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Acute myeloid leukemia

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Definition and epidemiology

Acute myeloid leukemia (AML) is a heterogeneous clonal hematopoietic progenitor and/or stem cell malignancy in which immature hematopoietic cells proliferate and accumulate in the bone marrow, blood, and/or other tissues (see video in online edition). This process results in the inhibition of normal hematopoiesis, manifesting as neutropenia, anemia, thrombocytopenia, and the clinical features of bone marrow failure. AML accounts for 90% of all acute leukemias in adults, with an estimated 20,240 new cases and 11,400 deaths expected in the United States in 2021. The annual incidence is approximately 4.3 per 100,000 and increases with age, with approximately a 10-fold increased risk between the ages of 20 (1 case per 100,000) and 65 (1 case per 10,000) years. The median age at diagnosis is approximately 68 years, with approximately 6% of patients younger than 20 years and 34% of patients 75 years or older. While gradually improving over time, average overall survival in adults is still poor, with ~25% 5-year survival in patients older than 20 years. Survival is highly dependent on age (~45% 5-year survival for patients aged 45, <10% for those older than 60 years). In children, 5-year survival now approaches 70%.

Most cases of AML have no known apparent cause. Clonal hematopoiesis, whether as age-related clonal hematopoiesis or clonal hematopoiesis of indeterminate potential (CHIP), can be found in apparently healthy individuals but has been established as an important predisposing mechanism for the development of myeloid malignancies; it can predate a diagnosis of AML by many years. The most common recognized risk factor is previous exposure to radiation or chemotherapeutics, particularly topoisomerase II inhibitors and alkylating agents, which result in therapy-related AML (t-AML) and account for ~10% to 20% of all AML cases. The incidence of AML arising after exposure to alkylating agents or radiation therapy increases with age, typically has a 5- to 10-year latency period, and frequently is associated with an antecedent therapy-related myeloid neoplasm, such as myelodysplastic syndrome (MDS) and unbalanced loss of genetic material involving chromosomes 5 or 7 and/or a mutation in *TP53*. t-AML associated with exposure to topoisomerase II inhibitors is less common, encompasses 20% to 30% of patients with t-AML, has a shorter latency period of 1 to 5 years, is less often preceded by a myelodysplastic phase, and may be associated with balanced recurrent chromosomal translocations involving



The online version of this chapter contains an educational multimedia component on acute myeloid leukemia.

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11q23 (*MLL* gene) or 21q22 (*RUNX1*). t-AML has also been observed after exposure to other drugs such as azathioprine or other immune suppressants. Environmental exposures linked to the development of t-AML include benzene and ionizing radiation. Moreover, recent studies have shown that CHIP mutations likely create a permissive state that allows for the development of t-AML resulting from cytotoxic damage from chemotherapy.

Clinical manifestations

Patients with AML generally present with signs and symptoms related to infiltration of leukemic blasts into the bone marrow resulting in disruption of normal hematopoiesis with clinical manifestations of infections, anemia, and thrombocytopenia. Symptoms include 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. Aberrancies of cellular adhesion molecules, chemokine receptors/ligands and, perhaps, Ras-MAPK/ERK signaling has been associated with increased risk of extramedullary disease at presentation. Patients with leukocytosis and >50,000 leukemic blasts per μL are at increased risk of pulmonary and CNS complications caused by microinfarction and hemorrhage from leukostasis.

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 these abnormalities may be present in all subtypes. Metabolic abnormalities related to tumor lysis, including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, may be present and can be life-threatening.

Diagnostic workup

The initial evaluation for patients with suspected AML consists of studies to confirm the diagnosis, characterize the disease and disease risk (eg, cytogenetic and molecular abnormalities, antecedent hematologic disorders, and prior toxic exposures), and assess patient-specific factors (eg, comorbid conditions). A bone marrow examination (aspiration and, if dry tap, biopsy) is typically central to establish a diagnosis of AML by demonstrating the presence of >20% blasts on an aspirate smear, immunophenotyping by flow cytometry to confirm the blasts are of myeloid lineage and, for classification purposes, to assess for the presence of dysplastic features. In addition,

traditional cytogenetics, fluorescence in situ hybridization (FISH) (if there are inadequate cells in metaphase for cytogenetics) and molecular testing for mutant genes as published in national consensus guidelines (*FLT3*, *NPM1*, *CEBPA*, *ASXL1*, *RUNX1*, *TP53*, *IDH1/IDH2*) should be undertaken for risk stratification and/or identification of therapeutic targets. In some patients, the diagnosis and risk stratification of AML can be established by examination of the peripheral blood alone, although this approach does not allow for a reliable assessment of cell lineage dysplasias.

Subtype classification

In the 1970s, the French-American-British classification system for AML was established and allowed subclassification using morphologic and cytochemical criteria to define 8 major AML subtypes (M0 to M7) on the basis of greater than or equal to 30% blasts, lineage commitment, and the degree of blast cell differentiation. The French-American-British system has now 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 classification system recognizes a number of genetically defined subgroups of AML (Table 19-1).

Currently, AML is (arbitrarily) 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 cell surface antigens remains important in AML and may include progenitor-associated antigens (eg, human leukocyte antigen-DR [HLA-DR], CD34, CD117) and myeloid antigens (eg, CD13, CD33). Complex composite immunophenotypes, including expression of lymphoid markers, also may be present.

