Acute Myeloid Leukemia

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INTRODUCTION

Acute myeloid leukemia (AML), also known as acute nonlymphocytic leukemia, represents a group of clonal hematopoietic stem cell disorders in which both failure to differentiate into mature cells and excessive proliferation in the bone marrow stem cell compartment result in the accumulation of myeloblasts. For over 3 decades, the French-American-British (FAB) classification system has been used to describe the different categories of AML. In 2001, the World Health Organization (WHO) published a new classification system for AML incorporating morphologic, genetic, immunophenotypic, biologic, and clinical features. This system was established in an attempt to more accurately predict the prognosis and biologic properties of the subcategories of AML. Intensive treatment entails remission induction followed by post-remission chemotherapy. For patients who have poor-risk disease or who relapse, this treatment approach may be followed by hematopoietic stem cell transplantation. However, treatment recommendations vary, and factors such as patient age, cytogenetics, performance status, and prognosis must be considered when choosing treatment options. This review will discuss epidemiology, pathogenesis, evaluation, and treatment of patients with AML.

EPIDEMIOLOGY AND PATHOGENESIS

Contrary to the popular impression that AML is a disease of children and young adults, the median age at diagnosis of AML is approximately 67 years in the United States. Prognostic and therapeutic information is determined by whether a patient is considered younger (< 60 yr) or older (≥ 60 yr). AML is the most common leukemia, with approximately 12,000 new diagnoses each year in the United States, and its incidence has increased from 1992 through 1998. It represents 1.2% of all new cancer diagnoses and 1.3% of estimated cancer deaths.

Similar to other malignancies, the pathogenesis of AML involves a combination of environmental insults and genetic predisposition leading to DNA damage or epigenetic changes in affected cells. In AML, the normal process of myeloid stem cell differentiation is interrupted, with a maturation block occurring at a granulocytic cell precursor stage. This transformation can occur either as a de novo event or be associated with previous therapy or an antecedent hematologic disorder. This transformation results in the clonal expansion of an immature precursor blast of myeloid lineage. The malignant myeloblasts are unable to differentiate into mature cells and disrupt normal bone marrow function, leading to impaired hematopoiesis.

What are the known risk factors for AML?

Several risk factors for AML have been identified. Germline mutations in the AML1 gene, chromosomal instability in certain autosomal dominant conditions (eg, Fanconi’s anemia, ataxia telangiectasia, neurofibromatosis, and Bloom syndrome) as well as congenital immunodeficiency disorders (including infantile X-linked agammaglobulinemia and Down syndrome) have been associated with an increased incidence of AML. Environmental exposures have also been implicated. Ionizing radiation and organic solvents such as benzene and other petroleum products have been associated with a higher risk of developing AML. Both RAS mutations and polymorphisms resulting in inactivation of NAD(P)H:quinone oxidoreductase have been found in patients with these exposures.

Other risk factors for AML may involve treatment of hematologic malignancies. Therapy-related AML typically develops following alkylating agent–induced damage at a median of 5 to 7 years following therapy for the primary malignancy. It usually is associated with an antecedent myelodysplastic disorder and abnormalities of chromosomes 5 and 7. DNA-topoisomerase II agents have also been shown to produce gene rearrangements leading to AML, typically involving an 11q23 abnormality (the MLL gene), with a short latency of 12 to 18 months following treatment. Secondary AML may also develop in patients with various hematologic disorders, including aplastic anemia, myelodysplastic
syndromes, myeloproliferative disorders, and severe congenital neutropenia. Other inherited hematologic conditions, such as Bloom syndrome and Fanconi’s anemia, have also been implicated. Finally, the incidence of AML increases with age. In the United States, the median age of patients with AML is 67 years. Age-adjusted population incidence is 17.6 per 100,000 for people aged 65 years or older, as compared with 1.8 per 100,000 for patients younger than age 65 years. Similarly, chromosomal abnormalities occur with greater frequency among this population of patients.

