of chemotherapy or autologous or allogeneic HCT.[59] A similar proportion of patients in each treatment arm received consolidation, specifically 26%–27% of third chemotherapy cycle patients, 10%–11% of autologous HCT patients, and 27%–29% of allogeneic HCT patients. 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%).[59] These results are comparable to those from the CALGB study with HiDAC.[46] 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).[59] Outcomes were poor for patients with monosomal karyotype at baseline (n=83), although the high-dose regimen was associated with significantly improved rates of 5-year EFS (13% vs 0%; *P*=.02) and OS (16% vs 0%; *P*=.02) compared with patients in this subgroup receiving the intermediate-dose. The incidence of grade 3 or 4 toxicities after cycle 1 was higher in the high-dose arm than in the intermediate-dose arm (61% vs 51%; *P*=.005), but the incidence of 30-day mortality was the same in both arms (10%).[59] This study suggests that 2 cycles of intermediate-dose cytarabine (1 g/m^2 every 12 hours for 6 days; total dose 12 g/m^2 per cycle) for each consolidation cycle may be a feasible alternative to 3 cycles of HiDAC (3 g/m^2 for 6 doses; total dose of 18 g/m^2 per cycle). This study and the MRC AML 15 study[50] suggest that doses of 3 g/m^2 of cytarabine are not clearly more effective than lower doses of 1.5–3 g/m^2; in the MRC AML 15 trial, the cumulative incidence of relapse was statistically lower for higher dose cytarabine but this did not translate into better RFS.[50]

Allogeneic Hematopoietic Transplantation

In the EORTC/GIMEMA trial, a 43% 4-year DFS rate was reported in the donor group of patients with poor-risk cytogenetics (n=64; 73% underwent HCT); this was significantly higher than the 4-year DFS rate (18%; *P*=.008) among the no-donor group (n=94; 46% underwent HCT).[60] The 4-year DFS rate among patients with intermediate-risk AML was 45% for the donor group (n=61; 75% underwent HCT) and 48.5% for the no-donor group (n=104; 62.5% underwent HCT).[60] The incidence of relapse was 35% and 47%, respectively, and the incidence of death in CR was 20% and 5%, respectively. The 4-year OS rate among intermediate-risk patients was 53% for the donor group and 54% for the no-donor group.[60]

The SWOG/ECOG trial reported a 5-year survival rate (from time of CR) of 44% with allogeneic HCT (n=18; 61% underwent HCT) and 13% with autologous HCT (n=20; 50% underwent HCT) among the subgroup of patients with unfavorable cytogenetics. Moreover, the 5-year survival rate was similar between those allocated to autologous HCT and those intended for chemotherapy consolidation alone (13% and 15%, respectively).[61] The 5-year survival rates (from time of CR) for patients with intermediate-risk cytogenetics were 52% for the allogeneic HCT group (n=47; 66% underwent HCT) and 36% for the autologous HCT group (n=37; 59% underwent HCT).[61]

In the UK MRC AML 10 trial, significant benefit with allogeneic HCT was observed for the subgroup of patients with intermediate-risk cytogenetics (but not for those with favorable or high-risk cytogenetics). In this subgroup, the DFS (50% vs 39%; *P*=.004) and OS rates (55% vs 44%; *P*=.02) were significantly higher among the donor groups than the no-donor groups.[62]

During the past decade, "normal" cytogenetics have been shown to encompass several molecular abnormalities with divergent risk behaviors.[63] The presence of an isolated *NPM1* or biallelic *CEBPA* mutation improves prognosis to one only slightly less than that of patients with CBF translocations, placing these patients in the favorable-risk molecular abnormalities category.[63] In contrast, patients with an isolated *FLT3*-ITD mutation and NK-AML have an outlook similar to those with poor-risk cytogenetics.[64] In a report that evaluated the ELN risk classification in a large cohort of patients, for

those in the "intermediate I" risk group (which includes all patients with NK-AML with *FLT3* abnormalities and those lacking both *FLT3* and *NPM1* mutations), RFS was more favorable with allogeneic HCT (94 vs 7.9 months without allogeneic HCT).[65]

NCCN Recommendations

CBF Cytogenetic Translocations Without KIT Mutation

The NCCN AML Panel recommends the following options for consolidation therapy in this subgroup: (1) participation in a clinical trial; (2) 3 to 4 cycles of HiDAC (category 1); or (3) intermediate-dose cytarabine (1,000 mg/m^2) plus daunorubicin and GO for patients with CD33-positive AML (category 2A).[26] Insufficient data are available to evaluate the use of allogeneic HCT in first remission for patients with AML and favorable-risk cytogenetics outside of a clinical trial.[66] Data suggest that the response to treatment is similar regardless of whether the favorable-risk cytogenetics are de novo and treatment-related.[66] However, outcomes for patients with t(8;21) with *KIT* mutations are less favorable. These patients should be considered for either clinical trials targeted toward the molecular abnormality, or allogeneic transplantation.

Intermediate-risk Cytogenetics and/or Molecular Abnormalities

The panel members agreed that transplant-based options (either matched sibling or alternate donor allogeneic HCT) or 3 to 4 cycles of HiDAC afforded a lower risk of relapse and a somewhat higher DFS when given as consolidation for patients with intermediate-risk cytogenetics. While 2 to 3 g/m^2 HiDAC is preferred, a range of 1 to <2 g/m^2 can be used to accommodate patients who are less fit. The role of autologous HCT in the intermediate-risk group outside of clinical trials is diminishing due to improvements in allogeneic transplants, which are expanding the pool of potential donors outside the family setting. Although autologous HCT is still incorporated into the clinical trial design in Europe, the consensus of the NCCN AML Panel was that autologous HCT should not be a recommended consolidation therapy outside the setting of a clinical trial. Clinical trial participation is encouraged. Other options for this group include multiple courses (3–4) of HiDAC consolidation.[67] HiDAC (1.5–3 g/m^2) with midostaurin may also be considered for patients with *FLT3*-mutation–positive AML.[68] Alternative regimens incorporating intermediate doses of cytarabine (1.5 g/m^2) may be reasonable in patients with intermediate-risk disease, including intermediate-dose cytarabine (1,000 mg/m^2) plus daunorubicin and GO for patients with CD33-positive AML.[26] However, the panel notes that intermediate-risk patients who receive a transplant shortly after GO administration may be at risk for developing veno-occlusive disease. Comparable 5-year DFS rates were reported in patients younger than 60 years with NK-AML after either 4 cycles of intermediate-dose cytarabine or HiDAC (41%) or autologous HCT (45%).[67] At this time, there is no evidence that HiDAC (2–3 g/m^2) is superior to intermediate-dose (1.5 g/m^2) cytarabine in patients with intermediate-risk AML.