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 older than 60

Table 19-1 World Health Organization 2016 classification of acute myeloid leukemia and related myeloid neoplasms

Acute myeloid leukemia and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i>
AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i>
APL with <i>PML-RARA</i>
AML with t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i>
AML with t(6;9)(p23;q34.1); <i>DEK-NUP214</i>
AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2, MECOM</i>
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); <i>RBM15-MKL1</i>
Provisional entity: AML with <i>BCR-ABL1</i>
AML with mutated <i>NPM1</i>
AML with biallelic mutations of <i>CEBPA</i>
Provisional entity: AML with mutated <i>RUNX1</i>
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia

years, and especially those older than 75 years, have particularly poor long-term survival because of disease- and host-related factors, medical comorbidities, and poor performance status; such patient-specific aspects play important roles as prognostic and treatment decision-making tools in AML.

Both chromosomal (cytogenetic) and molecular abnormalities present in the leukemic blasts are the primary disease characteristics used in assigning prognosis for patients with newly diagnosed AML and are integrated in contemporary risk schemes (Figure 19-1). Acquired, clonal chromosomal abnormalities, including balanced translocations, inversions, deletions, monosomies, and trisomies may be found in as many as 60% of patients with newly diagnosed AML. The karyotype is considered complex when there are more than 3 abnormalities, found in 10% to 20% of patients, often in association with a *TP53* gene mutation or deletion. Cytogenetic findings remain

an important prognostic tool and are classified into favorable-, intermediate-, and unfavorable-risk groups. It is universally agreed 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. However, outcomes are not universally favorable in these AML subtypes; eg, in some studies, the presence of a mutation in exon 17 of *KIT* has been associated with increased risk of relapse in patients with t(8;21)(q22;q22) AML. Complex karyotype, inv(3)(q21q26)/t(3;3)(q21;q26), and monosomal karyotypes (at least 2 autosomal monosomies or 1 single-autosomal monosomy combined with at least 1 structural abnormality) are associated with particularly poor outcomes.

Molecular alterations provide important prognostic information for many patients with AML, particularly those with a normal karyotype. These patients form the largest cytogenetic subset of AML and, without further ability to classify them, 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% to 25% of patients with AML have fms-like tyrosine kinase 3 (*FLT3*) length mutations (inclusive of internal tandem duplications [ITDs]), which are associated with an inferior prognosis, particularly when present at a high allelic ratio. A smaller subset of patients has mutations in the *FLT3* tyrosine kinase domain (TKD). In addition, heterozygous mutations in exon 12 of the nucleophosmin 1 (*NPM1*) gene have been found in 40% to 60% of AML patients with a normal karyotype, and mutated *NPM1*, in conjunction with wild-type *FLT3* or low allelic ratio *FLT3* ITD, is associated with a favorable prognosis. Biallelic mutations of the CCAAT-enhancer-binding protein A gene (*CEBPA*), a gene encoding a myeloid transcription factor important for normal granulopoiesis, are also associated with favorable clinical outcomes. Certain mutations, such as *IDH1/IDH2* and *FLT3*, may have therapeutic implications because specific inhibitors of these mutant proteins are available.

Whereas evaluating for mutations in *NPM1*, *FLT3*, and *CEBPA* has 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.

