Risk Stratification and Management of Acute Myeloid Leukemia

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Author's disclosures of potential conflicts of interest are found on page 4 and at the end of this article.

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Abstract

Acute myeloid leukemia (AML), a heterogeneous group of distinct clonal malignancies, accounts for 80% of acute leukemias in adults. The incidence of AML among US adults is increasing, particularly in those older than 60. Risk factors for AML include inherited genetic predisposition syndromes, congenital factors, and antecedent hematologic disorders. Acute myeloid leukemia is classified according to morphology, immunohistochemistry, cell surface markers, and cytogenetic and molecular abnormalities. The most important prognostic factors are cytogenetic/molecular characteristics of the AML, patient age, and patient performance status. Treatment depends on disease characteristics, patient comorbidities, and age. The goal of induction chemotherapy is to achieve a complete response; postinduction therapy is given to reduce the risk of relapse. Autologous or allogeneic hematopoietic cell transplantation for remission consolidation is an option for some patients. Prognosis is poor for patients more than 60 years of age, and newer approaches, such as the use of hypomethylating agents, are being investigated to improve outcomes in this age group. New therapies, including arsenic trioxide, are also being studied for acute promyelocytic leukemia, a subtype of AML. Supportive therapy, including blood products and antimicrobial, antiviral, and antifungal agents, is a main component of AML treatment.

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Acute myeloid leukemia (AML) is a heterogeneous group of distinct clonal malignancies that differ in their pathogenesis, clinical characteristics, genetic abnormalities, response to treatment, and prognosis (Swerdlow et al., 2008). Acute myeloid leukemia is characterized by a clonal proliferation of myeloid precursors with reduced or absent capacity for differentiation, as well as according to morphology, immunohistochemistry, cell surface markers, cytogenetic abnormalities, and molecular abnormalities. The most important prognostic factors have been shown to be cytogenetic/molecular characteristics of the AML, patient age, and patient performance status (Kantarjian, Schiffer, & Burnett, 2011).

Epidemiology

Acute myeloid leukemia is a relatively rare cancer. The median age at presentation for adults in the United States is 65 years (Jemal, Siegel, Xu, &

Ward, 2010). Acute myeloid leukemia accounts for 15% to 20% of acute leukemias in children but 80% of acute leukemias in adults. The incidence of adult AML is increasing, particularly in the older population (age > 60 years), with a reported incidence of approximately 17.6 cases per 100,000 for those > 65 years vs. 1.8 per 100,000 for those < 65 years old (Kuendgen & Germing, 2009; Applebaum et al., 2006).

As with many cancers, the etiology and risk factors for AML are poorly understood. We do know, however, that some risk factors can increase the risk of developing AML, including inherited genetic predisposition syndromes such as Li-Fraumeni syndrome and familial platelet disorder; congenital factors such as trisomy 21 and Klinefelter's syndrome (XXY); and the presence of antecedent hematologic disorders such as myelodysplastic syndromes, myeloproliferative diseases, aplastic anemia, and chronic myeloid leukemia in blast crisis (Swerdlow et al., 2008).

Classification and Prognosis

Two major classification systems exist for AML. The first is the French-American-British (FAB) system (Bennett et al., 1976), which consists of eight major categories based on morphology. It distinguishes different subtypes of AML based on precursor cells and stage of differentiation (Table 1). The second and more recent classification system is that of the World Health Organization (WHO), most recently updated in 2008; it is currently the preferred, accepted classification system. The WHO system now includes cytogenetic abnormalities and molecular detection of mutations to differentiate diagnosis and establishes the diagnosis of AML at a minimal blast count of 20%, which is lower than the previous threshold of 30% in the FAB system (Table 2) (Swerdlow et al., 2008).

Laboratory Characteristics

Laboratory features of AML include anemia, thrombocytopenia, and coagulation abnormalities. Myeloblasts are almost always present in the blood of a patient with AML (Swerdlow et al., 2008). Hyperleukocytosis, or a white blood cell count > 50,000, is a life-threatening laboratory feature, especially seen in acute promyelocytic leukemia (APL) and AML with monocytic differentiation. It is associated clinically with shortness of breath and cognitive impairment.