**CLINICAL EVALUATION AND TREATMENT OF AML**

**CASE PRESENTATION**

A previously healthy 47-year-old man presents to his primary care physician with generalized fatigue over several weeks. The patient’s past medical history is notable only for essential hypertension and an episode of acute cholecystitis 10 years ago that required laparoscopic cholecystectomy. He has not undergone any other surgeries. There is no family history of malignancy. He is a retired pesticide sales representative but had no significant exposure to organic chemicals. He lives with his wife of 45 years. He has never smoked and drinks alcohol only socially. Review of systems is negative for recurrent infections, weight loss, night sweats, fevers, bleeding, and dyspnea on exertion.

**Physical Examination and Laboratory Studies**

Other than fatigue, the patient has no other localizing symptoms. He is afebrile. With the exception of mild pallor, the physical examination is unremarkable. Specifically, there is no lymphadenopathy, hepatosplenomegaly, or rash. A complete blood count (CBC) performed reveals a hematocrit of 26% (normal, 41%–50%), platelet count of 48,000 cells/µL (normal, 150–450 cells/µL), and a total white blood cell (WBC) count of 55,000 cells/µL (normal < 10,000 cells/µL). A peripheral blood smear reveals 95% blasts, 4% lymphocytes, and 1% neutrophils.

- **What is a typical presentation for patients with AML?**

  AML often presents with the clinical sequelae attributable to pancytopenia. The deficient production of red blood cells can lead to patient complaints of weakness, fatigue, dyspnea on exertion, and even chest pain. Pallor is a common physical examination finding. Infection can result from insufficient numbers of WBCs or impaired WBC function. Collections of leukemic cells (seen in leukemia cutis, granulocytic sarcomas, or chloromas) also may occur rarely. These collections represent extramedullary sites of disease and may involve cutaneous as well as visceral tissues. In a minority of cases (5%–20%), hyperleukocytosis can lead to ocular or cerebral dysfunction. Low numbers of platelets can lead to petechiae, gingival bleeding, ecchymosis, epistaxis, or menorrhagia. Acute promyelocytic leukemia is a distinct variant of AML that often presents with hemorrhagic complications, including diffuse intravascular coagulation. Palpable lymphadenopathy and hepatosplenomegaly are rare findings in AML. It is typical for patients to complain of flu-like symptoms for 4 to 6 weeks prior to diagnosis.

**CASE CONTINUED**

The patient is admitted to the hospital for diagnostic evaluation of his abnormal blood count. Comprehensive metabolic panel, prothrombin time, and activated partial thromboplastin time are normal. Both the uric acid and lactate dehydrogenase levels are elevated at 8.6 mg/dL (normal, 2.5–8.0 mg/dL) and 378 U/L (normal, 60–100 U/L), respectively. Iron levels and total iron binding capacity are within normal limits, but ferritin is elevated at 472 mg/L (normal, 15–200 mg/L). A repeat CBC performed approximately 18 hours after the patient’s initial CBC test reveals that the WBC count has increased from 55,000 cells/µL to 69,000 cells/µL, with 98% blasts. Staining of peripheral blasts for myeloperoxidase is strongly positive. The patient is diagnosed with AML.