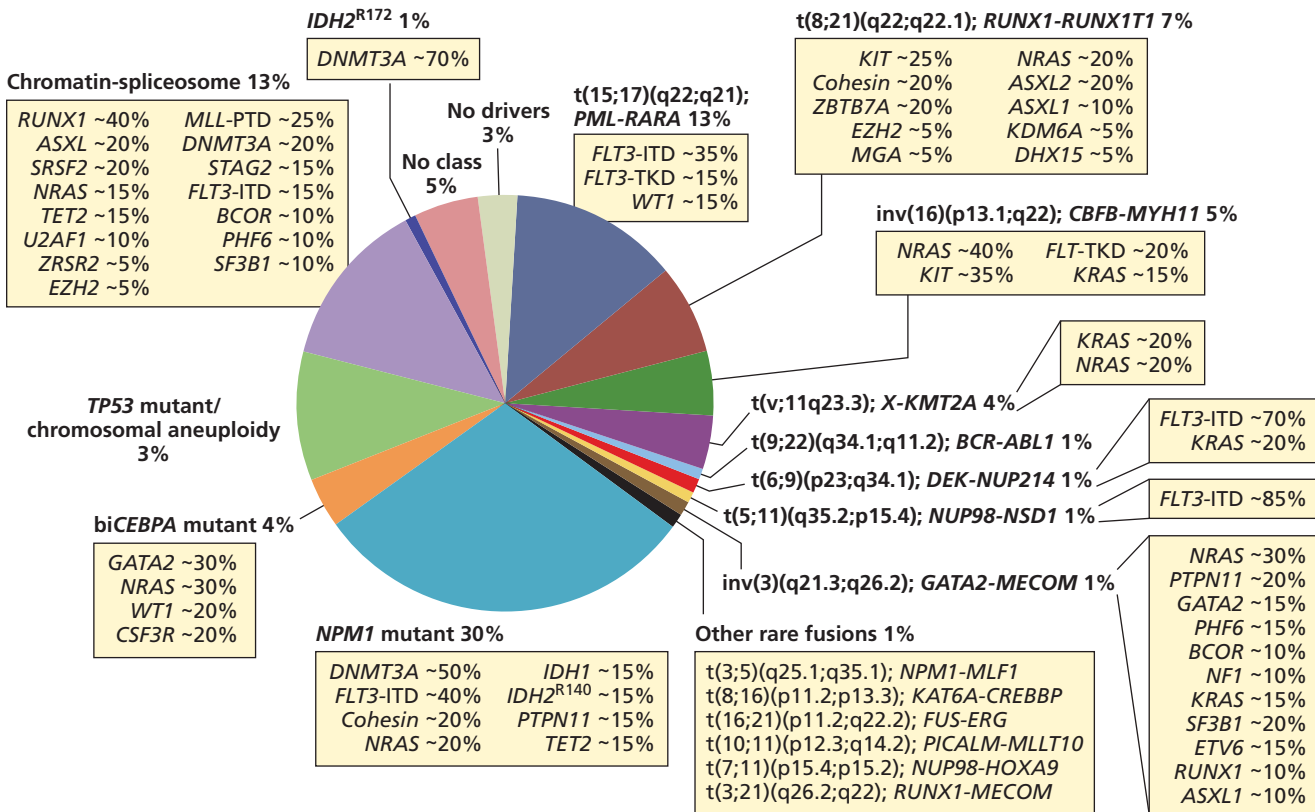


Figure 19-1 Major cytogenetic and molecular genetic subgroups of AML (and associated gene mutations). Adapted from Döhner H et al, *Blood*. 2017;129(4):424-447, with permission.

In addition, genetic profiling of patients with AML has started to yield insights into distinct prognostic subgroups of patients with various co-occurring mutations. Such analyses demonstrated that certain mutations, such as *NPM1* and *FLT3-ITD*, co-occur frequently, 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 distinct prognosis. Identification of recurrent mutations has also served as an impetus for the development of novel therapeutic inhibitors of the mutated proteins and has led to ongoing efforts to conduct clinical trials combining novel agents to target each genetic alteration. Because of the prognostic and therapeutic implications of certain genetic alterations, molecular genetic analysis for mutations with prognostic and therapeutic impact are imperative at the time of diagnosis. These mutations currently include *NPM1*, *FLT3*, *CEBPA*, *TP53*, *RUNX*, *ASXL1*, *IDH1*, and *IDH2*.

Recent efforts to combine the information from karyotypic and molecular aberrations have been set forth

by the European LeukemiaNet (ELN), which currently defines 3 risk groups (Table 19-2), but it is expected that risk classification schemes continue to evolve as the impact of cytogenetic/molecular abnormalities, alone or in combinations, becomes better understood.

KEY POINTS

- The most important prognostic indicators in AML are patient age, cytogenetics, and molecular genetics. At diagnosis, check for mutations in *NPM1*, *FLT3* (ITD and TKD), *CEBPA*, *ASXL1*, *RUNX1*, *TP53*, *IDH1*, and *IDH2*.
- Complex cytogenetic abnormalities and monosomal karyotypes are associated with poor clinical outcomes.
- t(15;17), t(8;21), and inv(16) are cytogenetic abnormalities associated with more favorable outcomes.
- Patients with cytogenetically normal AML and *FLT3* ITD mutations have an unfavorable prognosis particularly when present at high allelic ratio. Patients with wild-type *FLT3* (or low allelic ratio *FLT3* ITD), mutations of *NPM1*, or biallelic *CEBPA* mutations have more favorable prognoses.

Table 19-2 European LeukemiaNet risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i>
	inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i>
	Mutated <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i> ^{low†}
	Biallelic mutated <i>CEBPA</i>
Intermediate	Mutated <i>NPM1</i> and <i>FLT3-ITD</i> ^{high†}
	Wild-type <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i> ^{low†} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i> [‡]
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); <i>DEK-NUP214</i>
	t(v;11q23.3); <i>KMT2A</i> rearranged
	t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i>
	inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2,MECOM(EVI1)</i>
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype, [§] monosomal karyotype
	Wild-type <i>NPM1</i> and <i>FLT3-ITD</i> ^{high†}
	Mutated <i>RUNX1</i> [¶]
	Mutated <i>ASXL1</i> [¶]
	Mutated <i>TP53</i> [#]

Adapted from Döhner H et al, *Blood*. 2017;129(4):424–447, with permission.

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

*Prognostic impact of a marker is treatment-dependent and may change with new therapies.

[†]Low indicates low allelic ratio (<0.5); high indicates high allelic ratio (≥0.5); semiquantitative assessment of *FLT3-ITD* allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve “*FLT3-ITD*” divided by area under the curve “*FLT3-wild type*,” recent studies indicate that acute myeloid leukemia with *NPM1* mutation and *FLT3-ITD* low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.

[‡]The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

[§]Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

^{||}Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).