Cytogenetic and Molecular Characteristics

Cytogenetics/karyotype analysis is a key component when evaluating patients with AML. Specific cytogenetic abnormalities in AML have prognostic significance and influence treatment

Table 1. French-American-British Classification System for Acute Myeloid Leukemia

Stage	Definition
M0, myelogenous	Undifferentiated blasts, AML not otherwise categorized
M1, myelogenous	Blasts and promyelocytes predominate without further maturation of myelogenous cells
M2, myelogenous	Myelogenous cells demonstrate maturation beyond the blast and promyelocyte stage
M3, promyelocytic	Promyelocytes predominate in the bone marrow
M4, myelomonocytic	Both myelogenous and monocytic cells are present to the extent of at least 20% of the total leukocytes
M5, monocytic	Most cells are monocytic; two subtypes are recognized, one by large blasts in bone marrow and peripheral blood, the other (differentiated type) by monoblasts, promonocytes, and monocytes
M6, erythroleukemia	Known also as DiGuglielmo syndrome; abnormal proliferation of both erythroid and granulocytic precursors; may include abnormal megakaryocytic and monocytic proliferation
M7, megakaryocytic	Large and small megakaryoblasts with a high nuclear-cytoplasmic ratio; pale, agranular cytoplasm

Note. AML = acute myeloid leukemia. Adapted from Bennett et al. (1976).

Table 2. World Health Organization Classification System for Acute Myeloid Leukemia

Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- APL with t(15;17)(q22;q12); *PML-RARA*
- AML with t(9;11)(p22;q23); *MLLT3-MLL*
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- *Provisional entity: AML with mutated NPM1*
- *Provisional entity: AML with mutated CEBPA*

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukemia, NOS
- Acute myeloid leukemia with minimal differentiation
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemia
  - Pure erythroid leukemia
  - Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis (syn: acute myelofibrosis, acute myelosclerosis)

Myeloid sarcoma (syn: extramedullary myeloid tumor, granulocytic sarcoma, chloroma)

Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis (syn: transient myeloproliferative disorder)
- Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Acute leukemias of ambiguous lineage
- Acute undifferentiated leukemia
- Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*
- Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
- Mixed phenotype acute leukemia, B/myeloid, NOS
- Mixed phenotype acute leukemia, T/myeloid, NOS
- *Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma*

Note. AML = acute myeloid leukemia; APL = acute promyelocytic leukemia; NOS = not otherwise specified. Adapted, with permission, from S. H. Swerdlow et al. (2008).

planning. Dombret and Gardin (2009) have proposed four genetic groups of AML: favorable, intermediate I, intermediate II, and adverse (Table 3). Patients with favorable cytogenetics, that is, core binding factor karyotypes t(8:21), t(15:17), and inv(16), have been shown to have superior survival outcomes compared with those with the normal karyotype (Foran, 2010). Furthermore, patients with the normal karyotype have repeatedly been shown to have superior survival compared with those with adverse cytogenetic abnormalities, such as deletion 5 or 7, deletion 5q, abnormal 3q, and complex karyotype (three or more abnormalities) (Foran, 2010).

Although patients with cytogenetically normal AML are included in the intermediate-risk group

Table 3. Four Proposed Genetic Groups of Acute Myeloid Leukemia

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Mutated *CEBPA* (normal karyotype)
Intermediate I	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate II	t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *MLL* rearranged -5 or del(5q); -7; abnl(17p); complex karyotype

Note. Adapted, with permission, from Dombret & Gardin (2009).

category, more sophisticated analyses, including gene mutation, suggest that this group is more heterogeneous than previously thought. There is an increasing list of AML molecular features (*FLT3, NPM1, CEBPα*) that can predict treatment outcome and are being used to direct postinduction therapy. These molecular features also present a new generation of molecular targets for small-molecule inhibitors (Dombret & Gardin, 2009; Burnett, Wetzler, & Lowenberg, 2011).

