CHAPTER 18

Acute myeloid leukemia

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The online version of this chapter contains an educational multimedia component.

Definition and epidemiology

Acute myeloid leukemia (AML) is a heterogeneous clonal hematopoietic progenitor or stem cell malignancy in which immature hematopoietic cells proliferate and accumulate in bone marrow, peripheral blood, and other tissues. This process results in inhibition of normal hematopoiesis, characterized by neutropenia, anemia, thrombocytopenia, and the clinical features of bone marrow failure. AML accounts for 90% of all acute leukemias in adults, with an estimated 20,800 new cases and 10,500 deaths expected in the United States in 2015. The annual incidence is approximately 3.5 per 100,000 and increases with age, with approximately a tenfold increased risk between ages 30 (1 case per 100,000) and 65 years (1 case per 10,000). The median age at diagnosis is approximately 67 years, with ~6% of patients <20 years of age and 34% of patients 75 years or older. Overall survival in adults remains poor, with <50% 5-year survival in patients <45 years of age that continues to fall to <10% in patients >60 years of age at diagnosis. In children, overall survival has improved to ~60%.

Most cases of AML have no apparent cause. The most common known risk factor is previous exposure to radiation or chemotherapy, particularly topoisomerase II inhibitors and alkylating agents, which results in therapy-related AML (t-AML), and accounts for ~10%-20% of all AML cases. AML that arises after exposure to alkylating agents or radiation therapy have increased incidence with age, typically have a 5- to 10-year latency period, and frequently are associated with an antecedent therapy-related myelodysplastic syndrome (MDS) and unbalanced loss of genetic material involving chromosomes 5 or 7. t-AML associated with exposure to topoisomerase II inhibitors is less common and encompasses 20%-30% of t-AML patients, has a shorter latency period of 1-5 years, is less often preceded by a myelodysplastic phase, and may be associated with balanced recurrent chromosomal translocations involving 11q23 (*MLL* gene) or 21q22 (*RUNX1*). Other environmental risk factors include exposure to benzene and ionizing radiation. Patients with inherited bone marrow failure syndromes (eg, Fanconi anemia, Shwachman-Diamond syndrome, severe congenital neutropenia), genetic disorders (eg, Down syndrome), and MDS and myeloproliferative neoplasms are also at increased risk of developing AML. Patients with these conditions who develop AML have poorer treatment outcomes than patients with de novo AML.

Clinical manifestations

Patients with AML generally present with nonspecific signs and symptoms related to infiltration of the bone marrow and other organs with leukemic blasts, including pallor, fatigue, bone pain, hepatosplenomegaly, fever, bruising, and bleeding. Tissue infiltration of the skin, gingiva, and central nervous system (CNS) is more common with monocytic subtypes. CD56 expression, in addition to monocytic subtypes, increases extramedullary risk at presentation. Patients with leukocytosis and leukemic blasts >50,000/μL are at increased risk of pulmonary and CNS complications from leukostasis. Pathologically, this process shows a combination of microinfarction and hemorrhage.

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AML may be associated with a variety of laboratory derangements in addition to abnormal blood counts. Coagulation abnormalities are particularly common and severe in patients with acute promyelocytic leukemia (APL), but they may be seen in all subtypes. Metabolic abnormalities related to tumor lysis syndrome also may be present, including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. In patients with monocytic leukemia, severe hypokalemia may be present.

Subtype classification

In the 1970s, AML was subclassified according to the French-American-British (FAB) classification system using morphologic and cytochemical criteria to define eight major AML subtypes (M0-M7) on the basis of greater than or equal to 30% blasts, lineage commitment, and the degree of blast cell differentiation. The FAB system has been replaced by the World Health Organization (WHO) classification, which was developed to incorporate epidemiology, clinical features, biology, immunophenotype, and genetics into the diagnostic criteria. The WHO has identified a number of genetically defined subgroups of AML (Table 18-1). A new revision of the WHO classification, incorporating point mutations, will debut in 2016-2017.

AML is now defined as greater than or equal to 20% myeloblasts, monoblasts or promonocytes, erythroblasts, or megakaryoblasts in the peripheral blood or bone marrow, except in patients with the following cytogenetic abnormalities, who are classified as having AML irrespective of blast count: t(8;21)(q22;q22), inv(16)(p13q22), t(16;16)(p13;q22), and t(15;17)(q22;q12). Immunophenotypic characterization using surface antigens remains important in AML and may include progenitor-associated antigens (eg, human leukocyte antigen-DR [HLA-DR] [except in APL], CD34, CD117) and myeloid antigens (eg, CD13, CD33). Complex composite immunophenotypes, including expression of lymphoid markers, also may be seen.

