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were more effective than anagrelide and aspirin for prevention of TIA because hydroxyurea is a nitric oxide donor, but they were not more effective for the prevention of other types of arterial throm bosis and actually less effective for venous thrombosis. The risk of gastrointestinal bleeding is also higher when aspirin is combined with anagrelide. Normalizing the platelet count does not prevent either arterial or venous thrombosis. Pegylated IFN can produce a complete molecular remission in some ET patients, but a role for it or ruxolitinib in ET management has not yet been established. As more clinical experience is acquired, ET appears more benign than previously thought. Evolution to acute leukemia is more likely to be a consequence of therapy than of the disease itself. In manag ing patients with thrombocytosis, the physician's first obligation is to do no harm. ■ ■FURTHER READING Alvarez-Larran A et al: Antiplatelet therapy versus observation in low-risk essential thrombocythemia with CALR mutation. Haema tologica 101:926, 2016. Guglielmelli P et al: Clinical impact of mutated JAK2 allele burden reduction in polycythemia vera and essential thrombocythemia. Am J Hematol 99:1550, 2024. Passamonti F et al: Myelofibrosis. Blood 141:1954, 2023. Spivak JL: How I treat polycythemia vera. Blood 134:341, 2019. Wouters HJCM et al: Erythrocytosis in the general population: Clinical characteristics and association with clonal hematopoiesis. Blood Adv 4:6353, 2020. William Blum

Acute Myeloid Leukemia INCIDENCE Acute myeloid leukemia (AML) is a neoplasm characterized by infil tration of the blood, bone marrow, and other tissues by proliferative, clonal, poorly differentiated cells of the hematopoietic system. These leukemias comprise a spectrum of malignancies that untreated are uniformly fatal. In 2023, the estimated number of new AML cases in the United States was 20,380. AML is the diagnosis in 1% of all cancer cases and 31% of all new acute leukemias but causes 62% of leukemic deaths. AML is the most common acute leukemia in older patients, with a median age at diagnosis of 69 years. U.S. registry data report that only 32% of patients survive 5 years. ■ ■ETIOLOGY Most cases of AML are idiopathic. Genetic predisposition, radiation, chemical/other occupational exposures, and drugs have been impli cated in the development of AML, but AML with established etiology is relatively uncommon. No direct evidence suggests a viral etiology. Genome sequencing studies suggest that most cases of AML arise from a limited number of mutations that accumulate with advancing age. Indeed, genome sequencing provides paradigm-shifting advances in our understanding of leukemogenesis. The Cancer Genome Atlas (TCGA) and other databases demonstrate that blood cells from up to 5–6% of normal individuals aged >70 years contain potentially "prema lignant" mutations that are associated with clonal expansion. Use of the term premalignant to describe these lesions is not pre cisely accurate;

rather, these mutations represent clonal hematopoiesis of indeterminate potential (CHIP; sometimes called age-related clonal hematopoiesis). The genes most commonly mutated in CHIP are the epigenetic regulators DNMT3A, TET2, and ASXL1. Study of CHIP is

important because it has relevance not just to blood cancer evolution but also other medical conditions. Clonal expansion driven by the acquisition of new mutations is associated with a 10-fold increase in risk for developing a hematologic malignancy (compared to matched patients without CHIP), but it is clear that additional “hits” must occur to drive toward leukemia. We do not yet fully understand why or how these secondary lesions occur.

Patients with CHIP also have increased risk of cardiovascular mor tality that is not fully explained. The link between these two seemingly unrelated issues (cardiovascular and hematologic malignancy) may lie in the interactions between circulating clonally expanded blood cells and vascular endothelium. A “proinflammatory” state caused by clonal, infiltrating monocytes leads to accelerated atherosclerotic plaque development and altered cardiac remodeling. Similar phenom ena may occur in the marrow/blood. An altered relationship between hematopoietic stem cells and the marrow microenvironment (along with altered immune surveillance) contributes to clonal survival and expansion. These perturbations increase the likelihood that a clone with somatic mutations may survive, acquire additional mutations, and then further expand eventually to leukemia. Whether early identi fication of CHIP in patients will provide therapeutic opportunities for patients remains to be seen. Certainly, modifying cardiovascular risk in patients with CHIP seems prudent, but development of mutationdirected therapy designed to eliminate a problematic clone and prevent future leukemia is likely to be more elusive. CHAPTER 109 Genetic Predisposition Myeloid neoplasms occur sporadically in adults; inherited predisposition is uncommon. Yet, it is clear that myeloid neoplasms with germline predisposition represent an impor tant and growing subset of disease. Germline mutations associated with increased risk of developing a myeloid neoplasm include CEBPA, DDX41, TP53, RUNX1, ANKRD26, ETV6, and GATA2, and others (Table 109-1). Myeloid neoplasms with germline predisposition are Acute Myeloid Leukemia TABLE 109-1 World Health Organization 2022, Subtypes of Myeloid Neoplasms Associated with Germline Predisposition Myeloid neoplasms with germline predisposition without a preexisting platelet disorder or organ dysfunction • Germline CEBPA P/LP variant (CEBPA-associated familial AML) • Germline DDX41 P/LP varianta • Germline TP53 P/LP varianta (Li-Fraumeni syndrome) Myeloid neoplasms with germline predisposition and preexisting platelet disorder • Germline RUNX1 P/LP varianta (familial platelet disorder with associated myeloid malignancy [FPD-MM]) • Germline ANKRD26 P/LP varianta (thrombocytopenia 2) • Germline ETV6 P/LP varianta (thrombocytopenia 5) Myeloid neoplasms with germline predisposition and potential organ dysfunction • Germline GATA2 P/LP variant (GATA2 deficiency) • Bone marrow failure syndromes • Severe congenital neutropenia (SCN) • Shwachman-Diamond syndrome (SDS) • Fanconi anemia (FA) • Telomere biology disorders • RASopathies (neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disordersa) • Down syndromea • Germline SAMD9 P/LP variant (MIRAGE syndrome) • Germline SAMD9L P/LP variant (SAMD9L-related ataxia pancytopenia syndrome)b • Biallelic germline BLM P/LP variant (Bloom syndrome) aLymphoid neoplasms can also occur. bAtaxia is not always present. Abbreviations: LP, likely pathogenic; P, pathogenic. Source: Modified from JD Khoury et al: The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and histiocytic/ dendritic neoplasms. Leukemia 36:1703, 2022.

a feature of several well-described clinical syndromes, including bone marrow failure disorders (e.g., Fanconi anemia, Shwachman-Diamond syndrome, Diamond-Blackfan anemia) and telomere biology disorders (e.g., dyskeratosis congenita). As new mutations and associations are added to a rapidly growing list, it is clear that genetic predisposition plays a larger role than has been previously understood.