- **When does the diagnosis of AML constitute a medical emergency?**

  In some patients, particularly younger adults and those with higher presenting WBC counts, the diagnosis of AML can constitute a medical emergency, making prompt referral to a medical hematologist/oncologist requisite. Hyperleukocytosis and/or leukostasis can cause impairment of blood flow, most often resulting in central nervous system, cardiac, or pulmonary symptoms. Rapid lowering of the WBC count can be achieved with the institution of cytotoxic chemotherapy, leukapheresis, or low-dose cranial radiation. Central nervous system leukemia is not commonly seen in AML but may present as headache, lethargy, or cranial nerve signs. For these patients, intrathecal chemotherapy or, less commonly,
A double lumen central venous catheter is placed in the femoral vein, and the patient undergoes emergent leukapheresis. Hydroxyurea therapy is initiated at 0.75 g every 6 hours (total daily dose, 3 g). Aggressive intravenous fluid repletion is instituted with a 5% dextrose solution supplemented with 3 ampules of sodium bicarbonate and titrated to maintain a urine output greater than 60 mL/hr. In addition, allopurinol (300 mg/day) is initiated in order to minimize hyperuricemia. The patient undergoes a bone marrow biopsy and aspirate with cytogenetic analysis, flow cytometry measurements, and specific genetic testing (described below) on hospital day 1. Electrolyte, lactate dehydrogenase, and uric acid values are measured every 12 hours during the first several days of hospitalization. On hospital day 3, the patient’s electrolytes normalize and his WBC count stabilizes at approximately 8000 cells/µL. Renal function is preserved, and the patient is clinically stable.

CASE CONTINUED

A complete evaluation of a patient with newly diagnosed AML requires CBC and assessment of renal and hepatic function and electrolyte levels. Surveillance for spontaneous tumor lysis syndrome is essential. In addition, disseminated intravascular coagulation must be evaluated by D-dimer levels, fibrinogen levels, and standard coagulation screening. Baseline cardiac studies including electrocardiogram, chest radiograph, and echocardiogram should be obtained, as therapeutic approaches may involve cardiotoxic anthracycline drugs.

For most patients, the diagnosis of AML requires a bone marrow biopsy and aspirate. Within the aspirate specimen, the identification of at least 20% leukemic blasts confirms the diagnosis of acute leukemia. To determine commitment along the myeloid lineage, immunohistochemical staining for myeloperoxidase is performed, along with flow cytometry to identify myeloid-specific antigens on the myeloblast cell surface. The leukemic clone that gives rise to AML can occur at any point along differentiation of the myeloid cell, creating pathologic heterogeneity among patients. Cytogenetics and fluorescent in situ hybridization (FISH) testing may further differentiate the various AML subtypes. Table 1 shows a list of suggested tests that should be performed in newly diagnosed AML patients.

• What laboratory and imaging studies should be obtained for patients with an initial diagnosis of AML?

A complete evaluation of a patient with newly diagnosed AML requires CBC and assessment of renal and hepatic function and electrolyte levels. Surveillance for spontaneous tumor lysis syndrome is essential. In addition, disseminated intravascular coagulation must be evaluated by D-dimer levels, fibrinogen levels, and standard coagulation screening. Baseline cardiac studies including electrocardiogram, chest radiograph, and echocardiogram should be obtained, as therapeutic approaches may involve cardiotoxic anthracycline drugs.

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• How is AML classified?

The FAB classification system divided AML into 8 subtypes, M0 through M7. In 2001, however, the WHO reclassified AML into 4 categories (Table 2). This change in classification was made (1) to reflect entities with similar biologic features; (2) to incorporate the prognostic and therapeutic importance of cytogenetic distinctions and clinical history of antecedent hematologic disorders or previous treatment with radiation and/or chemotherapy; and (3) to enhance the clinical relevance of the system. In addition to these biologic and clinical features, the system also takes into account the morphologic and immunophenotypic features of the disease entities. The 4 categories include AML with recurrent genetic abnormalities, AML with multilineage dysplasia, AML-therapy related, and AML not otherwise categorized, which roughly correlates with the FAB classification. The WHO classification system also differs from the FAB system in that the previous blast cell threshold of 30% for diagnosis of AML was reduced to 20%, and patients with recurring cytogenetic abnormalities are now classified as AML regardless of blast percentage.

CASE CONTINUED

The patient’s bone marrow examination reveals a relatively hypercellular marrow (60%) with a high preponderance of immature myeloblasts. There is impairment of normal hematopoiesis. Cytogenetic and FISH analyses identify the presence of translocation of portions of chromosome 8 to chromosome 21 (t(8;21)—involving the AML1-ETO genes). Polymerase chain reaction does not reveal the presence of an internal tandem duplication or tyrosine kinase domain mutation in the FMS-like tyrosine kinase 3 (FLT3) gene; however, a common mutation in nucleophosmin (NPM1) gene is detected.