Prognostic factors

AML is a clinically and biologically heterogeneous disease. Adverse clinical prognostic features include advanced age at diagnosis, extramedullary disease (including CNS leukemia), disease related to previous chemotherapy or radiation treatment (t-AML), and the presence of an antecedent hematologic disorder (typically, MDS or myeloproliferative disorders). Patients >60 years and especially those >75 years of age have poor long-term survival because of both disease- and host-related factors, including increased expression of multidrug resistance genes, medical comorbidities, and poor performance status. An absolute blast count >50,000/μL at diagnosis is associated with increased risk of vascular complications.

Originally, the morphologic characteristics of the newly diagnosed disease were considered important determinants in prognostication. It now is evident, however, that chromosomal (cytogenetic) and molecular abnormalities are the primary tools and far better than morphology in assigning prognosis for patients with newly diagnosed AML. It is imperative that the initial diagnostic workup of suspected AML include testing for the commonly described abnormalities, typically determined by bone marrow aspirate studies.

Acquired, nonrandom, clonal chromosomal abnormalities, including balanced translocations, inversions, deletions,

Table 18-1 World Health Organization 2008 classification of acute myeloid leukemia (AML) and related myeloid neoplasms

1. AML with recurrent genetic abnormalities
   a. AML with balanced translocations/inversions
      i. AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
      ii. AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
      iii. Acute promyelocytic leukemia with t(15;17)(q22;q12); *PML-RARα*
      iv. AML with t(9;11)(p22;q23); *MLLT3-MLL*
      v. AML with t(6;9)(p23;q34); *DEK-NUP214*
      vi. AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
      vii. AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MLK1*
   b. AML with gene mutations
      i. Provisional entity: AML with mutated *NPM1* (nucleophosmin)
      ii. Provisional entity: AML with mutated *CEBPA* (CCAAT/enhancer binding protein A)
2. AML with myelodysplasia-related changes
3. Therapy-related myeloid neoplasms
4. AML, not otherwise specified
   a. AML with minimal differentiation
   b. AML without maturation
   c. AML with maturation
   d. Acute myelomonocytic leukemia
   e. Acute monoblastic/monocytic leukemia
   f. Acute erythroid leukemia
      i. Pure erythroid
      ii. Erythroleukemia, erythroid/myeloid
   g. Acute megakaryoblastic leukemia
   h. Acute basophilic leukemia
   i. Acute panmyelosis with myelofibrosis
5. Myeloid sarcoma
6. Myeloid proliferations related to Down syndrome
   a. Transient abnormal myelopoiesis
   b. Myeloid leukemia associated with Down syndrome
7. Blastic plasmacytoid dendritic cell neoplasm

monosomies, and trisomies may be found in up to 50% of patients with AML. The karyotype is considered complex when there are more than three abnormalities, and this is seen in 10%-20% of patients, often in association with *TP53* gene mutation or deletion. Cytogenetic findings remain one of the most important prognostic tools and often are classified into favorable, intermediate, and unfavorable risk groups, but clinical study groups have not always been consistent in assigning the Individual abnormalities. It is universally agreed, however, that patients with the t(15;17)(q22;q12-21) found in APL have excellent outcomes. Balanced abnormalities of t(8;21)(q22;q22), inv(16)(p13.1 q22), and t(16;16)(p13.1;q22) involve the heterodimeric components of core-binding factor (CBF) and are associated with a relatively favorable prognosis. Complex karyotype, inv(3)(q21q26)/t(3;3)(q21;q26), and monosomal karyotype (at least two autosomal monosomies or one single-autosomal monosomy combined with at least one structural abnormality) are associated with particularly poor outcomes.

Molecular alterations also provide important prognostic information for many patients with AML, particularly those with normal karyotype disease (Figure 18-1). This is the largest cytogenetic subset of AML, and without further ability to classify these patients, most generally fall into an intermediate-risk group. Yet, these intermediate-risk patients have variable outcomes with conventional treatment strategies, which may be explained by the underlying molecular heterogeneity associated with their disease. For example, 20%-25% of patients with AML have fms-like tyrosine kinase 3 (*FLT3*) length mutations (inclusive of ITDs, insertions, deletions), which are associated with inferior prognosis. In addition, heterozygous mutations in exon 12 of the nucleophosmin member 1 (*NPM1*) gene have been found in 40%-60% of AML patients with a normal karyotype, and mutated *NPM1*, in conjunction with wild-type *FLT3*, is associated with a favorable prognosis. Finally, mutations of the CCAAT–enhancer binding protein A (*CEBPA*), a gene encoding a myeloid transcription factor important for normal granulopoiesis, also appear to be associated with favorable clinical outcomes. Certain mutations such as IDH1/IDH2, KIT and FLT3 may have therapeutic implications, as specific inhibitors are available or in development.