Several genetic syndromes with somatic cell chromosome aneu ploidy, such as Down syndrome with trisomy 21, are associated with an increased incidence of AML. Down syndrome–associated AML in young children (<4 years) is typically of megakaryocytic differentiation and is associated with mutation in the GATA1 gene. Such patients have excellent clinical outcomes but require dose modification of chemo therapy due to high treatment-related toxicities. Inherited diseases with defective DNA repair (e.g., Fanconi anemia, Bloom syndrome, and ataxia-telangiectasia) are also associated with AML. Each syndrome is associated with unique clinical features and atypical toxicities with che motherapy, requiring expert care. Congenital neutropenia (Kostmann syndrome), due to mutations in the genes encoding the granulocyte colony-stimulating factor receptor and neutrophil elastase, is another disorder that may evolve into AML. Chemical, Radiation, and Other Exposures Anticancer drugs are the leading cause of therapy-associated AML. AML post chemo therapy (AML-pCT) with alkylating agents occurs 4–6 years after exposure; affected individuals often have multilineage dysplasia, monosomy/aberrations in chromosomes 5 and 7, mutations of TP53, and poor prognosis. AML-pCT with topoisomerase II inhibitors occurs 1–3 years after exposure; affected individuals often have AML with monocytic features and aberrations involving chromosome 11q23 (involved gene previously called MLL, now KMT2A). The risk of acute leukemia is much higher after combined-modality therapy with alkyl ating agent–based chemotherapy plus external beam radiation therapy. Exposure to ionizing radiation, benzene, chloramphenicol, phenylbu tazone, and other drugs can result in bone marrow failure that may evolve into AML. PART 4 Oncology and Hematology ■ ■CLASSIFICATION Historically, marrow (or blood) myeloid blast count of ≥20% estab lished the diagnosis of AML. However, biologically distinct groups are now primarily classified based on genetic aberrations, in addition to clinical features and light microscopy. It is increasingly understood that genetic aberrations drive clinical presentation and clinical course, and thus, in 2022, the World Health Organization (WHO) eliminated the blast percent requirement among cases with specific, defined genetic aberrations (Table 109-2). In the WHO system referenced here, genetic aberrations are notated by the gene mutation or fusion involved; learners may find clarity by also reviewing the European LeukemiaNet (ELN) risk classification (Table 109-3), which lists asso ciated cytogenetic abnormalities alongside the gene fusions. Dueling classification systems of the WHO and the International Consensus Classification (ICC) assign AML diagnosis inconsistently with regard to blast percent, but the differences are semantic. Cases with <20% blasts that are still classified as AML have recurrent genetic abnor malities including t(15;17), t(8;21), inv(16), t(16;16), rearrangements involving KMT2A (with many different fusion partners), mutations in NPM1 (nucleophosmin), and other defined genetic aberrations. The emergence of novel targeted treatment options for specific aberrations, such as menin inhibitors for patients with KMT2A rearrangement, NPM1 mutation, or (possibly) NUP98 rearrangement, suggests that a practical approach to classification based on the presence of a specific aberration regardless of blast count may indeed be most appropriate. All AML cells contain genetic mutations, most of which are recurring; in 2024, the majority of AML patients will have a genetic lesion that can be specifically targeted with a novel drug. Genetic Findings Subtypes of AML are recognized due to the presence or absence of specific, recurrent

cytogenetic, and/or genetic abnormalities. For example, the diagnosis of acute promy elocytic leukemia (APL) is based on the presence of the t(15;17)

TABLE 109-2 World Health Organization 2022 Classification of Acute Myeloid Leukemia Acute myeloid leukemia with defining genetic abnormalities Acute promyelocytic leukemia with PML::RARA fusion Acute myeloid leukemia with RUNX1::RUNX1T1 fusion Acute myeloid leukemia with CBFB::MYH11 fusion Acute myeloid leukemia with DEK::NUP214 fusion Acute myeloid leukemia with RBM15::MRTFA fusion Acute myeloid leukemia with BCR::ABL1 fusiona Acute myeloid leukemia with KMT2A rearrangement Acute myeloid leukemia with MECOM rearrangement Acute myeloid leukemia with NUP98 rearrangementb Acute myeloid leukemia with NPM1 mutation Acute myeloid leukemia with CEBPA mutationa,c Acute myeloid leukemia, myelodysplasia-relateda,d Acute myeloid leukemia with other defined genetic alterationsa Acute myeloid leukemia, defined by differentiation Acute myeloid leukemia with minimal differentiation Acute myeloid leukemia without maturation Acute myeloid leukemia with maturation Acute basophilic leukemia Acute myelomonocytic leukemia Acute monocytic leukemia Acute erythroid leukemia Acute megakaryoblastic leukemia aRequires ≥20% blasts. bNUP98 rearrangements involve 11p15, with many fusion partners, usually cryptic on cytogenetic analysis. cIncludes biallelic (biCEBPA) as well as single mutations located in the basic leucine zipper (bZIP) region. dDefining characteristics of Acute myeloid leukemia, myelodysplasia-related (AML-MR) include history of myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasm (MPN) and/or one of the following: complex karyotype, several other specific chromosome aberrations typical of MDS, or mutation of ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2. Source: Modified from JD Khoury et al: The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and histiocytic/ dendritic neoplasms. Leukemia 36:1703, 2022. (q22;q12) cytogenetic rearrangement or the PML-RARA fusion. Simi larly, core binding factor (CBF) AML is designated based on the pres ence of t(8;21)(q22;q22), inv(16)(p13.1q22), or t(16;16)(p13.1;q22) or the respective fusion products RUNX1-RUNX1T1 and CBFB-MYH11. Each of these three groups identifies patients with favorable clinical outcomes when appropriately treated. Many genetic AML subtypes are associated with a specific mor phologic appearance such as a complex karyotype (and/or mutation of TP53) and dysplastic morphology in AML, myelodysplasia-related (AML-MR). One abnormality is invariably associated with a spe cific morphologic feature: t(15;17)(q22;q12) or the molecular fusion PML-RARA with APL. Further examples include inv(16)(p13.1q22) with AML and abnormal bone marrow eosinophils; t(8;21)(q22;q22) and slender Auer rods, expression of CD19, and increased normal eosinophils; and rearrangements involving KMT2A with monocytic features. AML with mutation of NPM1, especially when co-occurring with mutation of FLT3 (fms-related tyrosine kinase 3), often pres ents with blasts having “cup-shaped” nuclear morphology. Recurring genetic aberrations in AML may also be loosely associated with spe cific clinical characteristics. More commonly associated with younger age are t(8;21) and t(15;17), and with older age are del(5q), del(7q), and mutated TP53. Myeloid sarcomas are associated with t(8;21); dis seminated intravascular coagulation (DIC) is associated with t(15;17). KMT2A aberrations and monocytic leukemia are associated with extramedullary sites of involvement at presentation, especially gingival hypertrophy. High leukocyte count is commonly observed with NPM1 and/or FLT3 mutation. Many other cytogenetic and genetic findings commonly, but not always, are associated with a morphologic descrip tion, highlighting the necessity of genetic and cytogenetic testing for precise diagnosis.