Nucleophosmin (*NPM1*) mutations are found in approximately one-third of adult cases of AML, making it the most frequently known mutation in AML (Marcucci, Haferlach, & Dohner, 2011). *NPM1* is a highly conserved phosphoprotein that physiologically resides in nucleoli and shuttles between nucleus and cytoplasm (Schlenk & Dohner, 2009). These mutations are associated with other recurrent genetic changes, most frequently in *FLT3*. The genotype "mutated *NPM1* without concurrent *FLT3* internal tandem duplication (ITD)," which is often found in younger patients, is associated with achievement of complete remission and favorable outcome (Dohner et al., 2010). Standard induction chemotherapy followed by three to four cycles of high-dose cytarabine is recommended for this group (Dohner et al., 2010). Mutated *NPM1* is also favorable in older patients. The impact of this mutation on therapy is that allogeneic hematopoietic cell transplantation (HCT) in first complete remission is not recommended with *NMP1* mut/*FLT3*-ITD neg. *NPM1* is also becoming a marker in minimal residual disease assessment (Schlenk & Dohner, 2009; Büchner et al., 2009).

FLT3 (FMS-like tyrosine kinase 3) mutations are associated with unfavorable, poor-risk AML (Estey, 2010; Santos et al., 2010). *FLT3* is a transmembrane tyrosine kinase receptor that stimulates cell proliferation. It is normally expressed in early bone marrow progenitors, where it plays an important role in hematopoiesis. Mutations in *FLT3* occur in approximately 25% of adults with AML (Santos et al., 2010). The most common mutation is an ITD (Foran, 2010). Patients with the *FLT3*-ITD mutation often have a higher white blood cell count and typically normal cytogenetics. It has been demonstrated that the *FLT3*-ITD mutation is consistently associated with significantly worse survival in younger adults (age < 60 years) but has less prognostic impact among adults > 60 years of age. A number of small-molecule inhibitors of *FLT3* are now available in clinical trials to treat patients with *FLT3*-positive AML, including lestaurtinib (CEP 701), midostaurin (PKC 412), AC 220, tandutinib (MLN 518), sorafenib (Nexavar), and sunitinib (Sutent) (Sanz, Burnett, Lo-Coco, & Lowenberg, 2009).

Another common molecular marker in normal karyotype AML is CCAAT/enhancer-binding protein alpha (CEBPα). *CEBPα* encodes an enhancer binding protein, important in the regulation of myeloid progenitors (Foran, 2010). In the absence of a *FLT3*-ITD, a *CEBPα* mutation confers a significantly better prognosis in normal cytogenetics AML, with approximately 60% long-term survival, particularly if there are two copies of the mutant allele; with monotype *CEBPα*, long-term survival is closer to 40% (Dufour et al., 2010).

Treatment

Therapy for AML consists of chemotherapy; however, the choice of treatment approach depends on disease characteristics, including molecular markers, cytogenetics, and age of the patient. Cytarabine combined with an anthracycline (usually daunorubicin) is the mainstay of induction chemotherapy, usually given as 7 con-

secutive days of cytarabine plus 3 days of daunorubicin (7+3), and is the accepted standard of care for induction (Burnett et al., 2011). The goal of induction chemotherapy is to achieve a complete response (CR). Based on international consensus, CR is defined as bone marrow blasts < 5%, hematologic recovery, and peripheral blood counts in the normal range (Cheson et al., 2003; Swerdlow et al., 2008). Failure to achieve a CR with one or two induction courses suggests a poor prognosis.

Postinduction therapy is given to further reduce the risk of relapse. Table 4 gives recommendations for initial therapy for younger patients with AML based on cytogenetics and molecular markers (Fernandez, 2010). Repetitive courses (usually 2–4) of high-dose cytarabine are better than a single course, but the optimal number is unknown (Burnett et al., 2011). For patients with intermediate-risk AML, there may be a role for autologous stem-cell transplant. In two of four comparative trials, disease-free survival was better in the group that received an autologous stem-cell transplant than in the intensive chemotherapy group because of a reduction in relapse. There was no effect on overall survival (OS), however (Dohner et al., 2010). Allogeneic HCT is potentially indicated for a select subset of patients, such as AML primary induction failure in younger patients with intermediate-risk cytogenetics, or first relapse or CR2 in older adults with intermediate- or high-risk cytogenetics, but it is the preferred therapy for AML in CR1 with poor-risk cytogenetics (Estey, 2010).