While evaluating for mutations in *NPM1, FLT3,* and *CEBPA* have become part of routine testing to aid in risk stratification for patients with AML associated with a normal karyotype, a host of other molecular alterations including mutations in genes defining epigenetic pathways such as *DNMT3A, IDH1, IDH2, TET2,* and others have been described in many patients with AML. In addition, genetic profiling of patients with a normal karyotype has started to yield insights into distinct prognostic subgroups of patients with various co-occurring mutations. The Eastern

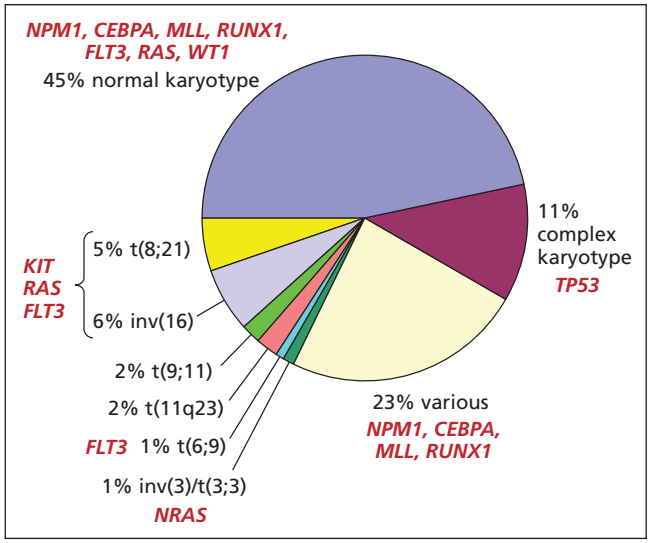

Figure 18-1 Major cytogenetic subgroups of AML (excluding acute promyelocytic leukemia) and associated gene mutations.

Cooperative Oncology Group genetically profiled all of the patients treated on protocol E1900, a randomized trial of 90 mg/m^2 daily × 3 vs. 45 mg/m^2 daily × 3 of daunorubicin with both trial arms receiving 7 days of infusional cytarabine. Analysis demonstrated that certain mutations co-occur frequently—like NPM1 and FLT3-ITD while others, such as IDH mutations and TET2 mutations, appear to be mutually exclusive, leading to insights into pathways of leukemogenesis and hierarchies of clonal evolution. In addition, combining clinical outcomes with genetic profiling has started to define new groups of patients with a favorable prognosis. For example, patients with co-occurring IDH2 R140Q and NPM1 mutations appear to have outcomes as good as or better than patients with core binding factor leukemias. Finally, identification of these mutations has served as a platform for the development of novel therapeutic inhibitors of the mutated proteins and led to the ongoing efforts to develop clinical trials combining novel agents to target each genetic alteration.

Recent efforts to combine the information from cytogenetics and molecular changes have been set forth by the European Leukemia Net (ELN) and have culminated in the evolution of the traditional risk groups into favorable, intermediate-1, intermediate-2, and adverse categories, which is a reminder that refining prognosis will continue to evolve as the impact of more targets is recognized (Table 18-2).

Key points

- The most important prognostic indicators in AML are patient age, cytogenetics, and molecular genetics.
- Complex cytogenetic abnormalities and monosomal karyotypes are associated with poor clinical outcomes.

Key points (*Continued*)

- t(15;17), t(8;21), and inv(16) are cytogenetic abnormalities associated with favorable outcomes.
- Patients with cytogenetically normal AML and FLT3-ITD mutations have an unfavorable prognosis, whereas those with wild-type FLT3 and mutations of NMP1 or CEBPA have a more favorable prognosis.