Treatment-Related Disease Other than CBF and/or Unfavorable Cytogenetics and/or Molecular Abnormalities

The panel strongly recommends clinical trials as standard therapy for patients with poor prognostic features, which include *FLT3*-ITD abnormalities in the setting of otherwise NK-AML, high WBC (>50,000/mcL) at diagnosis, or adverse cytogenetics/molecular markers as well as secondary and therapy related AML. If remission is observed, consolidation therapy is recommended, and strong consideration should be given to allogeneic HCT with matched sibling or alternative donor (including umbilical cord blood products) as part of consolidation strategy. HiDAC-based consolidation may be required to maintain remission while searching for a potential matched donor. If CPX-351 was given during induction, an additional treatment of CPX-351 [daunorubicin (29 mg/m^2) and cytarabine (65 mg/m^2)] as an intravenous infusion over 90 minutes on days 1 and 3 for 1 cycle is recommended for patients with therapy-related AML other than CBF/APL, antecedent MDS/ CMML, or AML-MRC.[40]

Management of AML in Patients Older Than 60 Years

Induction Therapy

The creation of separate guidelines for patients aged >60 years recognizes the poor outcomes in this group treated with standard cytarabine and an anthracycline. Although studies in the Swedish Acute Leukemia Registry documented improvement in outcomes for patients aged <60 years over the past 3 decades, no similar improvement was seen for patients aged >60 years.[69,70] Treatment-related mortality frequently exceeds any expected transient response in this group, particularly in patients aged >75 years or who have significant comorbid conditions or an ECOG performance status >2.

For patients aged >60 years with AML, the panel recommends using patient performance status, in addition to adverse features (eg, de novo AML without favorable cytogenetics or molecular markers; t-AML; antecedent hematologic disorder) and comorbid conditions, to select treatment options rather than rely on a patient's chronologic age alone. Comprehensive geriatric assessments are complementary to assessment of comorbid conditions and are emerging as better

predictive tools of functional status.[71,72] A treatment decision-making algorithm for previously untreated, medically fit, elderly patients aged ≥60 years with AML was developed by the German AML cooperative group. Based on data from a large study in elderly patients (n=1,406), patient and disease factors significantly associated with CR and/or early death were identified and risk scores were developed based on multivariate regression analysis.[73] The predictive model was subsequently validated in an independent cohort of elderly patients (n=801) treated with 2 courses of induction therapy with cytarabine and daunorubicin. The algorithm, with or without knowledge of cytogenetic or molecular risk factors, predicts the probability of achieving a CR and the risk for an early death for elderly patients with untreated AML who are medically fit and therefore considered eligible for standard treatments.[73] The factors included in the algorithm are the following: body temperature (≤38°C and >38°C), hemoglobin levels (≤10.3 and >10.3 g/dL), platelet counts (≤28K, >28K–≤53K, >53K–≤104K, and >104K counts/mcL), fibrinogen levels (≤150 and >150 mg/dL), age at diagnosis (60–64, >64–67, >67–72, and >72 years), and type of leukemia (de novo and secondary). The algorithm can be accessed online at http://www.aml-score.org/.

A comprehensive predictive model for early death after induction in patients with newly diagnosed AML suggests that age may be a reflection of other covariants, and the evaluation of these factors may provide a more accurate predictive model. The model includes performance score, age, platelet count, serum albumin, presence or absence of secondary AML, WBC count, peripheral blood blast percentage, and serum creatinine. These factors, when taken together, result in a predictive accuracy based on the area under the curve (AUC) of 0.82 (a perfect correlation is an AUC of 1.0).[74] This model is complex, and currently there is not a tool available to implement this model. A shortened form of the model was based on covariants that include age, performance status, and platelet count. The simplified model provides an AUC of 0.71, which is less accurate than the complex model but may be more accurate than decision-making strategies based solely on age.[74] In a retrospective cohort study of adult patients with AML (n=1,100; range, 20–89 years), a composite predictive model examined the impact of comorbidities on 1-year mortality after induction treatment.[75] This analysis incorporated patient-specific (ie, age, comorbidities) and AML-specific (ie, cytogenetic and molecular risks) features, and resulted in a predictive estimate of 0.76 based on AUC.[75] This model can be accessed online at http://www.amlcompositemodel.org/.

Older adults with intact functional status (ie, ECOG score 0–2), minimal comorbidity, and de novo AML without unfavorable cytogenetics or molecular markers, without antecedent hematologic disorder, and without therapy-related AML may benefit from intensive cytarabine-based therapy regardless of chronologic age.

Candidate for Intensive Remission Induction Therapy

Favorable- or Intermediate-Risk Cytogenetics

Cytarabine and Anthracycline

A reasonable treatment regimen for patients with favorable or intermediate risk cytogenetics includes standard-dose cytarabine (100–200 mg/m^2 by continuous infusion per day for 7 days) along with 3 days of anthracycline. Although patients aged >75 years with significant comorbidities generally do not benefit from conventional chemotherapy treatment, the rare patient with favorable-risk or NK-AML and no significant comorbidities might be the exception to this dogma. For patients with NK-AML, the remission rates are 40%–50% with cytarabine combined with idarubicin, daunorubicin, or mitoxantrone. The randomized study from the Acute Leukemia French Association (ALFA)-9801 study (n=468) showed that idarubicin induction (the standard 12 mg/m^2 daily for 3 days or intensified with 12 mg/m^2 daily for 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).[19] The median OS for all patients was 17 months. The estimated 2-year EFS and OS rates were 23.5% and 38%, respectively, and the estimated 4-year EFS and OS rates were 18% and 26.5%, respectively; however, no significant differences were seen between treatment arms with regard to EFS, OS, and cumulative relapse rates.[19]