[¶]These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

[#]*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

Treatment of newly diagnosed AML

The modern era of AML therapy began in 1973 with the introduction of combination chemotherapy with cytarabine for 7 days and an anthracycline for 3 days (“7+3”). Over the subsequent several decades, the treatment algorithm has remained largely unchanged. For medically fit patients (typically younger than age 60 to 65), cure was considered possible and 7+3 or some other type of intensive combination chemotherapy would be offered followed by further courses of chemotherapy and or allogeneic or autologous hematopoietic cell transplantation (HCT) if a complete remission (CR) was achieved. For medically less-fit patients (typically older), cure was considered very unlikely, and some form of less intensive, palliative chemotherapy would be

offered, most commonly with low-dose cytarabine or, more recently, an azanucleoside such as azacitidine or decitabine. With the availability of several new drugs—the United States Food and Drug Administration (FDA) has granted approval for 9 new agents between 2017 and 2020—the treatment options have substantially increased. Nonetheless, the assessment of the medical fitness of the patient, either informally or via use of 1 of several instruments that assess the burden of comorbidities, organ dysfunction, and/or frailty, has remained central to guide the choice of initial AML therapy. While AML is often perceived as medical emergency, several larger studies have indicated that the time between diagnosis of AML and treatment initiation is not related to survival. Therefore, it may be feasible to delay treatment for a few days to obtain genetic and molecular disease

information as long as the white blood cell (WBC) and blood blast count is not rapidly increasing to select the most appropriate therapy.

Treatment for medically fit patients

Induction therapy

For medically fit adults, initial treatment for AML is generally divided into remission induction and postremission therapy and may also include maintenance therapy. Except for APL (see “Acute promyelocytic leukemia” later in this chapter) and newly diagnosed t-AML or AML with myelodysplasia-related changes, standard AML remission induction therapy in the United States most commonly includes 7+3 with cytarabine 100 to 200 mg/m²/day (typically given via continuous infusion although twice daily subcutaneous administration is equally effective) and either idarubicin 12 mg/m²/day or daunorubicin. In large cooperative group trials, daunorubicin at a dose of 90 mg/m² was shown to be superior to 45 mg/m² even in selected patients older than 60 years. In a UK study that employed a tandem anthracycline induction regimen, daunorubicin 60 mg/m² was equivalent to 90 mg/m² in the first cycle. While conclusions from this study may not be directly applicable to a single induction 7+3 regimen, 60 mg/m² is nowadays often considered an appropriate standard dose and 90 mg/m² a reasonable alternative in patients with adequate cardiac status. With 7+3, achievement of a CR can be expected in 70% to 80% of adults younger than 60 years and 40% to 60% of fit adults older than 60 years. In some studies, use of higher doses of cytarabine during induction has led to higher CR rates and/or better event-free survival (EFS) or relapse-free survival (RFS) but overall survival (OS) has not been consistently longer. Current guidelines recommend that patients younger than age 60 who have significant residual disease without a hypocellular marrow on day 14 (nadir) should receive reinduction chemotherapy, either repeating 7+3 or using intensive, high-dose Ara-C (HiDAC)-based reinduction.

Remission induction in defined patient subgroups

While 7+3 remains the standard treatment for a large subgroup of patients, recent drug approvals have (Table 19-3) demonstrated improved survival with add-on and alternative agents in defined patient populations. The large, multinational randomized RATIFY trial reported that for patients between the ages of 18 and 60 with a *FLT3* mutation (ITD or TKD), the addition of the multikinase inhibitor midostaurin on days 8 to 21 of induction therapy with 7+3 and during postremission therapy decreased the risk of death by 22% and increased OS at 5 years by 7%. Several randomized

trials also demonstrated that the CD33 antibody-drug conjugate gemtuzumab ozogamicin (GO) improved outcomes in subsets of adults when added to intensive induction chemotherapy. For example, in the French ALFA 0701 trial, GO was combined with 7+3 in fractionated doses of 3 mg/m² on days 1, 3, and 7 and improved EFS and RFS compared to 7+3 alone in patients with favorable- and intermediate-risk AML. However, across the randomized trials, the exact benefit and patient subset benefiting from GO varied from study to study. An individual, patient-level meta-analysis of these clinical trials indicated GO does not improve remission rates but decreases relapse rates and prolongs EFS, RFS, and OS. However, OS benefit was not uniform across patient subsets but was especially apparent in patients with favorable cytogenetic characteristics (at 6 years, OS improvement of 20.7%) and to a lesser degree, patients with intermediate characteristics (at 6 years, OS improvement of 5.7%), whereas no benefit was seen in those with adverse cytogenetic features. While not widely used, some studies have shown a benefit of adding certain nucleoside analogs to 7+3, at least in certain patient subsets. Specifically, in one large, randomized trial, addition of cladribine to 7+3 improved survival in patients older than age 50, those with an initial high leukocyte count, and those with unfavorable cytogenetics. Moreover, clofarabine has been shown to improve survival in the subset of intermediate-risk AML patient subsets, but not others, when tested as add-on to 7+3 in a randomized trial in younger adults. However, the drug added grade 3 and 4 toxicities, delayed blood count recovery, and increased the probability of death in remission. In patients between the ages of 60 and 75 with t-AML or AML with myelodysplasia-related changes, CPX-351, a liposomal formulation of cytarabine/daunorubicin in a fixed 5:1 molar ratio, led to a higher remission rates and better OS than 7+3 induction; this benefit appeared greatest in patients who subsequently underwent allogeneic HCT.