Treatment

Treatment for AML generally is divided into remission induction and postremission therapy. Standard remission induction regimens in the United States for all AML subtypes, excluding APL (see section "Acute promyelocytic leukemia" later in this chapter), almost always include 7 days of infusional cytarabine and 3 days of an anthracycline, commonly known as the "7+3" or "3&7" strategy. This strategy results in complete remission (CR) in 70%-80% of adults <60 years of age and 30%-50% of selected adults >60 years of age with a good performance status. The Cancer and Leukemia Group B (CALGB) established that 3 days of daunorubicin and 7 days of cytarabine were more effective than 2 and 5 days, respectively, and that 10 days of cytarabine was not better than 7 days. Also, 100 mg/m^2 of cytarabine for 7 days was as effective as 200 mg/m^2 for the same duration. Daunorubicin at a dose of 30 mg/m^2 was inferior to 45 mg/m^2, and recently, daunorubicin 90 mg/m^2 has been shown, in large cooperative group trials, to be superior to 45 mg/m^2 even in selected patients >60 years of age. In a UK study, daunorubicin 60 mg/m^2 was equivalent to 90 mg/m^2, establishing 60 mg/m^2 as an appropriate standard dose and 90 mg/m^2 as a reasonable alternative in patients with adequate cardiac status.

Table 18-2 ELN standardized reporting system for correlation of cytogenetic and molecular genetic data in AML with clinical data

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

*Defined as 3 or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations of inversions: t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Despite many attempts to improve outcomes from "7+3" since it was first developed in the 1970s, no treatment regimen has succeeded in replacing it as standard induction, though this may be about to change. Recent efforts have focused on adding therapies targeting molecular mutations to traditional induction and include FLT3 inhibitors, polo-like kinase inhibitors, and agents blocking multidrug resistance gene overexpression without definitive evidence of bettering outcomes. Results for the targeted agent gemtuzumab ozogamicin (GO) have been conflicting to date, but a recent meta-analysis exploring its potential benefit when added to chemotherapy suggested that it can be safely added to chemotherapy and that it provides a survival advantage to patients without adverse prognostic factors. Unfortunately, GO remains unavailable in the United States as of 2015. Two studies have shown superiority for adding a kinase inhibitor to 3&7: sorafenib extended relapse-free survival regardless of FLT3 status, and in a large cooperative group study of midostaurin plus 3&7 for FLT3 mutant AML, both event-free and overall survival were improved.

Once remission has been achieved, further therapy is required to prevent relapse. Options include repeated courses of consolidation chemotherapy or allogeneic hematopoietic stem cell transplantation (HSCT). Allogeneic HSCT allows combination of myeloablative or nonmyeloablative chemotherapy with a graft-versus-leukemia effect from the donor cells. Autologous HSCT is routinely not done for patients with AML. Several studies have prospectively evaluated the role of intensive consolidation with HiDAC. The CALGB randomized patients in first remission to four courses of cytarabine using either a continuous infusion of 100 mg/m^2 for 5 days or a 3-hour infusion of 400 mg/m^2 or 3 g/m^2 twice daily on days 1, 3, and 5. Significant CNS toxicity was observed in patients >60 years old randomized to the high-dose arm, and thus, this regimen is not recommended for older patients. In patients <60 years old, there was a significant improvement in disease-free survival associated with the high-dose regimen, and this was most pronounced in patients with favorable cytogenetics, including t(8;21) and inv(16).

Although it has become standard to offer at least two cycles of HiDAC at 1 to 3 g/m^2 to younger patients with AML, there are no clear data defining the optimal number or intensity of HiDAC cycles. Randomized trials from the United Kingdom Medical Research Council failed to demonstrate that three cycles of HiDAC consolidation were better than two cycles. Although it is clear that patients with core binding factor (CBF) leukemias specifically benefit from HiDAC, some of these patients also have mutations in *KIT*, which are associated with an inferior outcome; clinical trials of chemotherapy combined with tyrosine kinase inhibitors including dasatinib (which inhibits KIT) are ongoing in these patients.

Consolidation chemotherapy, in general, has not been proven to be of benefit for patients >60 years old, but older patients able to tolerate additional treatment often are offered modified dosing of bolus cytarabine or additional courses of "7+3." Maintenance therapy outside of APL has not been adopted. Two pediatric randomized trials from the Leucémies Aiguës Myéloblastiques de l'Enfant (LAME) and the Children's Cancer Group (CCG) failed to demonstrate that maintenance therapy improves outcomes.

Several studies of postremission therapy in AML have compared intensive chemotherapy consolidation to HSCT by assigning younger patients with a human leukocyte antigen (HLA)-matched sibling donor to allogeneic HSCT and randomizing other patients to chemotherapy or autologous HSCT. Meta-analyses have shown that autologous HSCT decreases relapse risk but increases treatment-related mortality compared with chemotherapy consolidation, thus resulting in similar overall survival rates of approximately 40%-45% at 3-5 years. There is no specific indication for its use in any prognostic subgroup, but it continues to be used in some settings, especially in Europe.