TABLE 109-3 2022 European LeukemiaNet Risk Classification of Acute Myeloid Leukemia (AML) by Genetics at Initial Diagnosisa RISK CATEGORY GENETIC ABNORMALITY Favorable • t(8;21)(q22;q22.1)/RUNX1::RUNX1T1b,c • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11b,c • Mutated NPM1b,d without FLT3-ITD • bZIP in-frame mutated CEBPAe Intermediate • Mutated NPM1b,d with FLT3-ITD • Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/MLLT3::KMT2Ab,f • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse Adverse • t(6;9)(p23.3;q34.1)/DEK::NUP214 • t(v;11q23.3)/KMT2A-rearrangedg • t(9;22)(q34.1;q11.2)/BCR::ABL1 • t(8;16)(p11.2;p13.3)/KAT6A::CREBBP • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1) • t(3q26.2;v)/MECOM(EVI1)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,h monosomal karyotypei • Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2j • Mutated TP53k aFrequencies, response rates, and outcome measures should be reported by risk category and, if sufficient numbers are available, by specific genetic lesions indicated. Acute promyelocytic leukemia is excluded from this table. bMainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease. cConcurrent KIT and/or FLT3 gene mutation does not alter risk categorization. dAMLs with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse risk. eOnly in-frame mutations affecting the basic leucine zipper (bZIP) region of CEBPA, irrespective of whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome. fThe presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations. gExcluding KMT2A partial tandem duplication (PTD). hComplex karyotype: three or more unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities. iMonosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding corebinding factor AML). jFor the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes. kTP53 mutation at a variant allele fraction of at least 10%, irrespective of the TP53 allelic status (mono- or biallelic mutation); TP53 mutations are significantly associated with AML with complex and monosomal karyotype. Source: Reproduced with permission from H Döhner et al: Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 140:1345, 2022. WHO classification incorporates molecular abnormalities by rec ognizing fusion genes or specific genetic mutations with a role in leu kemogenesis. As a classic example, t(15;17) results in the fusion gene PML-RARA that encodes a chimeric protein, promyelocytic leukemia (Pml)–retinoic acid receptor α (Rarα), which is formed by the fusion of the retinoic acid receptor α (RARA) gene from chromosome 17 and the promyelocytic leukemia (PML) gene from chromosome 15. Unique clinical therapy with retinoic acid and arsenic trioxide has revolution ized the care of APL patients (see “Treatment of Acute Promyelocytic Leukemia” section). Similar examples of molecular subtypes included in the category of AML with recurrent genetic abnormalities are those characterized by the leukemogenic fusion genes RUNX1-RUNX1T1 and CBFB-MYH11 and the so-called CBF AML subtypes noted cytogenetically as t(8;21), inv(16), or t(16;16). Additional examples of fusions are MLLT3-KMT2A and DEK-NUP214, resulting from t(9;11) and t(6;9)(p23;q34). Mutated genes are also critical elements of AML classification. The most common is AML with mutated NPM1, a mutation seen in 30% of AML patients and in 60% of those with cytogenetically normal AML (CN-AML). Another

subtype is AML with mutated CEBPA (specifically in-frame bZIP mutation). Both are

associated with more favorable clinical outcomes, though the presence of coexisting mutation in FLT3 negatively affects NPM1 prognostic impact. Activating mutations of FLT3 are present in ~30% of adult AML patients, primarily due to internal tandem duplications (ITDs) in the juxtamembrane domain that have negative prognostic impact. In contrast, point mutations of the activating loop of the kinase, called tyrosine kinase domain (TKD) mutations, have uncertain prognostic impact. Aberrant activation of the FLT3-encoded protein provides increased proliferation and antiapoptotic signals to the myeloid pro genitor cell. FLT3-ITD, the most common of the FLT3 mutations, also occurs preferentially in patients with CN-AML. The importance of identifying FLT3-ITD at diagnosis relates to the fact that it is not only useful as a negative prognosticator but also predicts response to specific treatment such as a tyrosine kinase inhibitor (TKI). Several TKIs targeting FLT3 are either approved for AML (e.g., midostaurin or quizartinib, only in first-line therapy in combination with chemo therapy; gilteritinib, in relapse as monotherapy) or currently in clinical investigation.

Immunophenotypic Findings The immunophenotype of human leukemia cells can be studied by multiparameter flow cytom etry after the cells are labeled with monoclonal antibodies to cellsurface antigens. This can be important in quickly distinguishing AML from acute lymphoblastic leukemia and for identifying some subtypes of AML. For example, AML with minimal differentiation, character ized by immature morphology and no lineage-specific cytochemical reactions, may be diagnosed by flow-cytometric demonstration of the myeloid-specific antigens cluster designation (CD) 13 and/or 117. Similarly, acute megakaryoblastic leukemia can often be diagnosed only by expression of the platelet-specific antigens CD41 and/or CD61. Although flow cytometry is widely used, and in some cases essential for the diagnosis of AML, it has only a supportive role in establishing the different subtypes of AML through the WHO classification given the paramount importance of genetics. Increasingly, multiparameter flow cytometry is used for the measurement of measurable residual disease (MRD) after remission is achieved. CHAPTER 109 Acute Myeloid Leukemia ■ ■PROGNOSTIC FACTORS Several factors predict outcome of AML patients treated with che motherapy; they should be used for risk stratification and treatment guidance. Chromosome and molecular investigations performed at diagnosis provide the most important prognostic information. Patients with t(15;17) have a very good prognosis (~85% cured), and those with t(8;21) and inv(16) have a good prognosis (~55% cured), whereas those with no cytogenetic abnormality have an intermediate outcome risk (~40% cured). Patients with NPM1 mutation without a FLT3-ITD also have favorable risk and high cure rate; conversely, those with TP53 mutation, complex karyotype, t(6;9), inv(3), or –7 have adverse risk and very poor clinical outcomes with virtually no chance for cure without transplantation. For patients lacking prognostic cytogenetic abnormalities, i.e., those with CN-AML, testing for several mutated genes can help to risk-stratify. In addition to NPM1 mutation and FLT3-ITD as described above, in-frame bZIP CEBPA mutation has favorable prognosis. Given the proven prognostic importance of NPM1, FLT3, and CEBPA, molecular assessment of these genes and others at diagnosis has been incorpo rated into AML management guidelines by the National Comprehen sive Cancer Network (NCCN) and the ELN. The same markers help to define genetic groups in the ELN standardized reporting system, which is based on both cytogenetic and molecular abnormalities and is used for comparing clinical features/treatment response among subsets of patients reported across different clinical studies (Table 109-3). These genetic groups should be used for risk stratification and treatment guidance (note that APL is excluded from the table). In addition to NPM1, FLT3, CEBPA, and TP53 mutations,

molecu lar aberrations in other genes are routinely used for prognostication. Among these mutated genes are those encoding receptor tyrosine kinases, transcription factors (RUNX1 and WT1), and epigenetic

modifiers (ASXL1, DNMT3A, isocitrate dehydrogenase 1 [IDH1], IDH2, and TET2). Among an expanding panel of mutated genes associated with adverse risk (at least when not coexisting with favorable aber rations) are ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2, and TP53. Because prognostic molecular markers in AML are not mutually exclusive and often occur concurrently (>80% patients have at least two or more prognostic gene mutations), distinct marker combinations will certainly be part of continued evolution of AML classification, prognosis, and treatment.