The ALFA-9803 study (n=416) evaluated (during first randomization) induction with idarubicin (9 mg/m^2 daily for 4 days) compared with daunorubicin (45 mg/m^2 daily for 4 days) in patients aged 65 years or older.[76] In this trial, the CR rate after induction was 57% and induction death occurred in 10% of patients. The median OS for all patients was 12 months; the estimated 2-year OS rate was 27%. No significant differences in these outcomes were seen between anthracycline treatment arms.[76] Long-term outcomes based on a combined analysis of data from the 2 ALFA trials (9801 and 9803 studies; n=727) showed superior results with standard idarubicin induction (36 mg/m^2 total dose) compared with daunorubicin induction (240 mg/m^2 total dose for patients <65 years; 180 mg/m^2 total dose for patients ≥65 years) in older patients with AML (age ≥50 years).[77] At a median actuarial follow-up of 7.5 years, the median OS for all patients included in the analysis was 14.2 months. The estimated 5-year OS rate was 15.3%, and the overall cure rate was 13.3%. Induction with standard idarubicin

was associated with a significantly higher cure rate compared with daunorubicin (16.6% vs 9.8%; *P*=.018). In the group of patients younger than age 65 years, standard idarubicin was still associated with a significantly higher cure rate than daunorubicin despite the high dose (240 mg/m^2 total dose) of daunorubicin (27.4% vs 15.9%; *P*=.049).[77]

In the HOVON trial, which randomized patients aged ≥60 years to induction therapy with standard-dose cytarabine combined with either standard-dose daunorubicin (45 mg/m^2 daily for 3 days; n=411) or dose-escalated daunorubicin (90 mg/m^2 daily for 3 days; n=402), the CR rate was 54% and 64%, respectively (*P*=.002).[78] 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 daily for 3 days) from the ALFA-9801 study, in which the 4-year EFS and OS rates were 21% and 32%, respectively.[19] In the HOVON trial, the benefit in OS outcomes for the dose-escalated daunorubicin group was observed only in patients aged ≤65 years or in those with CBF translocations.[78]

For patients who exceed anthracycline dose or have cardiac issues but are still able to receive intensive therapy, alternative non–anthracycline-containing regimens, including clofarabine, may be considered.[79–83]

CD33-Positive AML

There are conflicting data about the use of GO for older patients with AML. Three phase III randomized trials evaluated the efficacy and safety of adding the anti-CD33 antibody-drug conjugate GO to induction therapy with daunorubicin and cytarabine in older patients with previously untreated AML.[84–86] In the phase III ALFA-0701 trial, patients aged 50 to 70 years with de novo AML (n=280) were randomized to receive induction with daunorubicin (60 mg/m^2 daily for 3 days) and cytarabine (200 mg/m^2 continuous infusion for 7 days), with or without (control arm) fractionated GO 3 mg/m^2 given on days 1, 4, and 7.[86] Patients with persistent marrow blasts at day 15 received additional daunorubicin and cytarabine. Patients with a CR/CR with incomplete recovery of peripheral blood counts (CRi) after induction received 2 consolidation courses with daunorubicin and cytarabine, with or without GO (3 mg/m^2 on day 1). The CR/CRi after induction was similar between the GO and control arms (81% vs 75%). The GO arm was associated with significantly higher estimated 2-year EFS (41% vs 17%; *P*=.0003), RFS (50% vs 23%; *P*=.0003), and OS (53% vs 42%; *P*=.0368) rates compared with control.[86] The GO arm was associated with a higher incidence of hematologic toxicity (16% vs 3%; *P*<.0001); this was not associated with an increase in the risk of death from toxicity.[86]

In another multicenter, phase III, randomized trial from the United Kingdom and Denmark (AML-16 trial), patients older than 50 years with previously untreated AML or high-risk MDS (n=1,115) were randomized to receive daunorubicin-based induction (daunorubicin combined with cytarabine or clofarabine) with or without (control) GO (3 mg/m^2 on day 1 of course 1 of induction).[85] The median age was 67 years (range, 51–84 years) and 98% of patients were aged ≥60 years; 31% were aged ≥70 years. The CR/CRi rate after induction was similar between the GO and control arms (70% vs 68%). The GO arm was associated with significantly lower 3-year cumulative incidence of relapse (68% vs 76%; *P*=.007) and higher 3-year RFS (21% vs 16%; *P*=.04) and OS (25% vs 20%; *P*=.05) rates compared with the control arm. The early mortality rates were not different between treatment arms (30-day mortality rate, 9% vs 8%); in addition, no major increase in adverse events was seen with GO.[85] These 2 trials suggest that the addition of GO to standard induction regimens reduced the risk of relapse and improved OS outcomes in older patients with previously untreated AML characterized by favorable or intermediate-risk cytogenetics, not adverse risk.

The third phase III trial combining GO with chemotherapy showed a different result than the other two. In this study, patients between the ages of 61 and 75 years were given chemotherapy consisting of mitoxantrone, cytarabine, and etoposide (n=472).[84] Half of the patients were given 6 mg/m^2 GO prior to chemotherapy on days 1 and 15. In remission, treatment included two courses of consolidation with or without 3 mg/m^2 GO on day 0. The OS between the two groups was similar (GO, 45% vs no GO, 49%), but the induction and 60-day mortality rates were higher in the patients given GO (17% vs 12% and 22% vs 18%, respectively). Only a small subgroup of patients younger than 70 years of age with secondary AML showed any benefit to treatment. Combined with the increased toxicity, the results of this study suggest that GO may not provide an advantage over standard chemotherapy for some older patients with AML.[84]

Conflicting studies have led to the publication of several systematic reviews and meta-analyses. A larger systematic review, inclusive of any RCTs that investigated the benefit of anti-CD33 antibody therapy, regardless of whether treatment was in de novo or secondary disease, concluded that the data from 11 trials showed increased induction deaths (*P*=.02) and reduced residual disease (*P*=.0009).[87] Despite improved RFS (HR, 0.90; 95% CI,

0.84–0.98; *P*=.01), no OS benefit was measured (HR, 0.96; 95% CI, 0.90–1.02; *P*=.2). Two other meta-analyses showed improved RFS, though induction death was elevated.[88,89] Conversely, a fourth meta-analysis evaluating 5 trials with 3,325 patients aged 15 years and older showed a reduced risk of relapse (*P*=.0001) and improved 5-year OS (OR, 0.90; 95% CI, 0.82–0.98; *P*=.01) with the addition of GO to conventional induction therapy.[27] It was noted that the greatest survival benefit was seen in patients with favorable cytogenetics. Some benefit was seen in patients with intermediate cytogenetics, but no benefit was reported with the addition of GO in patients with adverse cytogenetics. These studies underscore the need for further investigation that elucidates the benefits of GO for the treatment of AML.