Allogeneic HSCT is probably the most effective antileukemic therapy currently available and offers a combination of the therapeutic efficacy of the conditioning regimen and the graft-versus-leukemia effect from the donor cells. It is, however, associated with significant morbidity and mortality. A recent comprehensive meta-analysis by Koreth et al. (2009) of prospective clinical trials of allogeneic HSCT in AML patients in first CR evaluated 24 trials and more than 6,000 patients. In this analysis, allogeneic HSCT resulted in significantly improved 5-year overall survival, from 45% to 52% for patients with intermediate-risk cytogenetics and from 20% to 31% in patients with poor-risk cytogenetics. There was no benefit of allogeneic HSCT for patients with good-risk cytogenetics. Retrospective analyses of uniformly treated patients have shown that allogeneic HSCT was also beneficial for cytogenetically normal AML patients with *FLT3*-ITD$^+$, *FLT3*-ITD$^-$/*NPM1*$^-$, and *FLT3*-ITD$^-$/*CEBPA*$^-$, and prospective trials using molecular and cytogenetic risk stratification are under way. Other efforts are focusing on the use of alternative donor sources of stem cells to allow allogeneic transplant options for patients without fully matched sibling or unrelated donors. Trials utilizing partially matched-related donors, including haploidentical donors, as well as cord blood as sources of stem cells are under way by national cooperative transplant groups. Finally, using nonmyeloablative or reduced-intensity conditioning regimens is another way to broaden the application of allogeneic SCT toward patients who may not be medically fit to undergo a full preparative regimen.

Key points

- Treatment of AML generally involves remission induction followed by postremission therapy.
- The standard of care for induction for all AML subtypes in adults, excluding APL (FAB-M3), remains 3 days of an anthracycline combined with 7 days of cytarabine.
- Consolidation chemotherapy with two to four cycles of HiDAC is of particular benefit for patients <60 years old with favorable prognosis cytogenetics involving CBF [t(8;21) and inv(16)]; it is not routinely recommended for patients >60 years old.
- Allogeneic stem cell transplantation appears to be of benefit for AML patients in first remission who have intermediate- or poor-risk cytogenetics.
- Retrospective data suggest that allogeneic transplantation may be of benefit for patients with FLT3-ITD$^+$.

Monitoring residual disease

Although morphologic methods remain the gold standard for determining the status of disease in AML, more sensitive immunologic and molecular methods for detecting the presence of minimal residual disease (MRD) are available. Leukemia-associated immunophenotypes can be identified as "signatures" for some patients with AML, and the presence of MRD as measured by immunophenotype has been shown to predict for disease relapse in some studies. The genetic abnormalities associated with a significant proportion of AML cases provide unique markers that can be used to monitor MRD. Polymerase chain reaction (PCR) offers a qualitative detection of abnormal gene rearrangements or fusion genes, whereas real-time PCR offers both the advantage of higher sensitivity and the possibility of quantification. MRD is now being used to risk stratify patients in current clinical trials. The optimal sensitivity for detection methods remains to be determined, and prospective clinical trials are required to assess whether additional postremission treatment with chemotherapy, allogeneic transplantation, or other agents will improve outcomes for patients with persistent MRD.

AML relapse

The majority of adult patients with AML experience relapse despite initially attaining CR. The prognosis of relapsed disease is poor, and these patients should be considered for investigational trials. Most AML relapses occur within 2 years of diagnosis. The duration of first remission is of critical prognostic importance, and patients with an initial CR of <6 months are unlikely to respond to standard chemotherapeutic agents. Patients whose initial CR duration was >12 months may have up to a 50% chance of responding to a HiDAC-containing regimen, even if they had previous exposure to this agent. Examples of reinduction regimens include cytarabine, etoposide, and mitoxantrone (MEC), fludarabine, high-dose cytarabine and granulcoyte colony-stimulating factor priming (FLAG), clorfarabine and cytarabine, and cladribine, cytarabine, and growth factor (CLAG). No combination has proven more effective in the few randomized trials attempted. Likewise, moving the noted combinations into the frontline setting has not shown superior outcomes to "7+3" induction. Patients who achieve a second remission should be considered for standard or reduced-intensity allogeneic transplantation if possible because the duration of second remission with chemotherapy alone is generally short and almost always shorter than CR1. The prognosis for patients who relapse after allogeneic transplantation is dismal.