• What is the role of cytogenetics and other genetic testing in the treatment of AML?
A c u t e  M y e l o i d  L e u k e m i a

There are a number of well-described genetic variations that commonly occur in AML that confer important prognostic information. Cytogenetic prognostic risk schemas have been developed by the Medical Research Council, the Cancer and Leukemia Group B (CALGB), and the Southwest Oncology and Eastern Cooperative Oncology Groups (SWOG/ECOG). For instance, AML patients with abnormalities that include t(8;21), inv(16), and t(16;16) (associated with the transcription factor AML1-CBFβ) are placed in a favorable risk group. In contrast, 6% to 8% of AML patients harbor structural alterations of 11q23, leading to MLL rearrangement, which portends a worse outcome. A well-documented chromosomal abnormality in AML is the t(15;17), which results in acute promyelocytic leukemia. In this case, translocation of these chromosomes results in the fusion of the retinoic acid receptor gene alpha on chromosome 15 with the PML gene on chromosome 17, giving rise to a fusion product that prevents differentiation to mature granulocytes. Therapy specific for acute promyelocytic leukemia will be discussed later (see page 7).

Patients can be separated into 3 categories based on response to induction treatment, relapse risk, and overall survival: favorable, intermediate, and adverse cytogenetic groups. Typically, patients with favorable cytogenetic features have core binding factor (CBF) abnormalities, while those with adverse features include complex (≥ 3 abnormalities) cytogenetics or chromosome 7 abnormalities. Some of the more common cytogenetic abnormalities are shown in Table 3 according to their risk category.

More recently, gene-expression profiling has also been shown to improve the molecular classification and outcome prediction in patients with AML. In particular, testing for FLT3 and NPM1 has become increasingly common. The NPM1 gene encodes a nucleolar protein termed nucleophosmin. Wild-type nucleophosmin normally shuttles between the nucleus and cytoplasm, whereas a mutant version commonly found in AML localizes to the cytoplasm. NPM1 is the most commonly mutated gene in AML, occurring in approximately 50% to 60% of cases. Patients who have AML containing mutant NPM1 have a more favorable outcome than those who do not. Recently, the German-Austrian Acute Myeloid Leukemia Study Group published data on the impact of molecular lesions on outcome in 872 adults with cytogenetically normal AML. The investigators found that patients with a mutant CEBPA or NPM1 (without the FLT3 internal tandem duplication) were significantly more likely

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### Table 1. Recommended Laboratory Testing and Imaging for Patients Undergoing Initial Evaluation for Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Test</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>Assess degree of leukocytosis and monitor for anemia, thrombocytopenia</td>
</tr>
<tr>
<td>Comprehensive metabolic panel including phosphorous and uric acid</td>
<td>Evaluate for tumor burden and spontaneous tumor lysis syndrome</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Assess for coagulopathy</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>Assess for coagulopathy</td>
</tr>
<tr>
<td>Screen for diffuse intravascular coagulation including fibrinogen and D-dimer levels</td>
<td>Assess for diffuse intravascular coagulation</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Evaluate for pulmonary congestion secondary to leukostasis</td>
</tr>
<tr>
<td>Cardiac evaluation with electrocardiogram and either echocardiogram or multiple uptake gated acquisition scan</td>
<td>Baseline evaluation prior to administration of potentially cardiotoxic chemotherapy agents (ie, anthracycline drugs)</td>
</tr>
<tr>
<td>Tunned multilumen central venous catheter (eg, Hickman)</td>
<td>Central administration of chemotherapy and reduces frequent phlebotomy</td>
</tr>
<tr>
<td>Bone marrow biopsy/aspirate including:</td>
<td>Essential for the diagnosis of acute myeloid leukemia and subsequent risk stratification and prognosis</td>
</tr>
<tr>
<td>• Flow cytometry</td>
<td></td>
</tr>
<tr>
<td>• Cytogenetics</td>
<td></td>
</tr>
<tr>
<td>• Special studies for FLT3 and NPM1 gene mutations</td>
<td></td>
</tr>
<tr>
<td>• FISH for CBF abnormalities</td>
<td></td>
</tr>
<tr>
<td>HLA typing of patient and available siblings</td>
<td>Indicated prior to administration of induction chemotherapy if allogenic bone marrow transplant is to be considered in the future</td>
</tr>
</tbody>
</table>