The majority of AML patients are > 60 years of age and have a poorer prognosis than AML patients < 60 years. Acute myeloid leukemia in older patients is known to be biologically resistant and to have a complex karyotype, often with trilineage dysplasia (Burnett et al., 2011). There is some bias against treating elderly patients with AML because of concerns about toxicity, comorbid illnesses, and decreased organ function (Bur-

Table 4. Recomended Initial Therapy for Patients ≤ 60 With Acute Myeloid Leukemia

Induction regimen

Anthracycline intensification
First cycle: Daunorubicin 90 mg/m² x 3 days + cytarabine 100 mg/m² x 7 days
Alternatives: Daunorubicin 60 mg/m² x 3 days + cytarabine 100 mg/m² x 7 days
Daunorubicin 80 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days
Idarubicin 12 mg/m² x 3 days + cytarabine 100 mg/m² x 7 days
Second cycle (if necessary): Daunorubicin 45 mg/m² x 3 days + cytarabine 100 mg/m² x 7 days

Consolidation regimen

Favorable risk	**Normal cytogenetics**	**Unfavorable risk cytogenetics or *MLL* positive**
HIDAC consolidation 3–4 cycles HIDAC followed by autologous HCT	***NPMI positive or negative, FLT3 negative*** HIDAC consolidation 3–4 cycles or HIDAC followed by autologous HCT or Matched sibling or unrelated donor allogeneic HCT ***FLT3 positive*** Matched sibling or unrelated donor allogeneic HCT or Clinical trial	Matched sibling or unrelated donor allogeneic HCT or Clinical trial

Treatment of patients with cardiac dysfunction

Induction: HIDAC or FLAG or CLAG or clofarabine
Consolidation: Same induction 2–4 cycles
Reduced-intensity allogeneic HCT (if eligible)

Note. FLAG = fludarabine, cytarabine; CLAG = cladribine, cytarabine; HIDAC = high-dose cytarabine; HCT = hematopoietic cell transplantation; MLL = mixed lineage leukemia. Adapted, with permission, from Fernandez (2010).

nett et al., 2011). Remission rates in the elderly are approximately 50% but often short lived, and OS at 5 years is 10% (Luger, 2010). Developing more active regimens for the elderly, mostly through clinical trials, has been a core goal of the research community; recently, hypomethylating agents have been used (Cashen, Schiller, O'Donnel, & DiPersio, 2010; Kantarjian et al., 2010). Elderly AML patients have become a focus for new drug development. Some elderly patients are not treated with intensive therapy, however, either by choice or because the patient is medically unfit and treatment might curtail survival.

Acute promyelocytic leukemia is a subtype of AML that has the unique cytogenetic abnormality of t(15;17) (q22;q11-12). It was previously considered a highly lethal form of AML but is now the most curable subtype of adult AML. The fusion of the *PML* gene on chromosome 15 with the retinoic acid-receptor alpha (*RARα*) gene from chromosome 17 creates APL. Once a diagnosis of APL is suspected, the disease should be managed as a medical emergency. The diagnosis should be confirmed by molecular detection of the PML-RARα fusion protein. Fluorescence in situ hybridization or immunostaining with anti-*PML* antibody can also be used for rapid diagnosis (Sanz & Lo-Coco, 2011). Three simultaneous actions must be taken when a diagnosis of APL is suspected: (1) start all-*trans*-retinoic acid (tretinoin [Vesanoid]; ATRA) therapy, (2) provide supportive care with plasma and platelet transfusions, and (3) confirm genetic diagnosis.

The PML-RARα fusion protein has a reduced sensitivity to retinoic acid, preventing the terminal differentiation of malignant promyelocytes. This defect can be overcome, however, with the use of ATRA. ATRA therapy accelerates the terminal differentiation of malignant promyelocytes to mature neutrophils, leading to cellular apoptosis and complete remission without myelosuppression (Sanz & Lo-Coco, 2011). ATRA given before chemotherapy has been associated with decreased risk of coagulopathy (Sanz & Lo-Coco, 2011), which is the leading cause of mortality in APL. The standard induction treatment for newly diagnosed APL is the simultaneous administration of ATRA and anthracycline-based chemotherapy (Sanz et al., 2009).