There are many categories of novel agents for AML as well as new combination strategies that are under investigation, including chemotherapeutics (eg, topoisomerase II inhibitors, purine nucleoside analogs), signal transduction inhibitors (FLT3-ITD, PIM), hypomethylating agents and other epigenetic modifiers (HDAC, ASXL), cell cycle modulators (CDK, polo-like kinase), and agents targeting cellular metabolism (IDH1/2). In general, with the possible exception of the IDH inhibitors, targeted agents have had limited single-agent activity in relapsed AML and may be more effective in combination with chemotherapy.

Older patients with AML

Clinical case

An 82-year-old woman with a history of myocardial infarction, diabetes, and peripheral vascular disease presents with shortness of breath and is found to be pancytopenic. Bone marrow biopsy shows 40% myeloblasts with monosomy 7.

Most patients with AML are >60 years old, and their prognosis is dismal, with median survival times of only 8-12 months among the most "fit" patients. Older patients have a high frequency of poor prognostic features, including antecedent hematologic disorders, unfavorable cytogenetics, and multidrug resistance (*MDR1*) phenotypes. Also, older patients are often less able to tolerate intensive chemotherapy because of medical comorbidities, polypharmacy, poor performance status, and limited social supports. There is no universally accepted standard of care for the treatment of older patients, but they generally are offered either conventional "7+3" induction, hypomethylators, repeated cycles of low-dose subcutaneous cytarabine, supportive care with antibiotics and transfusions, hospice care, or an investigational trial. Although remission can be attained in ~50% of selected older patients with a good performance status using 7+3, these responses are offset by mortality rates of 5%-20% and their short duration, with <10% of elderly patients being long-term survivors.

The use of hypomethylating drugs (azacitidine and decitabine) has become a common treatment strategy for elderly patients or patients who are deemed unfit for traditional cytotoxic chemotherapy base on the findings that these agents can result in bone marrow stabilization, reduction in transfusion needs, and even complete remissions in between 10%-20% of patients. Decitabine is now approved for this indication in Europe and is often used off-label in the United States; azacitidine is approved in the US for patients with AML who have 20-30% blasts. There is controversy about how to define "unfit" patients; previous studies used physician judgment, and more recent studies have employed specific criteria for patients unlikely to benefit from intensive induction.

Major cooperative group or multicenter trials, which generally have focused on patients <75 years old with de novo AML and those having a good performance status, show 3- to 5-year overall survival rates of only 10%-20%; however, many of these patients are not offered any treatment for AML despite randomized data clearly demonstrating a survival benefit favoring treatment with chemotherapy over supportive care in this population. Clinical experience suggests that quality of life is better for those who achieve CR, but data are sparse. Although there are clearly frail and debilitated older patients who cannot tolerate any treatment, emerging data suggest that age alone should not be used as the major determinant of treatment because several intensive options, including intensified doses of daunorubicin and reduced-intensity stem cell transplantations, are both feasible and effective in selected patients >60 years old. Many, if not most, older patients with AML fail to benefit from therapy due to its lack of therapeutic efficacy, not due to intolerable toxicities. Novel therapies are clearly needed for this population, and there are many ongoing clinical trials with both single agent and combinations using cytotoxics, antibodies,

hypomethylating agents, and nonmyeloablative transplantations. Older AML patients should be encouraged to participate in clinical trials whenever possible.

Acute promyelocytic leukemia

Clinical case

A 23-year-old Hispanic female presents with 2 weeks of dyspnea, bruising, and menorrhagia. Laboratory evaluation shows pancytopenia with elevated prothrombin and partial thromboplastin times and markedly decreased fibrinogen. Bone marrow aspiration shows intensely myeloperoxidase-positive promyelocytes and t(15;17).

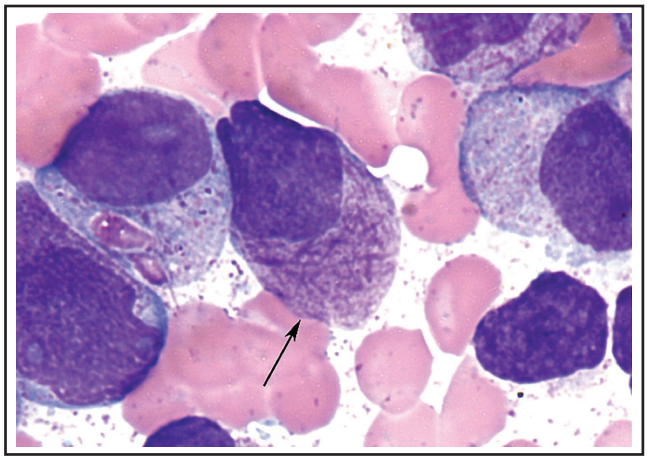

Figure 18-2 A faggot cell. Source: ASH Image Bank/Peter Maslak.