Postremission therapy

Once remission has been achieved, further therapy is required to prevent relapse. Options include repeated courses of consolidation chemotherapy, autologous HCT (not widely used in the United States but commonly performed in other parts of the world), or allogeneic HCT. The choice of whether to pursue consolidation chemotherapy or allogeneic HCT is dependent on balancing the risks of AML relapse with the risks of transplant-related mortality. In general, consolidation chemotherapy is recommended for patients with favorable-risk disease (unless induction chemotherapy is suboptimally effective), whereas HCT at first remission is recommended for patients with unfavorable-risk disease. For patients with

Table 19-3 Newly approved drugs for AML since 2017

Drug	Drug class	Indication
CC-486	Oral formulation of azacitidine	Adults with AML with CR/CRi after chemotherapy and are unable to complete intensive curative therapy
CPX-351	Liposomal cytarabine/daunorubicin	Adults and children with newly diagnosed t-AML or AML with myelodysplasia-related changes
Enasidenib	Inhibitor of mutant <i>IDH2</i>	Adults with relapsed/refractory AML with <i>IDH2</i> mutation
Gemtuzumab ozogamicin	Anti-CD33 antibody–drug conjugate	Adults and children with newly diagnosed CD33+ AML Adults and children with relapsed/refractory AML
Gilteritinib	Second-generation tyrosine kinase inhibitor	Adults with relapsed/refractory <i>FLT3</i> -mutated AML
Glasdegib	Inhibitor of hedgehog signaling pathway	Adults ≥ 75 years old with AML in combination with low-dose cytarabine or if unfit for intensive chemotherapy
Ivosidenib	Inhibitor of mutant <i>IDH1</i>	Adults with relapsed/refractory AML with <i>IDH1</i> mutation Adults with newly diagnosed AML with <i>IDH1</i> mutation if ≥ 75 years old or unfit for intensive chemotherapy
Midostaurin	First-generation tyrosine kinase inhibitor	Adults with newly diagnosed <i>FLT3</i> -mutated AML with intensive chemotherapy
Venetoclax	Selective B-cell lymphoma 2 inhibitor	With azacytidine/decitabine or low-dose cytarabine for adults ≥ 75 years old or unfit for intensive chemotherapy

intermediate-risk disease, the decision to pursue consolidation chemotherapy or allogeneic HCT is individualized. Allogeneic HCT allows the combination of myeloablative or nonmyeloablative chemotherapy with a graft-versus-leukemia effect from the donor cells. Several studies have prospectively evaluated the role of intensive consolidation with HiDAC. A pivotal trial from the *Cancer and Leukemia Group B (CALGB)* randomized patients in first remission to 4 courses of cytarabine using either a continuous infusion of 100 mg/m² or 400 mg/m² for 5 days or a 3-hour infusion of 3 g/m² twice daily on days 1, 3, and 5. Significant CNS toxicity was observed in patients older than 60 years randomized to the high-dose arm; therefore, this regimen is not recommended for older patients. In patients younger than 60 years, there was a significant improvement in disease-free survival associated with the high-dose regimen, most notably in patients with favorable cytogenetics (ie, patients with t(8;21) and inv(16)).

Although it has become standard to offer 3 or 4 cycles of HiDAC at 1 to 3 g/m² to younger patients with AML who are not undergoing allogeneic HCT, there are no clear data defining the optimal number or intensity of HiDAC cycles. Randomized trials from the United Kingdom failed to demonstrate that 3 cycles of HiDAC consolidation were better than 2 cycles. Recent retrospective data suggest that administering HiDAC on days 1, 2, and 3 has similar anti-AML efficacy but leads to a shortened duration of neutropenia, fewer infections, and shortened hospitalization needs than HiDAC given on days 1, 3, and 5.

Randomized studies have not demonstrated that consolidation chemotherapy, in general, is of benefit for patients older than 60 years, but older patients able to tolerate additional treatment often are offered modified dosing of bolus cytarabine or additional courses of 7+3.

Several studies of postremission therapy in AML have compared intensive chemotherapy consolidation to HCT by assigning younger patients with a human leukocyte antigen (HLA)-matched sibling donor to allogeneic HCT and randomizing other patients to chemotherapy or autologous HCT. Meta-analyses have shown that autologous HCT decreases relapse risk but increases treatment-related mortality compared with chemotherapy consolidation, thus resulting in similar overall survival rates of approximately 40% to 45% at 3 to 5 years. Many of these trials date back many years, and it is unclear whether these conclusions hold now that supportive care measures have improved and nonrelapse mortality rates with autologous HCT have decreased.

Allogeneic HCT is probably the most effective anti-leukemic 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. Allogeneic HCT is, however, associated with significant morbidity and mortality. A comprehensive meta-analysis by Koreth et al. of prospective clinical trials of allogeneic HCT in AML patients in first CR evaluated 24 trials and more than 6000 patients. In this analysis, allogeneic HCT 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 HCT for patients with good-risk cytogenetics. Retrospective analyses of uniformly treated patients have shown that allogeneic HCT was also beneficial for cytogenetically normal AML patients with *FLT3*-ITD⁺, *FLT3*-ITD⁻/*NPM1*⁻, and *FLT3*-ITD⁻/*CEBPA*⁻. 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.