FLT3-Positive AML

The results of the CALGB 10603/RATIFY Alliance trial[32] have been described in an earlier section (See "Management of AML in Patients Younger Than 60 Years; Intermediate-Risk Cytogenetics," page 727) and these data may be extrapolated to suggest benefit in fit older adults. In a phase II study in adult patients with previously untreated AML (n=284; range, 18–70 years; 86 older patients included [age range, 61–70 years]), the efficacy and safety of midostaurin added to intensive chemotherapy, followed by allogeneic HCT and single-agent midostaurin maintenance therapy for a year was evaluated.[90] All patients were confirmed to have *FLT3*-ITD-positive disease. The CR/CRi rate after induction therapy was 76.4% (age <60 years, 75.8%; age >60 years, 77.9%). Many patients proceeded to transplant (72.4%), and a subset started maintenance therapy (n=97; 75 after allogeneic HCT and 22 after HiDAC consolidation). The median time receiving maintenance therapy was 9 months after allogeneic HCT and 10.5 months after HiDAC consolidation. The 2-year EFS and OS rates were 39% and 34% in patients <60 years, and 53% and 46% in patients >60 years.[90]

Therapy-Related AML or Antecedent MDS/CMML or AML-MRC

The studies evaluating the efficacy and safety of CPX-351 in patients aged 60–75 years with newly diagnosed secondary AML have been described ("Management of AML in Patients Younger Than 60 Years," page 725; "Therapy-Related AML or Antecedent MDS/Chronic Myelomonocytic Leukemia or AML-MRC," page 728).[40]

Unfavorable-Risk Cytogenetics (Exclusive of AML-MRC)

Hypomethylating Agents

An international, randomized, phase III study by Fenaux et al[91] compared the hypomethylating agent (HMA) 5-azacitidine with conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy) in patients with MDS (n=358). Although this study was designed for evaluation of treatment in patients with high-risk MDS (based on FAB criteria), 113 study patients (32%) fulfilled criteria for AML using the 2008 WHO classification, with marrow-blast percentages between 20% and 30%.[91,92] In the subgroup of these patients with AML, a significant survival benefit was found with 5-azacitidine compared with conventional care regimens, with a median OS of 24.5 months versus 16 months (HR, 0.47; 95% CI, 0.28–0.79; *P*=.005).[92] The 2-year OS rates were 50% and 16%, respectively (*P*=.001). In a phase III study focused on older adult patients (aged ≥65 years), the efficacy and safety of azacitidine versus conventional care regimens (standard induction chemotherapy, low-dose cytarabine, or supportive care) was evaluated in patients with newly diagnosed AML with >30% blasts.[93] Compared with conventional care regimens, azacitidine was associated with an increase in median OS (6.5 months vs10.4 months; HR, 0.85; 95% CI, 0.69–1.03; stratified log-rank *P*=.1009).[93] The 1-year survival rates with azacitidine and conventional care regimens were 46.5% and 34.2%, respectively.

Another HMA, decitabine, has also been evaluated as remission induction therapy for older patients with AML.[94] In a phase II study in previously untreated patients aged ≥60 years (n=55; median age, 74 years), the overall CR rate with this agent (20 mg/m^2 for 5 days every 28 days) was 24% (including 6 of 25 patients [24%] with poor-risk cytogenetics), and the median EFS and OS were 6 and 8 months, respectively.[94] An earlier phase I study evaluated different dose schedules of decitabine in patients with R/R leukemias (n=50; AML diagnosis, n=37).[95] In this study, decitabine was given at 5, 10, 15, or 20 mg/m^2 for 5 days per week for 2 to 4 consecutive weeks (ie, 10, 15, or 20 days). The decitabine dose of 15 mg/m^2 for 10 days (n=17) was associated with the highest response rates, with an overall response rate (ORR) of 65% and CR rate of 35%. Among the patients with R/R AML (n=37), the ORR was 22% with a CR in 14% across all dose levels.[95] A phase II study targeting patients aged ≥60 years with AML who were not candidates for or refused intensive therapy, administered a decitabine dose of 20 mg/m^2 for 10 days and demonstrated CR rate of 47% (n=25) after a median of three cycles of therapy.[96] In a study aimed at identifying the relationship between molecular markers and clinical responses to decitabine, adult patients with AML and MDS (n=116; median age, 74 years; range, 29–88 years) were treated with decitabine (20 mg/m^2 for 10 days every 28 days).[97] Response rates were higher among patients with unfavorable-risk cytogenetics compared with patients with favorable- or intermediate-risk

(67% vs 34%, respectively; $P<.001$), and among patients with *TP53* mutations compared with patients with wild-type *TP53* (100% vs 41%; $P<.001$).[97] A recent phase II study comparing a 5-day versus 10-day treatment schedule for decitabine in older patients aged ≥60 years (n=71) with newly diagnosed AML determined that the efficacy and safety of both schedules were not significantly different.[98]

In an open-label randomized phase III study, decitabine (20 mg/m^2 for 5 days every 28 days) was compared with physician's choice (either low-dose cytarabine or supportive care) in older patients aged ≥65 years with newly diagnosed AML.[99] Based on the protocol-specified final analysis of the primary endpoint (OS), decitabine was associated with a statistically nonsignificant trend for increased median OS compared with physician's choice (7.7 months vs 5 months; HR, 0.85; 95% CI, 0.69–1.04; $P=.108$). A subsequent post hoc analysis of OS with additional follow-up time showed the same median OS with a statistically significant advantage associated with decitabine (HR, 0.82; 95% CI, 0.68–0.99; $P=.037$). The CR (including CRi) rate was significantly higher with decitabine (18% vs 8%; $P=.001$).[99] The most common treatment-related adverse events with decitabine versus cytarabine included thrombocytopenia (27% vs 26%), neutropenia (24% vs 15%), febrile neutropenia (21% vs 15%), and anemia (21% vs 20%). The 30-day mortality rates were similar between the decitabine and cytarabine groups (9% vs 8%).[99] Both azacitidine and decitabine are approved by the FDA for the treatment of patients with MDS.