CBF = core binding factor; FISH = fluorescent in situ hybridization; FLT3 = FMS-like tyrosine kinase 3; HLA = human-leukocyte antigen; NPM1 = nucleophosmin.
A c u t e  M y e l o i d  L e u k e m i a

Table 2. World Health Organization Classification of Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Abnormality</th>
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<tbody>
<tr>
<td>Favorable</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>Adverse</td>
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Table 3. Acute Myeloid Leukemia Cytogenetic Risk Groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21), t(15;17), inv(16)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal karyotype, +8, +21, +22, del(7q), del(9q) Abnormal 11q23, all other structural/numerical abnormalities</td>
</tr>
<tr>
<td>Adverse</td>
<td>−5, −7, del(5q), abnormal 3q, complex (≥ 3 abnormalities)</td>
</tr>
</tbody>
</table>


**CASE CONTINUED**

After confirming the diagnosis of AML with recurrent genetic abnormalities by bone marrow biopsy and aspirate, induction chemotherapy is initiated with a 7-day continuous infusion of cytarabine in addition to daunorubicin on days 1 through 3. There are no acute complications during chemotherapy administration. As anticipated, the patient develops progressive pancytopenia with a nadir in his neutrophil count (absolute neutrophil count, 40 cells/µL) occurring approximately 2 weeks after the first day of treatment. He is treated with supportive care consisting of periodic packed red blood cells and platelet transfusions. The patient experiences a fever associated with profound neutropenia 15 days after the initiation of treatment. He is treated with a broad-spectrum antipseudomonal β-lactam, and blood cultures do not grow any organisms. After 28 days, the patient’s neutropenia resolves and he is discharged. Two weeks later, the patient reports to his hematologist for a repeat bone marrow examination. The peripheral blood smear reveals improving hematocrit (43%), a platelet count of 175,000 cells/µL, and a normal absolute neutrophil count. Bone marrow examination demonstrates normal hematopoiesis with blasts numbering less than 5%, indicating a complete remission.

- **What is the role of induction chemotherapy in AML?**

Therapy for AML includes remission induction followed by post-remission chemotherapy. The goal of induction chemotherapy is to reduce the number of leukemic cells as well as return proper function of the

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Table 2. World Health Organization Classification of Acute Myeloid Leukemia

- Acute myeloid leukemia with recurrent genetic abnormalities
  - Acute myeloid leukemia with t(8;21)(q22;q22), (AML1/ETO)
  - Acute myeloid leukemia with abnormal bone marrow eosinophils and inv(16)(p13q22) or t(16;16)(p13;q22), (CBFβ/MLT1)
  - Acute promyelocytic leukemia with t(15;17)(q22;q12), (PML/RARA) and variants
  - Acute myeloid leukemia with 11q23 (MLL) abnormalities
- Acute myeloid leukemia with multilineage dysplasia
- Acute myeloid leukemia and MDS, therapy related
  - Alkylation agent/radiation-related type
  - Topoisomerase II inhibitor–related type (some may be lymphoid)
  - Others
- Acute myeloid leukemia, not otherwise categorized, classify as:
  - Acute myeloid leukemia, minimally differentiated
  - Acute myeloid leukemia without maturation
  - Acute myeloid leukemia with maturation
  - Acute myelomonocytic leukemia
  - Acute monocytic/acute monocytic leukemia
  - Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
  - Myeloid sarcoma


MDS = myelodysplastic syndromes; MPD = myeloproliferative disease.

to attain a complete remission (with odds ratios of 1.33 and 1.48, respectively) and have improved disease-free and overall survival (P < 0.001 for both) as compared with other genotypes.