Alternative donor sources such as haploidentical transplants (haplo-HCTs) are increasing in use. An analysis of the Center for International Blood and Marrow Transplant Research data for allogeneic transplants shows a striking increase in haplo-HCT in the United States: from less than 500 in 2012 to 1507 in 2018. Retrospective studies and meta-analyses report lower chronic graft-versus-host disease (GVHD) rates but higher nonrelapse mortality rates from haploidentical donors as compared to matched sibling donors, with similar relapse and overall survival rates between the 2 groups. A report by Cho et al. described outcomes of a prospective study comparing haplo-HCT with HLA-matched unrelated HCT for patients with AML in first or second CR. The study demonstrated noninferiority of haplo-HCT, with no significant differences in acute or chronic GVHD, DFS, or OS between the 2 groups. Results from a randomized phase 3 study of 368 patients with acute leukemia or lymphoma comparing haplo-HCT versus double unrelated umbilical cord blood-HCT were recently reported. There was no statistically significant difference in Progression-free survival between the 2 groups. However, nonrelapse mortality was significantly higher in the umbilical cord blood-HCT group as compared to the haplo-HCT group (18% versus 11%; $P = 0.04$). Additional ongoing phase 3 studies comparing alternative donor sources for allogeneic HCT will provide important outcome data for patients with AML.

Maintenance therapy

An important recent update in AML is the rediscovery of maintenance therapy. Investigated for more than 40 years, a large number of randomized trials have tested various therapies as maintenance therapy. Of these, low-dose IL-2 plus histamine dihydrochloride has been shown to improve EFS but not OS in this setting and is approved in Europe for this purpose, albeit not widely used. The first study that brought maintenance therapy back on the horizon was the HOVON97 trial, a randomized phase 3 trial testing azacitidine monotherapy in adults older than

age 60 who achieved a remission with intensive induction chemotherapy. While the study enrolled only 116 patients and was terminated early because of slow accrual, it suggested some benefit of maintenance therapy by showing improved RFS compared to observation alone, although OS was not improved. CC-486 is an oral formulation of azacitidine that is now approved for maintenance therapy. A randomized phase 3 trial (QUAZAR) compared CC-486 (given for 14 out of 28-day cycles until relapse or death) against placebo in adults older than age 55 who were in first remission after receipt of intensive induction chemotherapy, had intermediate- or high-risk cytogenetics, and were ineligible to proceed with allogeneic HCT. In this trial, CC-486, which has gastrointestinal toxicities and cytopenias as most important side effects, improved OS and RFS compared to placebo by a median of 9.9 and 5.3 months.

Treatment for medically less-fit patients

With a median age of 68 at diagnosis, AML is primarily a disease affecting older adults. Such individuals have a high frequency of disease-related adverse prognostic features, including antecedent hematologic disorders, unfavorable cytogenetic/molecular abnormalities, and multidrug resistance phenotypes. Partly as a reflection of this, median survival estimates are in the range of 4.5 to 6 months for 66- to 75-year-olds and 2 to 3 months for ≥ 76 -year-olds diagnosed with AML. However, these estimates are affected by the fact that a majority of these patients do not receive AML-directed therapy ($>50\%$ of individuals aged >65 years and $>80\%$ of those aged >80 years) and are managed with supportive care only (eg, antimicrobials, transfusions) or hospice care. The perception that treatment risks are not commensurate with potential benefits may play a big role in these outcomes. Still, even after receipt of some AML-directed therapy, the great majority of older patients will die within 1 year of diagnosis and long-term survival is a rare event.

As a complicating factor for therapeutic decision-making, older patients may have difficulties tolerating intensive chemotherapy because of medical comorbidities, polypharmacy, poor performance status, and limited social support. Indeed, until very recently, there was no universally accepted standard of care for the treatment of older adults with newly diagnosed AML if treatment was considered. Options included intensive chemotherapy (eg, 7+3), azanucleosides such as azacitidine or decitabine (hypomethylating agents [HMAs]), low-dose cytarabine (typically subcutaneously administered), or participation in a clinical trial. Several studies

have demonstrated that a remission can be attained in ~50% of selected older patients with a good performance status using 7+3, although these responses can be of short duration, and antileukemia effects offset by nonrelapse (treatment-related) mortality rates of 5% to 20%. Population-based registry data from Europe and the United States support the use of intensive chemotherapy (versus palliative or supportive therapy alone) in most AML patients up to age 80, but even analyses from excellent registries capturing country-wide population data carry the risk of biases given only the fittest, or most-likely-to-respond patients may be considered for intensive therapy and information on exact regimens, individual dose reductions, and supportive care measures is typically not available.

Different approaches have been taken to identify patients for whom intensive chemotherapy should not be used. It is now widely recognized that age alone should not be used as the major determinant of treatment intensity selection because several intensive options, including intensified doses of daunorubicin and reduced-intensity allogeneic HCT, are both feasible and effective in selected patients older than 60 years. In fact, most older patients will fail to benefit from AML therapy because of its lack of therapeutic efficacy, not from intolerable toxicities.