Novel drugs that inhibit/modulate cellular pathways activated by genetic aberrations (especially FLT3, IDH1, IDH2, and NPM1/ KMT2A/NUP98) have been remarkably effective in subsets of dis ease (see section on treatment of AML). Epigenetic changes (e.g., DNA methylation and/or posttranslational histone modification) and microRNAs are often involved in deregulation of genes involved in hematopoiesis, contribute to leukemogenesis, and may associate with the previously discussed prognostic gene mutations. These changes have been shown to provide biologic insights into leukemogenic mechanisms and provide independent prognostic information. Thera peutic progress based on advances in understanding the role of epi genetic changes in AML over the last decade has been tremendous. For example, in patients with mutations of IDH1 or IDH2, novel enzymes produced from these respective mutations have aberrant activity and “hijack” the citric acid cycle. These mutations lead to production of a novel “oncometabolite,” 2-hydroxyglutarate, which disrupts a myriad of epigenetic processes. Pharmacologic inhibition of these aberrant enzymes can reverse these leukemogenic activities and restore normal marrow function (though monotherapy is not typically curative). PART 4 Oncology and Hematology In addition to cytogenetic and molecular aberrations, several clini cal factors are associated with outcome in AML. Age at diagnosis is the most important. Advancing age is associated with a poor prognosis for two reasons: (1) its influence on the ability to survive induction therapy due to coexisting medical comorbidities, and (2) with each successive decade of age, a greater proportion of patients have intrinsically more resistant disease/adverse genetic risk. Next, a prolonged symptomatic interval with cytopenias preceding AML diagnosis, or a history of antecedent hematologic disorders including myelodysplastic syndrome (MDS) or myeloproliferative neoplasm, is often found in older patients. Preexisting cytopenia is a clinical feature associated with a lower com plete remission (CR) rate and shorter survival time. The CR rate is lower in patients who have had anemia, leukopenia, and/or thrombo cytopenia for >3 months before the diagnosis of AML when compared to those without such a history. Responsiveness to chemotherapy declines as the duration of the antecedent disorder increases. Likewise, AML-pCT, typically developing after treatment with cytotoxic agents for other malignancies, is often resistant to treatment given its associa tion with adverse genetic features. In general, older patients less fre quently harbor favorable genetic aberrations (e.g., t[8;21], inv[16], and t[16;16], NPM1 mutation) and more frequently harbor adverse genetic aberrations (e.g., complex karyotypes, mutations in ASXL1, TP53). Other factors independently associated with worse outcome are poor performance status, which influences ability to survive induction therapy, and a high presenting leukocyte count that in some series is an adverse prognostic factor for attaining a CR. Among patients with hyperleukocytosis (>100,000/μL), early central nervous system bleed ing and pulmonary leukostasis contribute to

poor outcomes. Following administration of therapy, achievement of CR is associ ated with better outcome and longer survival, of course. CR is defined after examination of both blood and bone marrow and essentially rep resents eradication of detectable leukemia and restoration of normal hematopoiesis. The blood neutrophil count must be ≥1000/μL and the platelet count ≥100,000/μL for formal criteria; CR with incomplete recovery of counts is a lesser but still meaningful response. Hemoglo bin concentration is not considered in determining CR. Circulating blasts should be absent. Although rare blasts may be detected in the blood during marrow regeneration, they should disappear on succes sive studies. At CR, the bone marrow should contain <5% blasts, and extramedullary leukemia should not be present.

■ ■CLINICAL PRESENTATION Symptoms Patients with AML usually present with nonspecific symptoms that begin gradually, though sometimes abruptly, and are the consequence of anemia, leukocytosis, leukopenia/leukocyte dys function, or thrombocytopenia. Nearly half have symptoms for ≤3 months before the leukemia is diagnosed. Fatigue is a frequent first symptom among AML patients. Anorexia and weight loss are common. Fever with or without an identifiable infection is the initial symptom in ~10% of patients. Signs of abnor mal hemostasis (bleeding, easy bruising) are common. Bone pain, lymphadenopathy, nonspecific cough, headache, or diaphoresis may also occur. Rarely, patients may present with symptoms from a myeloid sar coma (a tumor mass consisting of myeloid blasts occurring at anatomic sites other than bone marrow). Sites involved are most commonly the skin, lymph node, gastrointestinal tract, soft tissue, and testis. This may precede or coincide with blood and/or marrow involvement by AML. Patients who present with isolated myeloid sarcoma typically develop blood and/or marrow involvement quickly thereafter and cannot be cured with local therapy (radiation or surgery) alone. Physical Findings Fever, infection, and hemorrhage are often found at the time of diagnosis; splenomegaly, hepatomegaly, lymph adenopathy, and “bone pain” may also be present but less commonly. Hemorrhagic complications are most commonly and, classically, found in APL. APL patients often present with DIC-associated minor hem orrhage but may have significant gastrointestinal bleeding, intrapul monary hemorrhage, or intracranial hemorrhage. Counterintuitively, thrombosis while less frequent is another well recognized clinical feature of DIC in APL. Complications associated with coagulopathy may also occur in monocytic AML and with extreme degrees of leuko cytosis or thrombocytopenia in other morphologic subtypes. Retinal hemorrhages are detected in 15% of patients. Infiltration of the gin giva, skin, soft tissues, or meninges with leukemic blasts at diagnosis is characteristic of the monocytic subtypes and those with KMT2A chromosomal abnormalities. Hematologic Findings Anemia is usually present at diagnosis, although it is not typically severe. The anemia is usually normocytic normochromic. Decreased erythropoiesis in the setting of AML often results in a reduced reticulocyte count, and red blood cell (RBC) sur vival is decreased by accelerated destruction. Active blood loss may rarely contribute to the anemia. The median presenting leukocyte count for new AML cases is ~15,000/μL. Lower presenting leukocyte counts are more typical of older patients and those with antecedent hematologic disorders. Between 25 and 40% of patients have counts <5000/μL, and 20% have counts >100,000/μL. Fewer than 5% have no detectable leukemic cells in the blood. In AML blasts, the cytoplasm often contains primary (nonspecific) granules, and the nucleus shows fine, lacy chromatin with one or more nucleoli characteristic of immature cells. Abnormal rod-shaped granules called Auer rods are not uniformly present, but when they are, AML (and not acute lymphocytic leukemia) is certain (Fig. 109-1). Platelet counts <100,000/μL are found at diagnosis in ~75% of patients, and ~25% have counts <25,000/μL. Both morphologic and functional platelet abnormalities can be observed, including

large and bizarre shapes with abnormal granulation and inability of platelets to aggregate or adhere normally to one another. Pretreatment Evaluation Once the diagnosis of AML is suspected, thorough evaluation and initiation of appropriate therapy should follow. In addition to clarifying the subtype of leukemia, initial studies should evaluate the overall functional integrity of the major organ systems, including the cardiovascular, pulmonary, hepatic, and renal systems (Table 109-4). Factors that have prognostic significance, either for achieving CR or for CR duration, should also be assessed before initiat ing treatment including cytogenetics and molecular markers. Leukemic