Venetoclax-Containing Regimens

Emerging studies have evaluated the combination of HMAs with venetoclax, an oral B-cell lymphoma 2 (*BCL2*) inhibitor, as an induction therapy strategy for older patients with AML. In a phase Ib study, older patients aged ≥65 years with previously untreated AML (n=57) were enrolled into 3 groups: group A (n=23) received venetoclax and decitabine (20 mg/m^2 daily for 5 days of each 28-day cycle); group B (n=22) received venetoclax and azacitidine (75 mg/m^2 daily for 7 days of each 28-day cycle); and group C, a substudy of venetoclax and decitabine (n=12), received an oral CYP3A inhibitor, posaconazole, to determine its effect on the pharmacokinetics of venetoclax.[100] Daily target doses for venetoclax in different cohorts within groups A and B were 400 mg, 800 mg, and 1200 mg. The most common treatment-related adverse event in groups A and B was febrile neutropenia (30% and 32%, respectively), with an overall CR/CRi rate of 61% (95% CI, 47.6–74.0).[100] In groups A and B, the CR/CRi rate was 60% (95% CI, 44.3–74.3).[100]

In a follow-up to this study, the efficacy of either 400 mg or 800 mg of venetoclax combined with either decitabine or azacitidine was evaluated in older patients aged ≥65 years with previously untreated AML and who were ineligible for intensive chemotherapy (n=145; median age, 74 years).[101] The venetoclax dose of 400 mg was found to be the recommended phase II dose. With a median time on study of 8.9 months (range, 0.2–31.7 months) and median duration of follow-up of 15.1 months (range, 9.8–31.7 months), 67% of patients achieved CR/CRi.[101] The median duration of CR/CRi and median OS was 11.3 months and 17.5 months, respectively.[101] In a subgroup analysis, the CR/CRi rates of patients with intermediate- and poor-risk cytogenetics were 74% and 60%, with a median duration of 12.9 months (95% CI, 11.0 months–NR) vs 6.7 months (95% CI, 4.1–9.4 months), respectively.[101] The CR/CRi rates in patients with *TP53*, *IDH1/2* and *FLT3* mutations were 47%, 71% and 72%, respectively. In addition, patients with de novo AML and secondary AML, respectively, had the same CR/CRi rate of 67%, with a median duration of CR/CRi of 9.4 months (95% CI, 7.2–11.7 months) versus NR (95% CI, 12.5 months–NR).[101]

Another phase Ib/II study evaluated the efficacy of venetoclax combined with low-dose cytarabine (20 mg/m^2 daily for 10 days) in older patients aged ≥60 years with previously untreated AML ineligible for intensive chemotherapy (n=82; median age, 74 years).[102] All patients received at least one dose of venetoclax at 600 mg. The CR/CRi rate was 54% (95% CI, 42%–65%) with a median duration of remission of 8.1 months (95% CI, 5.3–14.9 months), and the median OS for all patients was 10.1 months (95% CI, 5.7–14.2 months).[102] Patients with de novo AML, intermediate-risk cytogenetic features, and no prior HMA exposure showed CR/CRi rates of 71%, 63%, and 62%, respectively.[102] The average CR/CRi rates in patients with *NPM1* or *IDH1/2* mutations was higher than those with *TP53* or *FLT3* mutations (89% and 72% vs 30% and 44%, respectively).[102] Based on these studies, venetoclax in combination with HMAs, decitabine or azacitidine, or low-dose cytarabine are approved by the FDA for the treatment of newly diagnosed AML in older adults aged ≥75 years, or in patients who have comorbidities that preclude use of intensive induction chemotherapy.

Not a Candidate for or Declines Intensive Remission Induction Therapy

AML Without Actionable Mutations

In older adult patients who cannot tolerate intensive treatment strategies, low-intensity approaches have been investigated (see AML-13, page 728), including use of HMAs alone or combined with venetoclax (see "Candidate for Intensive Remission Induction

Therapy," page 737; "Hypomethylating Agents," page 739; and "Venetoclax-Containing Regimens," page 740).

Low-Dose Cytarabine-Containing Regimens

Other approaches have evaluated low-dose cytarabine. The UK NCRI AML 14 trial randomized 217 older patients, primarily aged >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).[103] Patients were also randomized to receive all-trans retinoic acid (ATRA) or no ATRA. Low-dose cytarabine resulted in a CR rate of 18% (vs 1% with hydroxyurea) and a survival benefit compared with hydroxyurea in patients with favorable or NK-AML. No advantage was seen with the addition of ATRA. The median DFS in patients who attained a CR with low-dose cytarabine was 8 months.[103] Even with this "low-intensity" treatment approach, induction death occurred in 26% of patients, and overall prognosis remained poor for older patients who cannot tolerate intensive chemotherapy regimens. A phase II study evaluated a regimen with low-dose cytarabine (20 mg twice daily for 10 days) combined with clofarabine (20 mg/m^2 daily for 5 days) in patients aged ≥60 years with previously untreated AML (n=60; median age, 70 years; range, 60–81 years).[104] Patients with a response received consolidation (up to 17 courses) with clofarabine plus low-dose cytarabine alternated with decitabine. Among evaluable patients (n=59), the CR rate was 58% and median RFS was 14 months. The median OS for all patients was 12.7 months. The induction mortality rate was 7% at 8 weeks.[104] Although this regimen appeared to be active in older patients with AML, the authors noted that the benefits of prolonged consolidation remain unknown.