In addition to informal criteria such as physician judgment, numerous scoring systems have been developed that consider information on comorbidities, organ function abnormalities, disease characteristics, and/or global geriatric assessments, to aid in the identification of patients at high risk of either early death or treatment resistance after conventional intensive AML therapy. Such systems offer an empiric approach in the treatment selection process, but their accuracy is imperfect. Still, with the concerns related to intensive chemotherapies, the use of HMAs has become common in elderly patients and those who are deemed unfit for traditional cytotoxic chemotherapy based on the findings that these agents can result in stabilization of bone marrow abnormalities, reduction in transfusion needs, and even complete remission in 10% to 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 United States for patients with AML who have 20% to 30% blasts in the bone marrow.

The treatment landscape for older less-fit adults with AML fundamentally changed with recent availability of new drugs, in particular the oral B-cell lymphoma 2 inhibitor venetoclax. In one pivotal trial (VIALE-A), previously untreated patients with AML who were deemed ineligible

for intensive chemotherapy because of coexisting medical problems or age >75 years were randomized 2:1 to azacitidine/venetoclax (target dose of 400 mg) or azacitidine alone. The CR+Complete remission with incomplete count recovery (CRi) rate was significantly higher in patients receiving venetoclax (66.4% versus 28.3%), and the median survival was approximately 5 months longer (14.7 versus 9.6 months). A similar randomized trial (VIALE-C) compared low-dose cytarabine/venetoclax with low-dose cytarabine alone. The CR/CRi rate was higher with venetoclax (48% versus 13%). This improvement, however, did not translate into a statistically significant survival improvement in the primary analysis (median OS 7.2 versus 4.1 months; $P = 0.11$). An unplanned secondary analysis with an additional 6-month of follow-up then indicated a slight improvement in median OS (8.4 versus 4.1 months; $P = 0.04$). Besides the choice of partner drug, the main difference between VIALE-A and VIALE-C was that patients with prior HMA exposure were only allowed participation in VIALE-C. Venetoclax is now approved by the FDA in combination with azacitidine, decitabine, or low-dose cytarabine in adults 75 years or older or those who have comorbidities precluding intensive chemotherapy. Based on the data from VIALE-A, azacitidine/venetoclax has become a new standard of care for those individuals in the United States and other countries in which there is access to venetoclax. Further data will be required to delineate which subsets of these patients indeed derive benefit from the addition of venetoclax. Better-controlled data will also be necessary to understand the relative benefit of venetoclax-based therapy relative to intensive chemotherapy in these patients or other subsets of AML patients, eg, medically fit individuals with AML predicted to poorly respond to intensive chemotherapy based on cytogenetic/molecular profiles. Profound myelosuppression manifesting as prolonged cytopenias and associated risks is the clinically most concerning adverse effect of venetoclax and requires diligence in patient management.

A second drug approved by the FDA for the treatment of less-fit adults with newly diagnosed AML is the oral hedgehog signaling pathway inhibitor glasdegib. Approval was largely based on a randomized trial comparing low-dose cytarabine/glasdegib with low-dose cytarabine alone. This trial found a statistically significantly longer survival with glasdegib of 8.8 versus 4.9 months—an improvement similar to that observed when venetoclax was added to low-dose cytarabine. Efforts testing other doublet therapies, eg, those using HMAs together with an inhibitor of mutant *IDH* or a *FLT3* inhibitor are ongoing, as are studies testing triplet therapies. The value of such therapies is currently unknown.

KEY POINTS

- Treatment of AML generally involves remission induction followed by postremission therapy. In some patients, it also includes maintenance therapy.
- CPX-351, a liposomal formulation of cytarabine and daunorubicin shows an overall survival benefit for patients with t-AML and AML with myelodysplasia-related changes.
- The standard of care for induction for all other AML subtypes in adults, excluding APL, remains 7 days of cytarabine combined with 3 days of an anthracycline.
- Patients with a FLT3-ITD or TKD at diagnosis should have the multikinase inhibitor midostaurin given on days 8 to 21 of induction and consolidation.
- Patients with favorable-risk AML should have the CD33 antibody-drug conjugate gemtuzumab ozogamicin added during induction chemotherapy.
- Consolidation chemotherapy with HiDAC is of particular benefit for patients younger than 60 years old with favorable cytogenetics involving CBF (t(8;21) and inv(16)); however, the optimal number of cycles of postremission HiDAC remains to be clearly defined across all age groups.
- Allogeneic stem cell transplantation appears to be of benefit for AML patients in first remission who have intermediate- or poor-risk cytogenetics or may provide benefit to those with favorable-risk disease but residual measurable residual disease (MRD) after induction chemotherapy.
- Venetoclax-based doubled therapy establishes a new standard of care for medically less-fit adults with newly diagnosed AML.

Measurable residual disease

MRD (previously referred to as *minimal residual disease*) denotes leukemia cells which survive seemingly successful remission induction therapy, hide below the cytomorphological detection limit, and are responsible for disease relapse. With technological advances, methods to detect MRD in AML have evolved over time. Today, assays are available to detect and quantify immunophenotypic and/or genetic/molecular abnormalities of AML cells via multiparameter flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing. Additional techniques such as digital droplet PCR have been used as well. In addition to methodological refinements, efforts are ongoing to standardize (ie, use the exact same) testing or, at the minimum, harmonize (ie, use similar) assays across different laboratories. This lack of standardization/harmonization has affected the generalizability and applicability of MRD testing outside of clinical trials.