The FLT3 gene encodes a receptor tyrosine kinase that is involved in cell proliferation and differentiation signaling. In approximately 30% of AML patients, the malignant clone harbors an FLT3 mutation. In general, these patients have a poorer clinical outcome than patients in whom AML expresses normal copies of FLT3. Thus, it is crucial to test for cytogenetics and FISH for the t(15;17) or CBF abnormalities as well as mutations in FLT3 and NPM1 at the time of diagnosis, as the results of these studies may help dictate therapy.
bone marrow. Treatment recommendations for AML are often divided into those for patients younger than age 60 years (“younger” adults) and those aged 60 years and older (“older” adults). The most common induction regimen for both age-groups is cytarabine administered on days 1 through 7 plus an anthracycline or anthracenedione (daunorubicin, idarubicin, or mitoxantrone) administered on days 1 through 3.38-43

- What is the role of post-remission chemotherapy in AML?

Post-remission chemotherapy aims to eradicate any residual disease in an attempt to obtain a cure. Post-remission chemotherapy includes high-dose cytarabine (HiDAC) for patients younger than age 60 years, given every 12 hours on days 1, 3, and 5 of a 28-day cycle for up to 3 or 4 cycles, while cytarabine administered by continuous infusion over 5 days with or without an anthracycline or anthracenedione given by bolus for 2 days is preferred for patients age 60 years and older for 1 to 2 cycles. HiDAC has proven to be quite efficacious in younger patients, particularly those with CBF abnormalities.29 In patients younger than age 60 years, HiDAC yields a 44% 4-year disease-free survival with relatively few relapses but carries with it a 5% treatment-related mortality rate.41 In contrast, HiDAC failed to improve the outcome of patients aged 60 years and older and was associated with higher toxicities including severe neurologic complications.45

- What other therapies are being studied?

Gemtuzumab ozogamicin, an anti-CD33 immunotoxin conjugate, has been approved by the US Food and Drug Administration for use in refractory AML. It was shown to have a 30% response rate (complete response as well as pathologic complete response) in AML patients in first relapse with previous first remission duration of 6 months or longer.46 To determine if upfront chemotherapy plus gemtuzumab ozogamicin has a role in previously untreated patients, a phase 3 Medical Research Council trial compared cytarabine-based therapy with gemtuzumab to standard cytarabine-based induction therapy in 1115 younger AML patients. Patients randomized to the gemtuzumab arm had a similar complete remission rate and rates of induction death and resistant disease but higher disease-free survival at 3 years of follow-up when compared with patients randomized to standard therapy (51% versus 40%; P = 0.008).47

Clofarabine is a purine nucleoside analogue with several purported mechanisms of action that has shown promise in older AML patients. Inhibition of ribonucleotide reductase, incorporation into DNA, and induction of apoptosis are all thought to underlie clofarabine’s action. Data from 1 trial that used single-agent clofarabine in newly diagnosed older adults demonstrated a complete remission rate of 59%.48 It is being studied alone and in combination with cytara-bine in the upfront and refractory setting.49

CASE CONTINUED

Because of the patient’s age, good underlying functional status, and his CBF cytogenetic abnormality, his best chance for long-term survival is to receive 4 cycles of HiDAC. He completes all 4 cycles but develops febrile neutropenia during the second and fourth cycles, requiring readmission for therapy with intravenous antibiotic drugs. Following his fourth cycle, he undergoes a repeat bone marrow biopsy and aspirate, which demonstrates that he remains in complete response, and cytogenetic analysis and FISH studies for the t(8;21) are negative.

- What is the role of bone marrow transplantation in AML patients?