A C FIGURE 109-1 Morphology of acute myeloid leukemia (AML) cells. A. Uniform population of primitive myeloblasts with immature chromatin, nucleoli in some cells, and primary cytoplasmic granules. B. Leukemic myeloblast containing an Auer rod. C. Promyelocytic leukemia cells with prominent cytoplasmic primary granules. D. Peroxidase stain shows dark blue color characteristic of peroxidase in granules in AML. cells should be obtained from all consenting patients and cryopreserved for future investigational testing as well as potential use as new diagnos tics and therapeutics become available. All patients should be evaluated for infection. Patients with respiratory symptoms should undergo test ing for the presence of the novel coronavirus, SARS-CoV-2, and other viruses before initiation of chemotherapy. Most patients are anemic and thrombocytopenic at presentation. Replacement of the appropriate blood components, if necessary, should begin promptly. Because qualitative platelet dysfunction or the pres ence of an infection may increase the likelihood of bleeding, evidence of hemorrhage justifies the immediate use of platelet transfusion even if the platelet count is only moderately decreased. About 50% of patients have a mild to moderate elevation of serum uric acid at presentation. Only 10% have marked elevations, but renal precipitation of uric acid and the nephropathy that may result is a seri ous but uncommon complication. The initiation of chemotherapy may aggravate hyperuricemia, and patients are usually started immediately on allopurinol and hydration at diagnosis. Rasburicase (recombinant uric oxidase) is also useful for treating uric acid nephropathy and often can normalize the serum uric acid level within hours with a single dose of treatment, although its expense suggests that limiting its

use to patients with severe hyperuricemia and/or kidney injury may be prudent (and it should be avoided in setting of glucose-6-phosphate dehydrogenase deficiency). The presence of high concentrations of lysozyme, a marker for monocytic differentiation, may be etiologic in renal tubular dysfunction for a minority of patients.

B CHAPTER 109 Acute Myeloid Leukemia D TREATMENT Acute Myeloid Leukemia Treatment of the newly diagnosed patient with AML is usually divided into two phases, induction and postremission management (consolidation) (Fig. 109-2). The initial goal is to induce CR. Once CR is obtained, further therapy must be given to prolong sur vival and achieve cure. The initial induction treatment and subse quent postremission therapy are chosen based on the patient’s age, overall fitness, and cytogenetic/molecular risk. Intensive therapy with cytarabine and anthracycline in younger patients (<60 years) increases the cure rate of AML. In older patients, the benefit of intensive therapy is controversial in all but favorable-risk patients; novel approaches for selecting patients predicted to be responsive to treatment and new therapies are being pursued. Importantly, even infirm older patients should be considered for therapy; treat ment is better than supportive care for all candidates. Improved options have emerged for older AML patients such as the addition of the BCL2 antagonist venetoclax to one of several low-intensity chemotherapies. Venetoclax is currently

in testing in combination with intensive chemotherapies as well. Likewise, novel oral drugs targeting IDH1/IDH2, alone (IDH1) or in combination (IDH1 and IDH2) with low-intensity chemotherapy, may be considered as initial therapy for unfit older patients who have mutations in those respective pathways.

TABLE 109-4 Initial Diagnostic Evaluation and Management of Adult Patients with AML History Increasing fatigue or decreased exercise tolerance (anemia) Excess bleeding or bleeding from unusual sites (DIC, thrombocytopenia) Fevers or recurrent infections (neutropenia) Headache, vision changes, nonfocal neurologic abnormalities (CNS leukemia or bleed) Early satiety (splenomegaly) Family history of AML (Fanconi, Bloom, or Kostmann syndromes or ataxia-telangiectasia) History of cancer (exposure to alkylating agents, radiation, topoisomerase II inhibitors) Occupational exposures (radiation, benzene, petroleum products, paint, smoking, pesticides) Physical Examination Performance status (prognostic factor) Ecchymosis and oozing from IV sites (DIC, possible acute promyelocytic leukemia) Fever and tachycardia (signs of infection) Papilledema, retinal infiltrates, cranial nerve abnormalities (CNS leukemia) PART 4 Oncology and Hematology Poor dentition, dental abscesses Gum hypertrophy (leukemic infiltration, most common in monocytic leukemia) Skin infiltration or nodules (leukemia infiltration, most common in monocytic leukemia) Lymphadenopathy, splenomegaly, hepatomegaly Back pain, lower extremity weakness (spinal granulocytic sarcoma, most likely in t[8;21] patients) Laboratory and Radiologic Studies CBC with manual differential cell count Chemistry tests (electrolytes, creatinine, BUN, calcium, phosphorus, uric acid, hepatic enzymes, bilirubin, LDH, amylase, lipase) Clotting studies (prothrombin time, partial thromboplastin time, fibrinogen, d-dimer) Viral serologies (CMV, HSV-1, varicella-zoster) RBC type and screen HLA typing for potential allogeneic HCT Bone marrow aspirate and biopsy (morphology, cytogenetics, flow cytometry, molecular studies) Cryopreservation of viable leukemia cells Myocardial function (echocardiogram or MUGA scan) PA and lateral chest radiograph Placement of central venous access device Interventions for Specific Patients Dental evaluation (for those with poor dentition) Lumbar puncture (for those with symptoms of CNS involvement) Screening spine MRI (for patients with back pain, lower extremity weakness, paresthesias) Social work referral for patient and family psychosocial support Counseling for All Patients Provide patients with information regarding their disease and genetic risks, sperm banking or menstrual suppression, financial counseling, support group contact, and consent for tissue banking of leukemic cells Abbreviations: AML, acute myeloid leukemia; BUN, blood urea nitrogen; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; DIC, disseminated intravascular coagulation; HLA, human leukocyte antigen; HCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; IV, intravenous; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PA, posteroanterior; RBC, red blood (cell) count. INDUCTION CHEMOTHERAPY The most commonly used induction regimens (for patients other than those with APL) consist of combination chemotherapy with cytarabine and an anthracycline (e.g., daunorubicin, idarubicin).

Cytarabine is a cell cycle S-phase–specific antimetabolite that becomes phosphorylated intracellularly to an active triphosphate form that interferes with DNA synthesis. Anthracyclines are DNA intercalators. Their primary mode of action is thought to be inhibi tion of topoisomerase II, leading to DNA breaks. In adults, cytarabine used at standard dose (100–200 mg/m2) is administered as a continuous intravenous infusion for 7 days. With cytarabine, anthracycline therapy generally consists of dau norubicin (60–90 mg/m2) or idarubicin (12 mg/m2) intravenously

on days 1, 2, and 3 (the 7+3 regimen). Other agents can be added (e.g., gemtuzumab ozogamicin) when 60 mg/m2 of daunorubicin is used. Patients failing remission after one induction are offered reinduction with the same (or slightly modified) therapy. The CD33-targeting immunoconjugate gemtuzumab ozogamicin may be added to induction therapy for subsets of patients, especially those with CBF AML. Many alternative intensive approaches other than 7+3 chemotherapy exist and are commonly used. In older patients (age ≥60–65 years), the outcome with conventional intensive therapy is generally poor due to a higher frequency of resistant disease and increased rate of treatment-related morbidity and mortal ity. Patients still fare far better with treatment than with supportive care only. Conventional therapy for fit older patients is similar to that for younger patients: the 7+3 regimen with standard-dose cytarabine and idarubicin (12 mg/m2) or daunorubicin (60 mg/m2). For patients aged >65 years, high-dose daunorubicin (90 mg/m2) has increased toxicity and is not recommended. A liposomal preparation of cytarabine and daunorubicin in a fixed molar ratio may instead be administered, especially to fit patients with AML-MR. Patients over