In a phase II trial, low-dose cytarabine was combined with glasdegib, a selective inhibitor of the smoothened protein in the Hedgehog signaling pathway, and evaluated in adult patients (age ≥55 years) with previously untreated AML or high-risk MDS ineligible for intensive chemotherapy (n=132).[105] Criteria for unsuitability for intensive chemotherapy included ≥75 years of age, serum creatinine >1.3 mg/dL, severe cardiac disease or ECOG score =2. Patients were randomized 2:1 to receive low-dose cytarabine alone (20 mg twice daily for 10 days every 28 days) or combined with oral glasdegib (100 mg daily). The addition of glasdegib to low-dose cytarabine also improved OS compared with low-dose cytarabine alone (8.8 vs 4.9 months, respectively), and the CR rates were higher in the low-dose cytarabine and glasdegib arm (17%, n=15/88) compared with low-dose cytarabine alone (2.3%; n=1/44).[105] In the glasdegib plus low-dose cytarabine arm, the benefit in CR was primarily seen in patients with favorable-/intermediate-risk cytogenetics (n=10/52) when compared with patients with poor risk cytogenetics (n=5/36).[105] Glasdegib in combination with low-dose cytarabine is currently approved by the FDA for the treatment of newly diagnosed AML in older adults aged ≥75 years, or in patients who have comorbidities that preclude use of intensive induction chemotherapy.

CD33-Positive AML

Single-agent GO has also been evaluated as an option. A randomized phase III study evaluated the efficacy of single-agent GO (6 mg/m^2 on day 1 and 3 mg/m^2 on day 8) versus best supportive care as first-line therapy in older patients aged ≥61 years with AML who were not eligible for intensive chemotherapy (n=237).[106] Compared with best supportive care, GO alone improved the 1-year OS rate (9.7% vs 24.3%, respectively). In the GO group, the median OS was 4.9 months (95% CI, 4.2–6.8 months) and 3.6 months (95% CI, 2.6–4.2 months) in the best supportive care group.[106]

Androgen-Containing Regimens

Emerging data are exploring the use of lower-intensity maintenance therapies to prolong remission duration and improve survival of elderly patients with AML after intensive treatment.[107] A multicenter, phase III randomized study investigated the survival benefit of adding androgens to maintenance therapy in patients with AML aged ≥60 years (n=330).[108] In this study, induction therapy included cytarabine (100 mg/m^2 on days 1–7), idarubicin (8 mg/m^2 on days 1–5), and lomustine (200 mg/m^2 on day 1). Patients in complete remission or partial remission (n=247) were treated with 6 reinduction courses, alternating idarubicin on day 1, cytarabine on days 1 to 5, and a regimen of methotrexate and mercaptopurine, and randomized to receive androgen (norethandrolone; 10 or 20 mg/day), according to body weight, or not for a 2-year maintenance therapy regimen. Compared with the arm that received no androgens, norethandrolone improved 5-year DFS (31.2% vs 16.2%, respectively), EFS (21.5% vs 12.9%, respectively), and OS (26.3% vs 17.2%, respectively).[108]

IDH Mutation-Positive AML

Initially approved by the FDA for use in the R/R AML setting, *IDH*-targeted inhibitors, enasidenib and ivosidenib, have demonstrated utility in the frontline setting.[109,110] In a phase I/II study, the clinical activity and safety of enasidenib, an *IDH2* mutant inhibitor, was evaluated in adult patients with *IDH2*-mutated advanced AML including R/R disease.[111] Approximately 19% of patients (n=34 of 176) with R/R AML attained

complete remission, with an OS of 19.7 months with a median OS of 9.3 months.[111] In older patients aged ≥60 years with newly diagnosed AML, the efficacy of enasidenib was evaluated in a phase Ib/II substudy within the Beat AML trial.[110] Patients were treated with enasidenib (100 mg/day) in continuous 28-day cycles. Azacitidine (75 mg/m^2 days 1–7) was added to enasidenib for some patients who did not achieve CR/CRi by cycle 5. Of 23 evaluable patients receiving enasidenib monotherapy, CR/CRi was achieved in 43% of patients (7 CR/2 CRi).[110]

Ivosidenib, an *IDH1*-mutation inhibitor, demonstrated durable remissions in *IDH1* R/R AML, with 30.2% of patients (n=54 of 179) with R/R AML achieving CR/CRh.[112] As an extension of this study, the safety and efficacy of ivosidenib in patients with untreated AML was evaluated (n=34; median age, 76.5 years).[109] In phase I dose-escalation and expansion, patients received ivosidenib once a day or twice daily in 28-day cycles, and a dose of 500 mg per day was selected as the dose for expansion groups. The CR/CRh rate was 41.2% (95% CI, 24.6%–59.3%), and the ORR was 58.8% (20/34; 95% CI, 40.7%–75.4%).[109] Based on these data, ivosidenib was approved by the FDA in May 2019 as a first-line treatment option for AML with an *IDH1* mutation in patients who are aged ≥75 years or who have comorbidities that preclude the use of intensive induction chemotherapy. Treatment with both enasidenib and ivosidenib may induce differentiation syndrome and hyperleukocytosis, which may be managed with corticosteroids and hydroxyurea.[113–115]

Alternatively, emerging data suggest that patients with de novo AML characterized by *IDH1/2* mutant AML may benefit from venetoclax/HMA based therapy with reported remission rates of greater than 70%, albeit in a relatively small number of patients.[101]

FLT3-Positive AML

In a phase II study, the efficacy of azacitidine and sorafenib, an *FLT3* inhibitor, was evaluated in adult patients with R/R AML (n=43; median age, 67 years; range, 24–87 months).[116] The response rate was 46%, with CR, CR/CRi, and PR rates of 16%, 27%, and 3%, respectively.[116] In addition, the degree of *FLT3*-ITD inhibition appeared to correlate with plasma sorafenib concentrations. In adult patients with newly diagnosed *FLT3*-mutation positive AML (n=15; median age, 76 years; range, 65–86 years), an ongoing trial is evaluating the safety and tolerability of the combination of azacitidine and gilteritinib,[117] a *FLT3* inhibitor that has demonstrated antileukemic activity in *FLT3*-positive R/R AML.[118] Of 15 evaluable patients, a CR/CRi rate of 67% was observed.[117]

NCCN Recommendations

Similar to recommendations for adults aged <60 years, the NCCN AML Panel encourages enrollment in a clinical trial for treatment induction of older patients aged ≥60 years with AML. For patients not enrolled in a clinical trial, cytogenetics, overall functional status, and the presence or absence of actionable mutations should guide treatment strategies.