Allogenic bone marrow transplantation is an additional option for post-remission therapy. For some patients under age 60 years with poor-risk cytogenetic abnormalities and for whom a human leukocyte antigen–matched sibling or matched-unrelated donor is available, allogenic stem cell transplantation may follow induction chemotherapy. This procedure is not without risk and has an associated 20% to 25% treatment-related mortality rate and a 1-year mortality rate that may approach 40%.50 It also represents the only potentially curative therapy for patients with relapsed or refractory disease. Because of the patient’s relatively young age, favorable cytogenetic status, and achievement of complete response, he does not undergo hematopoietic stem cell transplant as it is unlikely to provide survival benefit. Older patients and those with suboptimal performance statuses may undergo reduced intensity (nonmyeloablative) bone marrow transplantation.

- How is treatment of acute promyelocytic leukemia different from AML?

A discussion of AML would not be complete without reviewing the unique characteristics of acute promyelocytic leukemia. Much like other leukemias, acute
promyelocytic leukemia is treated using remission induction therapy but with the addition of differentiation therapy with all-trans retinoic acid (ATRA), a vitamin A derivative. ATRA promotes differentiation of leukemic promyelocytes into mature cells and has been shown to improve both disease-free and overall survival as compared with chemotherapy alone. ATRA, along with an anthracycline, is currently the standard of care for patients with acute promyelocytic leukemia. Arsenic trioxide, another differentiation agent, has been shown in a large intergroup trial to improve survival when administered in the post-remission setting and may become a standard part of therapy for acute promyelocytic leukemia.

OUTCOMES

Success in the treatment of patients with AML has only modestly improved for patients under age 60 years over the past few decades. In 1966, the median survival of patients with AML was 40 days. Today, AML patients younger than age 60 years have complete response rates of 70% to 80% after induction chemotherapy. Overall survival, however, remains at approximately 50% for those whom attain a complete response, which translates into 30% overall survival when all patients under age 60 years are considered. In 1998, the Medical Research Council AML 10 trial found that patients could be separated into 3 prognostic groups: favorable, intermediate, and adverse, defined by pretreatment cytogenetics. Overall survival at 5 years was found to be 65%, 41%, and 14%, respectively. If a patient undergoes an allogeneic hematopoietic stem cell transplant while in first remission, the complete response rate has been shown to range from 45% to 65%, although patient selection influences these numbers. In relapsed AML, however, complete response after allogeneic hematopoietic stem cell transplant was shown to be 35% or less.

The prognosis for older patients with AML remains poor. In the Medical Research Council AML 8 trial, the remission rate was 70% for patients under age 50 years, 52% for those aged 60 to 69 years, but only 26% for those over age 70 years. One theory for such disparity in results is that neutropenia after chemotherapy lasts longer and is less well-tolerated among older adults as compared with younger patients. Another possible answer is the finding that hematopoietic cells of older patients are derived from a leukemic clone at diagnosis, in contrast to normal stem cells found in their younger counterparts. The use of colony-stimulating factors following the completion of induction chemotherapy has been shown to reduce the period of neutropenia and the duration of hospitalization by approximately 2 days; unfortunately, this has not translated into improved overall survival or a decrease in infectious complications; hence, the use of these agents is not indicated in this patient population.

CONCLUSION

Although the diagnosis of leukemia is frequently suggested by routine laboratory evaluation, prompt recognition of AML is required to prevent early complications. Rapid cy toreduction and attention to the patient’s clinical status is essential while establishing the diagnosis. Bone marrow biopsy specimens should routinely be analyzed for cytogenetic abnormalities in addition to specific gene mutations, as these studies have significant bearing on prognosis and course of treatment. Chemotherapy with standard regimens for AML is intense and requires prolonged hospitalization but is reasonably effective at achieving a complete response, particularly in younger patients. For older patients, standard chemotherapy is often less effective. The role of hematopoietic stem cell transplant in AML continues to be defined but represents the best chance for long-term survival for many patients. As new drugs are developed, future treatment of AML may be tailored to the specific genetic defect(s) found in individual patients.

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