APL (FAB-M3) is a clinically, cytogenetically, and prognostically distinct subtype of AML that accounts for ~5%-15% of all adult AML cases, with a higher incidence in younger patients and among Hispanics. It is the most curable form of AML in adults. Almost all leukemic cells from patients with APL have a balanced reciprocal translocation between chromosomes 15 and 17, which results in the fusion of the promyelocytic leukemia (PML) and retinoic acid receptor-α (*RARα*) genes, a *PML-RARα* fusion gene product, and disruption of normal differentiation. APL blasts contain granules with proteolytic enzymes, the release of which induces severe coagulopathy and fibrinolysis, predisposing patients to both hemorrhage and thrombosis.

APL exists in hypergranular (typical) and microgranular forms. In hypergranular APL, the promyelocytes are strongly myeloperoxidase positive and have bi-lobed or kidney-shaped nuclei. The cytoplasm has densely packed, large granules, and characteristic cells containing bundles of Auer rods (faggot cells, named after a chiefly British English term for the bundle of sticks that these Auer rods resemble) may be found in most cases (Figure 18-2). Cases of microgranular APL have predominantly bi-lobed nuclei, are strongly myeloperoxidase positive, and often have a very high leukocyte count and doubling time. APL is characterized by low expression or absence of HLA-DR, CD34, CD117, and CD11b. The diagnosis is confirmed with cytogenetics, reverse transcriptase PCR (RT-PCR) for the *PML-RAR* fusion transcript, and fluorescence in situ hybridization with probes for *PML* and *RARα*, or anti-*PML* antibodies.

APL promyelocytes have the unique ability to undergo differentiation with exposure to all-trans retinoic acid (ATRA). Detection of t(15;17) or the underlying *PML-RARα* rearrangement is predictive of response to ATRA in virtually 100% of cases. Some infrequent APL variants, such as t(11;17)(q23;q21) with *ZBTB16-RARα* and cases with *STAT5B-RARα* fusions, are resistant to ATRA. It is crucial that ATRA is started as soon as the diagnosis of APL is suspected, even before pathologic confirmation, as this agent reverses the coagulopathy common at presentation and is the cornerstone of all treatment plans for APL.

Combination regimens with ATRA and an anthracycline (with or without cytarabine) induces remission in >90% of patients, and long-term cures are achieved in >70%-80% of patients in many series. Primary resistance to chemotherapy is virtually nonexistent. Arsenic trioxide may be the single most active agent in APL, and efforts to incorporate this agent early into treatment have confirmed its importance. In addition to offering a survival benefit when given as consolidation for newly diagnosed patients (as opposed to cytotoxic chemotherapy-based consolidations), arsenic combined with ATRA produces high rates of durable CR in newly diagnosed patients with low-risk disease (less than 10,000 peripheral white cell count at presentation) with low rates of hematologic toxicity as compared to ATRA plus an anthracycline. The ATRA/arsenic combination led to an enviable 100% complete remission rate, a 97% event-free survival, and a 99% overall survival at 2 years. ATRA/Arsenic is now the considered the standard of care for patients with low risk APL. Finally, early use of arsenic has also been recognized as contributing to the elimination of maintenance ATRA and chemotherapy in most lower-risk APL patients.

Higher-risk APL patients continue to receive combination therapy with ATRA + chemotherapy, typically an anthracycline. There is some controversy regarding the best chemotherapy to include with ATRA during induction, but an anthracycline alone appears to be sufficient, and either daunorubicin 60 mg/m^2 for 3 days or idarubicin 12 mg/m^2 on days 2, 4, 6, and 8 can be used. Consolidation protocols differ between the United States and European cooperative groups but generally include several cycles of

anthracycline-based chemotherapy. The role of infusional cytarabine during induction is not clear, but patients presenting with a white blood cell (WBC) count of ≥10,000/μL may benefit from intermediate-dose cytarabine or HiDAC during either induction or consolidation. Some protocols for high-risk patients have also incorporated prophylactic intrathecal chemotherapy. The role of maintenance therapy is also debated in APL, but ATRA with or without 6-mercaptopurine and oral methotrexate frequently is offered to patients in CR, particularly in patients not treated with arsenic as part of their regimen. The optimal combination and duration of maintenance have not been defined.