75 years and those unable to receive intensive therapy due to medi cal comorbidity may receive repetitive cycles of lower intensity ther apy with a hypomethylating agent (HMA; decitabine or azacitidine) or low-dose cytarabine in combination with daily venetoclax (BCL2 antagonist). As noted, targeted IDH1- or IDH2-directed therapy is another consideration for particularly infirm patients. All patients should be considered for clinical trials. With the 7+3 regimen (or other similar approaches), 60–80% of younger and 33–60% of older patients (among those who are candidates for intensive therapy) with primary AML achieve CR. Response rates around 60% in first line have been similarly reported with the combination of HMA plus venetoclax in older or infirm patient groups. Induction death is more frequent with advancing age and medical comorbidity, but the most common reason for treatment failure is lack of remission. Patients with refractory dis ease after inductions should be considered for salvage treatments, preferably on clinical trials. Planning for the possibility of alloge neic hematopoietic stem cell transplantation (HCT) for all eligible patients under age 75 years is part of optimal initial AML care. Typi cally, allogeneic HCT is performed only for patients who are in CR but at risk for relapse, but fit younger patients with primary refrac tory disease (not in remission after initial induction) have ~15–20% cure rates with allogeneic HCT after myeloablative conditioning. For this reason, early planning for possible future allogeneic HCT (including human leukocyte antigen [HLA] typing, donor search, etc.) should be part of the initial approach for most AML patients. POSTREMISSION THERAPY Induction of a durable first CR (CR1) is critical to long-term survival in AML. However, without further therapy, virtually all CR patients will eventually relapse. Thus, postremission therapy is designed to eradicate residual (typically undetectable) leukemic cells to prevent relapse and prolong survival. As with induction, the type of postremission therapy in AML is selected for each indi vidual patient based on age, fitness, and cytogenetic/molecular risk. The choice between consolidation with chemotherapy or with transplantation is complex and based on age, risk, and practi cal considerations. In younger patients receiving chemotherapy, postremission therapy with intermediate- or high-dose cytarabine for two to four cycles is standard practice. Higher doses of cyta rabine during postremission therapy appear more effective than

Refractory or relapsed Previously untreateda Favorable-risk Intermediate-risk Either option acceptable Either option acceptable Induction therapy: Daunorubicin+ cytarabine-based regimen Induction therapy: Daunorubicin+ cytarabine-based regimenb,c Investigational therapyb

Investigational therapyc If CR, consolidation therapy: Allogeneic HCT (preferred), or IDAC or autologous HCT if age <60d If CR: Investigational therapyd If CR: Investigational therapyd If CR, consolidation therapy: IDACd Refractory (no CR) or relapsed FIGURE 109-2 Algorithm for the therapy of newly diagnosed acute myeloid leukemia (AML). aRisk stratification according to the European LeukemiaNet (see Table 109-3). bYounger patients (<60–65 years) should routinely be offered investigational therapy on a backbone of standard intensive chemotherapy for induction and consolidation. cOlder patients, especially those >65 years or with adverse risk disease, or those who are unfit for intensive anthracycline + cytarabine regimens, may be considered for investigational therapy alone or in combination or lower intensity chemotherapy plus venetoclax. Whether venetoclax-containing regimens will be effective in younger, fit patients when compared to intensive chemotherapy is an important question. dNovel allogeneic transplantation approaches are preferred for nonfavorable risk when available; other investigational therapy or oral azacitidine (approved in nonfavorable risk) as maintenance should be considered following consolidation. Allogeneic hematopoietic cell transplantation (HCT) is a consideration for all eligible patients in first complete remission (CR) with non–favorable-risk disease and highly recommended for all older patients (60–75 years) and those with adverse risk. For all forms of AML in fit patients, except acute promyelocytic leukemia (APL), standard induction therapy includes a regimen based on a 7-day continuous infusion of cytarabine (100–200 mg/m2/d) and a 3-day course of daunorubicin (60–90 mg/m2/d) with or without additional drugs. Idarubicin (12 mg/m2/d) can be used in place of daunorubicin (not shown). The value of postremission/consolidation therapy for older patients (>60 years) who do not have favorable-risk disease is uncertain. Patients who achieve CR undergo postremission consolidation therapy, including sequential courses of intermediate-dose cytarabine, allogeneic HCT, autologous HCT, or novel therapies, based on their predicted risk of relapse (i.e., risk-stratified therapy). Patients receiving induction of lower intensity chemotherapy with venetoclax (or investigational therapy) typically receive repetitive cycles of same on an attenuated schedule, if necessary due to myelotoxicity, after achieving remission. Patients with APL (see text for treatment) usually receive tretinoin and arsenic trioxide–based regimens with or without anthracycline-based chemotherapy and possibly maintenance with tretinoin. HLA, human leukocyte antigen; IDAC, intermediate-dose cytarabine. standard doses (such as are used in induction) for those who do not have adverse-risk genetics. Studies have shown that the longstanding practice of high-dose cytarabine (3 g/m2, every 12 h on days 1, 3, and 5) may not improve survival over intermediate-dose cytarabine (IDAC; 1–1.5 g/m2) for such patients. Thus, the ELN has recommended IDAC at 1–1.5 g/m2, every 12 h, on days 1–3, as the optimal postremission chemotherapy approach for favorable- and

intermediate-risk younger patients, for two to four cycles. While high-dose cytarabine may not be necessary, it is important to note that younger, favorable-risk patients have worse outcomes when doses

<1 g/m2 are used. In contrast to favorable-risk patients, intermediate- or adverse-risk patients should proceed with allogeneic HCT in CR1 when feasible (see transplant discussion below). Because older patients have increased toxicities with higher doses of cytarabine, ELN recommends relatively attenuated cytarabine doses (0.5–1 g/m2, every 12 h, on days 1–3) in favorable-risk older patients. There is no clear value for intensive postremission therapy in non–favorable-risk

older patients; allogeneic HCT in CR1 (up to age 75 years) or investigational postremission therapy is recommended. Indeed, postremission therapy is an appropriate setting for introduction of new agents in both older and younger patients. For older patients (with nonfavorable cytogenetic risk) in CR after intensive therapy who have no transplantation option, maintenance treatment with prolonged low-dose oral azacitidine improves survival.

Diagnosis AML Salvage treatment Adverse-risk Patient with primary induction failure and candidate for myeloablative allogeneic HCT or CR2 achieved with salvage treatment and has suitable donor available Either option acceptable Induction therapy: Daunorubicin+ cytarabine-based regimenb,c Investigational therapyc Yes: Allogeneic HCT If CR, consolidation therapy: Allogeneic HCT (alternative donor transplant if no HLAmatched donor available)d If CR: Investigational therapyd No: Investigational therapy, autologous HCT considered for favorable-risk patients in CR2 with prolonged CR1 duration (>12 months) CHAPTER 109 Acute Myeloid Leukemia For patients treated initially with lower intensity regimens that include venetoclax, the current practice is to continue repetitive cycles of the same combination of agents after remission until disease progression. Therapy often must be abbreviated over time due to cumulative myelotoxicity. In the largest published trial with azacitidine and venetoclax in older AML, patients had median survival of <15 months; survival depended on genetic risk. The median duration of remission (including those with incomplete count recovery) was 17.5 months. Allogeneic HCT is the best relapse-prevention strategy cur rently available for AML. Allogeneic HCT is best understood as an opportunity for immunotherapy; residual leukemia cells potentially elicit an immunologic response from donor immune cells, the socalled graft-versus-leukemia (GVL) effect. The benefit of GVL in relapse risk reduction unfortunately is offset somewhat by increased morbidity and mortality from complications of HCT including graft-versus-host disease (GVHD). Given that relapsed AML is typically resistant to chemotherapy, allogeneic HCT in CR1 (i.e., before relapse ever occurs) is a favored strategy. We have often explained to patients that transplant can effectively “eliminate the needle in a haystack, but not a stack of needles.” Transplant is recom mended for patients age <75 years who do not have favorable-risk disease and who have an available HLA-compatible donor (related or unrelated). We recommend allogeneic HCT in CR1 for patients