Retinoic acid differentiation syndrome or "ATRA syndrome" is seen in 25% of APL patients between days 2 and 21 of induction (Sanz et al., 2009). The symptoms, including fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, episodic hypotension, renal and hepatic dysfunction, and pleural and pericardial effusions, can be subtle or severe. The mortality rate of this syndrome is approximately 50%. It is more common in patients who have hyperleukocytosis and has been reported in patients with relapsed APL treated with arsenic trioxide (Trisenox; ATO) (Kantarjian et al., 2011; Sanz & Lo-Coco, 2011). It is highly treatable if identified. Treatment includes the following: (1) discontinuation of ATRA or ATO, (2) diuresis as tolerated, and (3) dexamethasone 10 mg IV twice daily for approximately 4 days. ATRA can be reinitiated once the syndrome has resolved (Sanz & Lo-Coco, 2011).

Acute promyelocytic leukemia treatment also includes consolidation therapy after the achievement of remission. There is much discussion regarding optimal consolidation therapy, but the generally accepted practice is to administer two to three cycles of anthracycline-based regimens along with ATRA, followed by a maintenance regimen. The molecular marker PML-RARα allows precise monitoring of residual disease via peripheral blood. Monitoring of PML-RARα every 3 to 6 months for 2 to 3 years is recommended. If the test result is positive, a repeat analysis from the bone marrow is recommended to verify relapse of APL. If relapse occurs, ATO or autologous stem-cell transplant is suggested to achieve remission (Kantarjian et al., 2011).

ATO, a medicinal arsenic that is given intravenously, has had excellent results in treating relapsed APL (Douer & Tallman, 2005; Sanz & Lo-Coco, 2006). Clinical trials are underway to assess ATO in induction and consolidation. ATO degrades the PML-RARα fusion protein and induces apoptosis and differentiation of promyelocytes (Sanz & Lo-Coco, 2011). Therefore, ATO can cause a differentiation syndrome, which presents clinically like ATRA syndrome and is treated as such. When ATO is given, cardiac monitoring is required. It is associated with several electrolyte abnormalities and QT interval prolongation, which can lead to a potentially fatal torsades de pointes–type ventricular arrhythmia (Cephalon, 2010; Sanz & Lo-Coco, 2006). Serum potassium must be maintained above 4.0 mEq/L and serum magnesium above 1.8 mg/dL. Medications known to prolong the QT interval should be discontinued. An electrocardiogram must be done at baseline and monitored twice weekly during therapy.

In patients who reach an absolute QT interval value longer than 500 msec, ATO should be held until the interval is less than 460 msec (Sanz & Lo-Coco, 2006; Cephalon, 2010).

Transfusions of packed red blood cells (PRBCs) along with platelets are a mainstay of supportive therapy for all patients with acute leukemia. In general, transfusion of PRBCs is not based solely on hemoglobin level but also takes into account patient signs and symptoms of hypoxia and cardiopulmonary disease status. All blood products given to patients with AML should be leukocyte-depleted and irradiated to prevent febrile, allergic reactions, graft-vs.-host disease, and transfusion-related acute lung injury (Alter & Klein, 2008; Shaz, Stowell, & Hillyer, 2011).

Patients with AML are immunocompromised hosts and need antimicrobial, antiviral, and antifungal therapy as components of successful antileukemic therapy. The Infectious Diseases Society of America has developed evidence-based guidelines for the care of immunocompromised hosts (Freifeld et al., 2011). In general, early diagnosis and specific treatment of opportunistic infections is the cornerstone of successful therapy for immunocompromised hosts (Freifeld et al., 2011). Fever in the setting of AML and neutropenia can be life-ending and may be the only indication of severe underlying infections because signs and symptoms of inflammation are suppressed. A neutropenic fever will require hospitalization and empirical IV antibiotic therapy. Tests including complete blood count, blood cultures, and chest radiograph are suggested for a neutropenic fever workup. The specifics of antibiotic therapy for neutropenic fever is beyond the scope of this article. Readers should consult the clinical practice guidelines of both the Infectious Diseases Society of America, the NCCN guidelines (NCCN, 2011), and their own institutions.

Summary

The prognostic stratification of patients with AML continues to be refined, with follow-up of known abnormalities and identification of new mutations through sophisticated genomic techniques. Despite this, there has been little change in the overall prognosis for adults with AML in large intergroup trials. New targeted therapies continue to have an impact on subgroups of patients, and newer targeted drugs offer hope of greater impact on survival to come. Supportive care, including blood products and infection control, remains a main component in the treatment of AML.

DISCLOSURES

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