Despite the success of ATRA-based regimens, there is still an early mortality of ~10% in APL patients, primarily because of hemorrhagic complications. Predictors of early death resulting from hemorrhage include WBC count at presentation, abnormal creatinine, peripheral blast count, presence of coagulopathy, and age. Also, patients must be closely monitored for the development of APL differentiation syndrome, a potentially fatal constellation of findings, including interstitial pulmonary infiltrates, hypoxemia, respiratory distress, fluid retention, weight gain, pleural or pericardial effusions, and, sometimes, renal failure. Rapid administration of dexamethasone 10 mg twice daily for at least 3 days at the earliest manifestations of the syndrome can be lifesaving.

The persistence or reappearance of *PML-RARα* fusion gene transcripts in patients with APL is highly predictive of clinical relapse, and frequent monitoring by RT-PCR has been integrated into most clinical trials. The ideal monitoring approach is not clear, as most patients achieving a molecular remission will not relapse. However, relapsed disease can be treated effectively with arsenic trioxide, which causes differentiation and apoptosis of APL cells, alone or in combination with ATRA. In addition, autologous stem cell transplantation can be considered for patients in second remission if the stem cells are negative for *PML-RARα*. Allogeneic stem cell transplantation generally is not recommended for patients with APL but may be considered for patients beyond first relapse.

Key points

- APL is a unique subtype of AML that is exquisitely sensitive to ATRA, anthracyclines, and arsenic trioxide.
- ATRA should be started immediately if the diagnosis of APL is suspected.
- Cure rates are high in APL.
- APL may be complicated by a life-threatening coagulopathy or differentiation syndrome.
- APL differentiation syndrome should be treated promptly with dexamethasone 10 mg twice daily for at least 3 days.

Pediatric AML, including Down syndrome

Clinical case

A 6-year-old boy presents with a 4-week history of fatigue and fever and a 1-week history of bruising and pallor. Laboratory evaluation shows pancytopenia. Bone marrow aspiration shows myeloblasts with granules and an occasional Auer rod. Cytogenetic studies reveal t(8;21).

Pediatric AML has unique clinical features, risk stratification schemas, and therapeutic approaches. Cutaneous involvement is more common in children, particularly in infants diagnosed at <1 year of age. Poor-prognosis cytogenetics are less frequent in children, and within the pediatric spectrum, age is not a critical prognostic indicator, except for children with Down syndrome. Children may tolerate intensive chemotherapy better than adults, and this may affect the optimal therapeutic approach. Standard induction chemotherapy in pediatrics typically includes cytarabine and an anthracycline with the addition of a third agent, such as etoposide. Most current pediatric AML protocols use at least four cycles of chemotherapy with HiDAC-based consolidation. Autologous HSCT has been abandoned by most pediatric groups, whereas the role of allogeneic HSCT is highly variable. In North America, most children with favorable features are treated with chemotherapy alone, whereas most children with poor-risk features are offered allogeneic HSCT from either a related or unrelated donor. Children with favorable cytogenetics have an overall survival rate of ~70% irrespective of response to the first cycle of induction, whereas children with adverse cytogenetics or poor response to the first cycle of induction therapy with >15% residual blasts have an overall survival rate of only 15%.

Children with Down syndrome have a 46- to 83-fold increased risk of AML and are generally younger than other pediatric AML patients. AML associated with Down syndrome tends to be classified as FAB-M7 (acute megakaryoblastic leukemia [AMKL]), and acquired *GATA1* mutations have been described in the leukemic blasts. AMKL in Down syndrome may be preceded by transient myeloproliferative disorder (TMD), a condition unique to children with Down syndrome. TMD is a clonal disorder characterized by circulating blasts and dysplastic features and usually is diagnosed in the first few weeks after birth. Although TMD typically resolves spontaneously within the first 3 months, intensive supportive care may be required, and early death has been reported in as many as 15%-20% of cases. For those who survive, ~20%-30% will later develop AMKL. Children with Down syndrome and AML who are <2-4 years of age have better prognosis compared with both non-Down syndrome

AML and Down syndrome AML patients >4 years of age at diagnosis. This superior prognosis may be related to enhanced sensitivity of the leukemic blast to cytarabine. Children with Down syndrome have greater toxicities with treatment and usually are not offered HSCT in first remission.

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