Candidate for Intensive Remission Induction Therapy

Standard infusional cytarabine and anthracycline is recommended. For patients who exceed anthracycline dose guidelines or have cardiac issues but who are still fit enough to receive aggressive therapy, alternative non-anthracycline–containing regimens may be considered. Gemtuzumab ozogamicin may be added to standard-dose cytarabine combined with daunorubicin for patients with CD33-positive AML and who have favorable- or intermediate-risk cytogenetics. Midostaurin is added to standard-dose cytarabine combined with daunorubicin for patients with *FLT3*-mutated AML and who have intermediate-risk cytogenetics. For patients with t-AML, antecedent hematologic disorder, or AML-MRC, treatment options include CPX-351 [daunorubicin (44 mg/m^2) and cytarabine (100 mg/m^2)] as an intravenous infusion over 90 minutes on days 1, 3, and 5 of 1 cycle (a category 1 recommendation) or standard infusional cytarabine and anthracycline (see AML-12, page 727).

For patients with unfavorable-risk cytogenetics exclusive of AML-MRC, recommended options include venetoclax combined with azacitidine, decitabine or low-dose cytarabine, lower-intensity therapy with HMAs (azacitidine or decitabine), or standard infusional cytarabine and anthracycline.

Not a Candidate for or Declines Intensive Remission Induction Therapy

Treatment options include a clinical trial or lower-intensity therapy based on the presence or absence of actionable mutations. These regimens include venetoclax combined with chemotherapy (azacitidine, decitabine or low-dose cytarabine (LDAC)), or glasdegib combined with LDAC. Patients not considered candidates for combination or targeted therapy may receive monotherapy with HMA (azacitidine or decitabine either 5 or 10 day; preferred), GO, or LDAC alone. Best supportive care with hydroxyurea and transfusion support should also be considered and has been used as the comparator arm in several clinical trials in older unfit patients.

For patients with *IDH1* or *IDH2* mutant AML, ivosidenib or enasidenib, respectively, or HMAs alone are recommended. For patients with *FLT3*-mutant AML, HMAs alone or in combination with sorafenib are recommended (see AML-13, page 728).

Postinduction Therapy

After Standard-Dose Cytarabine Induction

Similar to younger patients, older patients who receive standard cytarabine/anthracycline induction with or without midostaurin or GO, or a dual-drug encapsulation of daunorubicin and cytarabine, receive a bone marrow evaluation 14 to 21 days after start of therapy and are categorized according to the presence of blasts or hypoplasia (see AML-14, page 729). Patients with hypoplasia should await recovery of counts before continuing to postremission therapy. Patients with residual disease without hypoplasia may receive additional standard-dose cytarabine with an anthracycline or mitoxantrone, or CPX-351 [daunorubicin (44 mg/m^2) and cytarabine (100 mg/m^2)] if given during induction for patients with t-AML, antecedent hematologic disorder, or AML-MRC. Alternatively, patients with *FLT3*-mutation–positive AML may receive additional standard-dose cytarabine with daunorubicin and midostaurin.

If daunorubicin (90 mg/m^2) was used in induction, the recommended dose for reinduction prior to count recovery is 45 mg/m^2 for no more than 2 doses. Similarly, if idarubicin (12 mg/m^2) was used for induction, the early reinduction dose should be limited to 10 mg/m^2 for 1 or 2 doses. Intermediate-dose cytarabine-containing regimens, RIC allogeneic HCT, and best supportive care are also treatment options. Reduced-intensity transplant is a reasonable option, preferably in the context of a clinical trial, in patients with low-level residual disease postinduction. In addition, it is recommended that identified donors are available to start conditioning within 4 to 6 weeks from start of induction therapy. Patients without an identified donor would most likely need some additional therapy as a bridge to transplant. Additionally, it is acceptable to await recovery in these patients as many will enter remission without further treatment. Regardless of treatment, all patients receiving postinduction therapy after standard-dose cytarabine should have a repeat bone marrow evaluation to document remission status. Because many older patients have some evidence of antecedent myelodysplasia, full normalization of peripheral blood counts often does not occur even if therapy clears the marrow blasts. Thus, many phase I/II trials for AML in the older patient include categories such as CRi for patients who have fewer than 5% marrow blasts but mild residual cytopenias.

Many 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 azacitidine) or increase apoptosis (eg, histone deacetylase inhibitors). Thus, success in these trials may be assessed using indirect measures such as hematologic improvement or decreased transfusion requirements and survival without actually achieving CR. Frequently, in these trials, marrow examination is not performed until completion of 1 to 2 cycles of therapy. However, the NCCN Guidelines do not currently recommend postinduction HMAs.

Postremission or Consolidation Therapy

Patients who attain a CR (including CRi) with standard induction chemotherapy may receive further consolidation with these same agents (see AML-15, page 730).

Standard/Intermediate-Dose Cytarabine

The French ALFA 98 trial randomized patients aged ≥65 years who achieved remission (n=164; randomized for postremission therapy) to consolidation with either 1 additional course of standard-dose cytarabine (200 mg/m^2 daily for 7 days) plus the anthracycline to which they had been randomized for induction (idarubicin, 9 mg/m^2 daily for 4 days or daunorubicin, 45 mg/m^2 daily for 4 days) or 6 monthly courses of anthracycline (1 day only) at the previously noted doses and 60 mg/m^2 of cytarabine every 12 hours as a subcutaneous infusion at home for 5 days each month.[76] 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 difference was observed in the cumulative relapse rate between arms.[76] 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 daily for 4–6 doses) without an anthracycline.