with intermediate-risk disease (Table 109-3). However, consider able debate exists regarding whether allogeneic HCT in CR1 is a requirement for younger patients with intermediate-risk AML, as one large series from the Medical Research Council reported that such patients have similar outcomes if transplanted only after relapse (and achievement of CR2), sparing some the long-term morbidity of transplantation. That said, allogeneic HCT is generally recommended as soon as possible after CR1 is achieved unless the patient is in a favorable-risk group. Patients without HLA-matched donors are considered for alternative donor transplants (e.g., HLAmismatched unrelated, haploidentical related, and umbilical cord blood) even in CR1. More effective and safe methods of in vivo T-cell depletion (e.g., posttransplant cyclophosphamide following mismatched transplantation or use of abatacept) have broadened the availability of potential allogeneic HCT donors. Now, virtually any patient with a healthy parent or child has an available donor suitable for allogeneic HCT if desired. Long-term outcomes with conventional chemotherapy for older patients are dismal; trans plantation for such patients is expanding and improving outcomes.

Trials comparing allogeneic HCT with intensive chemotherapy or autologous HCT have shown improved duration of remission with allogeneic HCT. The relapse risk reduction observed with

allogeneic HCT, however, is partially offset by the increase in fatal treatment-related toxicity (GVHD, organ toxicity). Despite this, there is no debate that patients with adverse-risk AML have improved long-term survival with early allogeneic HCT. For rare patients with no allogeneic donor option, high-dose chemotherapy with autologous HCT rescue is another postremission approach in non–adverse-risk subsets. Autologous HCT patients receive their own stem cells (collected during remission and cryopreserved), fol lowing administration of myeloablative chemotherapy. The toxicity is relatively low with autologous HCT (5% mortality rate), but the relapse rate is higher than with allogeneic HCT due to the absence of the GVL effect. Favorable- and intermediate-risk patients may benefit from autologous HCT; it is not recommended in adverserisk patients. Practically speaking, autologous HCT in AML patients is less frequently employed currently due to enhanced relapse risk reduction seen with allogeneic HCT and the growing availability of HLA-mismatched donors (and novel transplantation approaches). PART 4 Oncology and Hematology Prognostic factors help to select the appropriate postremission therapy in patients in CR1. Our approach includes allogeneic HCT in CR1 for patients without favorable cytogenetics or genotype. Patients with adverse-risk disease should proceed to allogeneic HCT at CR1 if possible. The decision for allogeneic HCT for younger intermediate-risk patients is complex and individualized as described above; we recommend it. Subsets of patients may benefit from targeted therapy given during remission; emerging data demonstrate survival benefit from incorporation of the FLT3 inhibitors midostaurin or quizartinib, for example, into induction and postremission therapies for patients with FLT3-mutated AML. Allogeneic transplantation in CR1 is still recommended for most of these patients. For patients in morphologic CR, measurement of MRD remains a very important and challenging research area. Cytogenetics are a mainstay of disease assessment, and persistence of abnormal karyotype (despite morphologic CR) is clearly associated with poor clinical outcomes. Immunophenotyping (flow cytometry) to detect minute populations of blasts and/or sensitive molecular assays such as quantitative reverse transcriptase polymerase chain reaction (RT-PCR) to detect AML-associated molecular abnormalities when present (e.g., NPM1, RUNX1/RUNX1T1 and CBFB/MYH11 tran scripts, PML/RARA) can be performed to assess MRD at sequential time points during or after treatment. We know that continued detection of MRD after therapy is unfavorable. Whether emerg ing next-generation sequencing or serial quantitative assessment using flow or PCR, performed during remission, can effectively direct subsequent therapy and improve clinical outcome remains to be determined for most subtypes. Currently, no consensus exists for the optimal MRD measurement technique or its application,

although testing is increasingly employed in clinical practice. Data suggest that MRD measurement can in some settings be a reliable discriminator between patients who will continue in CR or relapse, but whether subsequent therapy (i.e., allogeneic HCT or additional therapy) can effectively eradicate disease in such patients is not yet clear. For patients with NPM1 mutation, MRD-negative status by NPM1 PCR after two courses of chemotherapy predicts favorable outcome without transplantation (even for patients with coexisting FLT3 mutation); emerging data demonstrate that transplantation of MRD-positive patients does indeed improve outcome (rather than just predict they will do poorly irrespective of subsequent therapy given). In the subset of patients with APL, serial PCR (for the PML/ RARA transcript) is a very useful and reliable tool to detect early relapse and to direct initiation of reinduction therapy prior to onset of overt relapse. Critical in the general understanding of MRD in all disease subsets is the recognition that even patients with undetect able levels of MRD remain at risk for leukemic relapse. SUPPORTIVE CARE Measures geared to supporting patients through several weeks of neutropenia and thrombocytopenia are critical to

successful AML therapy. Patients with AML should be treated in centers expert in providing supportive care. Multi-lumen central venous catheters should be inserted as soon as newly diagnosed AML patients have been stabilized. They should be used thereafter for administration of intravenous medications/chemotherapy and transfusions, as well as for blood drawing instead of venipuncture during prolonged periods of myelosuppression. Adequate and prompt blood bank support is critical to therapy of AML. Platelet transfusions should be given as needed to maintain a platelet count ≥10,000/μL. The platelet count should be kept at higher levels in febrile patients and during episodes of active bleeding or DIC. Patients with poor posttransfusion platelet count increments may benefit from administration of ABO-matched platelets or platelets from HLA-matched donors. RBC transfusions should be considered to keep the hemoglobin level >70–80 g/L (7–8 g/dL) in the absence of active bleeding, DIC, or congestive heart failure, which may require higher hemoglobin levels. Blood products leukodepleted by filtra tion should be used to avert or delay alloimmunization as well as febrile reactions. Blood products may also be irradiated to prevent transfusion-associated GVHD. Neutropenia (neutrophils <500/μL or <1000/μL and predicted to decline to <500/μL over the next 48 h) can be part of the initial presentation and/or a side effect of the chemotherapy treatment in AML patients. Thus, infectious complications remain the major cause of morbidity and death during induction and postremission chemotherapy for AML. Antibacterial (e.g., quinolones) and anti fungal (e.g., posaconazole) prophylaxis, especially in conjunction with regimens that cause mucositis, is beneficial. For patients who are herpes simplex virus or varicella-zoster seropositive, antiviral prophylaxis should be initiated (e.g., acyclovir, valacyclovir). Fever develops in most patients with AML, but infections are documented in only half of febrile patients. Empiric initiation of empirical broad-spectrum antibacterial and antifungal antibiotics has significantly reduced the number of patients dying of infectious complications (Chap. 79). An antibiotic regimen adequate to treat gram-negative organisms should be instituted at the onset of fever in a neutropenic patient after clinical evaluation, including a detailed physical examination with inspection of the indwelling catheter exit site and a perirectal examination (for perirectal abscess), as well as procurement of cultures and radiographs aimed at docu menting the source of fever. Specific antibiotic regimens should be based on institutional antibiotic sensitivity data obtained from where the patient is being treated. Acceptable regimens for empiric antibiotic therapy include monotherapy with imipenem-cilastatin, meropenem, piperacillin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime or ceftazidime). The combination of an aminoglycoside with an antipseudomonal peni cillin (e.g., piperacillin) or an aminoglycoside in combination with

an extended-spectrum antipseudomonal cephalosporin should be considered in complicated or resistant cases. Aminoglycosides should be avoided, if possible, in patients with renal insufficiency. Empirical vancomycin should be added in neutropenic patients with catheter-related infections, blood cultures positive for grampositive bacteria before final identification and susceptibility test ing, hypotension or shock, or known colonization with penicillin/ cephalosporin-resistant pneumococci or methicillin-resistant Staphylococcus aureus. In special situations where decreased sus ceptibility to vancomycin, vancomycin-resistant organisms, or van comycin toxicity is documented, other options including linezolid and daptomycin need to be considered. Caspofungin (or a similar echinocandin), voriconazole, isavu conazonium, or liposomal amphotericin B should be considered for antifungal treatment if fever persists for 4–7 days following initiation of empiric antibiotic therapy. Although liposomal for mulations of amphotericin B have improved the toxicity profile of this agent, use has been limited to situations with high risk of or documented mold

infections, especially in those in whom an azole fails. Caspofungin has been approved for empiric antifungal treat ment. Voriconazole has also been shown to be equivalent in efficacy and less toxic than amphotericin B; isavuconazonium may also be effective with fewer drug-drug interactions. Unfortunately, use of prophylactic or empiric antibiotics contributes to the development of resistance and increased incidence of nosocomial infections such as Clostridium difficile colitis, so hospital-wide antibiotic surveil lance and isolation strategies should be employed to reduce these complications. Recombinant hematopoietic growth factors have a limited role in AML; myeloid growth factors may be useful in the postremission setting but are not recommended in induction or for “palliative” care for patients not in remission. TREATMENT FOR REFRACTORY OR RELAPSED AML In patients who relapse after achieving CR, the length of first CR is predictive of response to salvage chemotherapy treatment; patients with longer first CR (>12 months) generally relapse with drugsensitive disease and have a higher chance of attaining a CR, even with the same chemotherapeutic agents used for first remission induction. Patients with short prior CR duration are at high risk for treatment failure. Similar to patients with refractory disease, patients with relapsed disease are rarely, if ever, cured by salvage chemotherapy treatments alone. Therefore, patients who eventually achieve a second CR and are eligible for allogeneic HCT should be transplanted. For patients who relapse after allogeneic HCT, no consensus for best therapy exists; outcomes in this setting are very poor. Because achievement of a second CR with routine salvage thera pies is relatively uncommon, especially in patients who relapse rapidly after achievement of first CR (<12 months), these patients and those lacking HLA-compatible donors or who are not candidates for alloge neic HCT should be considered for innovative approaches on clinical trials. Many new agents are in current testing (Table 109-5). The dis covery of novel gene mutations and mechanisms of leukemogenesis that might represent actionable therapeutic targets has prompted the development of many new targeting agents. In addition to kinase inhibitors for FLT3-mutated AML, other compounds target ing the aberrant activity of mutant proteins (e.g., IDH1/2 inhibi tors) and numerous other biologic mechanisms are either approved by the Food and Drug Administration (FDA) or being tested in clinical trials. Inhibitors of FLT3 (gilteritinib, quizartinib), IDH1 (ivosidenib, olutasidenib), or IDH2 (enasidenib) are approved in AML. Exciting early clinical data with menin inhibitors in AML with KMT2A rearrangement, NPM1 mutation, or other genetic aberrations with shared biology of HOXA cluster gene upregulation are likely to result in FDA approval of the first agent in this pathway during 2024. Furthermore, approaches with antibodies targeting markers commonly expressed on leukemia blasts (e.g., CD33) or leukemia-initiating cells (e.g., CD123) are also under investiga tion. Next-generation immune compounds such as bispecific or

TABLE 109-5 Novel Therapies in Clinical Development in Acute Myeloid Leukemia (AML) APPROVED BY FOOD AND DRUG ADMINISTRATION

SINCE 2017 UNDER INVESTIGATION Kinase inhibitors/ cell signaling FLT3 inhibitors IRAK-4 inhibitors KIT inhibitors PI3K/AKT/mTOR inhibitors Aurora and polo-like kinase inhibitors, CDK4/6 inhibitors, CDK9 inhibitors, CHK1, WEE1, CSFR1, and MPS1 inhibitors SRC and HCK inhibitors Syk inhibitors Midostaurin (FLT3) Gilteritinib (FLT3) Quizartinib (FLT3) Pemigatinib (FGFR1) Epigenetic modulators Menin inhibitors, other spliceosome modulators DNA methyltransferase inhibitors Histone methylation or acetylation modulators Other spliceosome modulators IDH1 and IDH2 inhibitors DOT1L inhibitors BET-bromodomain inhibitors Revumenib (menin inhibitor; FDA review pending, 2024) Enasidenib (IDH2) Ivosidenib (IDH1) Olutasidenib (IDH1) CHAPTER 109 Chemotherapeutic agents Liposomal preparations Nucleoside analogues CPX-351 (liposomal cytarabine and daunorubicin) Oral azacitidine Acute Myeloid Leukemia Mitochondrial inhibitors BH3 mimetics; Bcl-

2, Bcl-xL, and Mcl-1 inhibitors Caseinolytic protease inhibitors Venetoclax (BCL2) Therapies targeting oncogenic proteins Fusion transcript targeting EVI1 targeting NPM1 targeting Hedgehog inhibitors Glasdegib (hedgehog) Antibodies and immunotherapies Monoclonal antibodies against CD33, CD44, CD47, CD123, CLEC12A Immunoconjugates Bispecific T-cell engagers (BiTEs) and dual-affinity retargeting molecules (DARTs) for CD33, CD123, others Trispecific T-cell or NK-cell engagers Chimeric antigen receptor (CAR) T cells, genetically engineered T-cell receptor (TCR) T cells, CAR-NK cells Immune checkpoint inhibitors (PD-1/PD-L1, CTLA-4, LAG-3, LILRB4) Vaccines Gemtuzumab ozogamicin (CD33-toxin) Therapies targeting AML environment CXCR4 and CXCL12 antagonists Antiangiogenic therapies Source: Reproduced with permission from H Döhner et al: Diagnosis and management of acute myeloid leukemia in adults: 2017 recommendations from an international expert panel. Blood 129:424, 2017. trispecific antibodies are promising and under study. Investigation of these in combination with other molecular targeting compounds and/or chemotherapy should be pursued. TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA APL is a highly curable AML subtype, and ~85% of these patients achieve long-term survival with current approaches. APL has long been shown to be responsive to cytarabine and daunorubicin. However, in the past, patients who were treated with these drugs

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Revision #1
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