Allogeneic Hematopoietic Transplantation

The role of myeloablative allogeneic HCT is limited in older patients because of significant comorbidities; however, ongoing interest has been shown in RIC allogeneic HCT as consolidation therapy.[119,120] Case series and analysis of registry data have reported encouraging results, with 40%–60% 2-year OS rates and 20% nonrelapse mortality for patients who underwent transplant in remission.[119,120] In a retrospective analysis comparing outcomes with RIC allogeneic HCT and autologous HCT in patients aged 50 years and older based on large registry data, RIC allogeneic HCT was associated with lower risk for relapse and superior DFS and OS relative to autologous HCT.[119] The authors also

noted that a survival benefit was not observed in the subgroup of patients undergoing RIC allogeneic HCT in first CR because of an increased incidence of nonrelapse mortality.

Estey et al[121] prospectively evaluated a protocol in which patients aged ≥50 years with unfavorable cytogenetics would be evaluated for a RIC allogeneic HCT.[121] Of the 259 initial patients, 99 experienced a CR and were therefore eligible for HCT evaluation. Of these patients, only 14 ultimately underwent transplantation because of illness, lack of donor, refusal, or unspecified reasons. The authors compared the results of RIC allogeneic HCT with those from matched subjects receiving conventional-dose chemotherapy. This analysis suggested that RIC allogeneic HCT was associated with improved RFS, and the authors concluded that this approach remains of interest.[121] In an analysis of outcomes between 2 different strategies for matched-sibling allogeneic HCT, outcomes in younger patients aged ≤50 years (n=35) receiving conventional myeloablative allogeneic HCT were compared with those in older patients aged >50 years (n=39) receiving RIC allogeneic HCT.[122] This study showed similar rates of 4-year nonrelapse mortality (19% and 20%, respectively), and no difference was seen in relapse and OS rates.[122]

A retrospective study based on data in older patients (range, 50–70 years) with AML compared outcomes in patients who underwent allogeneic HCT (either myeloablative conditioning or RIC; n=152) and those who did not receive HCT in first CR (chemotherapy only; n=884).[123] Allogeneic HCT in first CR was associated with a significantly lower 3-year cumulative relapse rate (22% vs 62%; $P<.001$) and a higher 3-year RFS rate (56% vs 29%; $P<.001$) compared with the non-HCT group. Although HCT was associated with a significantly higher rate of nonrelapse mortality (21% vs 3%; $P<.001$), the 3-year OS rate showed a survival benefit with HCT (62% vs 51%; $P=.012$).[123] Among the patients who underwent allogeneic HCT, myeloablative conditioning was used in 37% of patients, whereas RIC was used in 61%. Survival outcomes between these groups were similar, with 3-year OS rates of 63% and 61%, respectively.[123]

Another study evaluating treatment in older patients (range, 60–70 years) compared outcomes between RIC allogeneic HCT reported to the Center for International Blood and Marrow Transplant Research (n=94) and standard chemotherapy induction and postremission therapy from the CALGB studies (n=96).[124] Allogeneic HCT 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 HCT was associated with a significantly higher rate of nonrelapse mortality (36% vs 4%; $P<.001$) at 3 years; the 3-year OS rate was not significantly different between the groups (37% vs 25%; $P=.08$), although there was a trend favoring allogeneic HCT.[124] A prospective multicenter phase II study examined the efficacy of RIC allogeneic HCT in older patients (range, 60–74 years) with AML in first CR (n=114).[125] After allogeneic HCT, DFS and OS at 2 years were 42% (95% CI, 33%–52%) and 48% (95% CI, 39%–58%), respectively, for the entire group.[125] A time-dependent analysis of 4 successive prospective HOVON-SAKK AML trials examined data from patients aged ≥60 years who obtained a first CR after induction chemotherapy (n=640).[126] For patients who received allogeneic HCT as postremission therapy (n=97), a 5-year OS rate was 35% (95% CI, 25%–44%).[126]

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

NCCN Recommendations

Previous Intensive Therapy

For patients who had previously received intensive therapy, a marrow to document remission status on hematologic recovery should be performed after 4 to 6 weeks (see AML-15, page 730). If a CR is observed, a clinical trial is recommended. Other recommendations include allogeneic HCT; standard-dose cytarabine with or without an anthracycline, and GO for CD33-positive AML; intermediate-dose cytarabine (for patients who are more fit); intermediate-dose cytarabine and midostaurin for patients with *FLT3*-mutation–positive AML[32]; or CPX-351 [daunorubicin (29 mg/m^2) and cytarabine (65 mg/m^2)], if given during induction for patients with t-AML, antecedent hematologic disorder, or AML-MRC. If the patient received HMAs in induction, maintenance therapy with HMAs or observation may be appropriate. Observation is recommended, as some patients have been able to maintain a CR without further treatment.

For patients in induction failure, a clinical trial, low-intensity therapy (azacitidine, decitabine), allogeneic HCT (preferably in the context of a clinical trial), or best supportive care are recommended treatment options.

Previous Lower Intensity Therapy

For patients who previously received lower-intensity therapy, a marrow to document remission status on hematologic recovery should be performed after 8 to 12 weeks (see AML-16, page 731). If a response is seen, allogeneic HCT may be considered for select patients. Alternatively, low-dose therapies may be continued until progression, including venetoclax plus HMAs; venetoclax plus LDAC; enasidenib (for *IDH2*-mutated AML); ivosidenib (for *IDH1*-mutated AML); glasdegib plus LDAC; or HMAs alone or combined with sorafenib (for *FLT3*-mutant AML). If no response or progression is seen, a clinical trial, therapies for R/R AML, or best supportive care are recommended treatment options.

Summary of Principles of AML Treatment

Current management of AML is divided into induction chemotherapy and postremission (eg, consolidation) therapy. The induction strategy is influenced by individual patient characteristics such as age, cytogenetics, molecular genetics, presence of comorbid conditions affecting performance status, and preexisting hematologic disorder (MDS, myeloproliferative disorder), and prior cytotoxic or radiation therapy. Although obtaining remission is the first step in controlling the disease, it is also important for patients to emerge from the induction phase in a condition to tolerate subsequent, more intensive treatments during consolidation to achieve durable disease control and/or allogeneic stem cell transplantation. Strategies for postremission are based on cytogenetics, molecular genetics, and potential risk of relapse, with higher-risk patients receiving therapy that is more aggressive, including allogeneic stem cell transplantation. The role of measurable/minimal residual disease detection in AML is currently under active investigation. Consistent with NCCN philosophy, participation in clinical trials is always strongly encouraged.

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