Multiparameter flow cytometry can detect immunophenotypic abnormalities in neoplastic cells in over 90% of AML patients. Its current sensitivity can reach a level of $1:10^4$ to $1:10^5$. The 2 main approaches developed to assess MRD via flow cytometry include (1) the leukemia-associated immune phenotype (LAIP) approach and (2) the different-from-normal approach. The LAIP approach defines LAIPs at diagnosis and tracks these in subsequent samples. The different-from-normal approach, which can be used even if no pretreatment sample is available for testing, identifies MRD as a cell population showing deviation from the normal patterns of antigen expression found on specific cell lineages at specific states of maturation as compared with either normal or regenerating bone marrow. Using a minimum of 8 markers, experts recommend the integrated use of both detection strategies to track not only the leukemia clone(s) detected at diagnosis but also the aberrancies that might emerge during the disease course.

For AML subsets with canonical mutations, such as mutations in *NPM1* or translocations in CBFs or PML-RARA, sensitive PCR assays are available for MRD detection with sensitivities reaching $1:10^6$. However, the intra- and interpatient genetic heterogeneity of most AMLs does not lend itself to MRD detection focusing on 1 molecular target. Next-generation sequencing (NGS) approaches to MRD detection aim to address this heterogeneity, with current panels providing coverage to detect abnormalities in approximately 90% of patients with AML although first-generation platforms do not reach great sensitivity; emerging error-corrected assays address this limitation. Still, it is important to note that not every mutation identified can be used to follow for MRD. Some mutations, such as those in the *DNMT3A*, *ASXL1*, and *TET2* genes, may represent preleukemic founder mutations and may persist upon achievement of complete remission. The detection of these mutations may not represent the presence of AML MRD and thus may not be of prognostic significance for AML relapse. Mutations in these genes, manifesting as clonal hematopoiesis, are known to occur with increasing frequency as some individuals age. Furthermore, several mutations, including *ANKRD26*, *CEBPA*, *DDX41*, *GATA2*, and *RUNX1*, may be mutated in the germ line (and are associated with AML development). These mutations will not correlate with disease burden and the variant allele frequency is expected to remain at ~50% throughout the treatment course; genes mutated in the germline are not useful for following for MRD.

Numerous studies have demonstrated that results from MRD tests have prognostic significance for AML patients in morphological remission. Specifically, patients with

MRD have higher cumulative incidence rates of relapse and, often, shorter relapse-free and/or overall survival than similarly treated patients without MRD. Because of this, MRD assessment is now incorporated into ELN guidelines by including a new response category of “Complete remission with negative MRD.” The association between MRD status and relapse risk has been confirmed at several timepoints throughout the nontransplant and transplant treatment course that AML patients undergo, regardless of the detection method used. At least at the current time, however, the concordance between the different MRD assays is not absolute, and different assays (eg, flow cytometry and NGS) provide complementary information, with patients testing positive for MRD by both methodologies having particularly poor outcomes, patients testing negative for MRD by both methodologies having particularly good outcomes, and patients testing positive by one but not the other methodologies having intermediate outcomes.

The now-established association between MRD and increased risk of relapse has raised great interest in using results from MRD testing as biomarker in the routine care of patients with AML as well as during the drug testing/approval process. Some data suggest that MRD data could inform the selection of the optimal postremission strategy (eg, choice between chemotherapy-only therapy versus allogeneic HCT, or conditioning intensity before allogeneic HCT) for some patient subsets. MRD testing may also be useful in the monitoring of patients after completion of planned therapy for early relapse detection, but this approach is complicated by significant differences in relapse kinetics between patients, and the lack of data, at least for non-APL AML, convincingly demonstrating that treatment at the MRD level improves outcomes. Of great interest is the potential use of MRD data as surrogate efficacy-response biomarker but further data will be required to further establish such a role.

AML relapse

The majority of adult patients with AML experience relapse despite initially attaining CR. The prognosis for patients with relapsed disease is poor, and they should be considered for investigational trials. Most AML relapses occur within 2 to 3 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 as high as a 50% chance of responding to a conventional multiagent

chemotherapy regimen, even if they had previous exposure to this agent. Examples of reinduction regimens include mitoxantrone, etoposide, and cytarabine; fludarabine, cytarabine and granulocyte colony-stimulating factor (G-CSF); clofarabine and cytarabine; and cladribine, cytarabine, and G-CSF with or without mitoxantrone. All of these regimens use higher doses of cytarabine than what is used in 7+3. No combination has proven more effective in the few randomized trials attempted. 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 shorter than the first. The prognosis for patients who relapse after allogeneic transplantation, especially if relapse occurs early after allografting, is dismal.

Patients with molecularly defined subsets of AML, including those with mutations in *FLT3* or isocitrate dehydrogenase 1 (*IDH1*) or *IDH2*, may benefit from targeted molecular therapies at the time of relapse. Gilteritinib, a selective, oral *FLT3* inhibitor, was approved by the FDA for use as single agent for patients with relapsed *FLT3*-mutated AML based on data from a randomized phase 3 trial (ADMIRAL). In this study, patients who received gilteritinib more often achieved a CR with full or partial hematologic recovery (34.0% versus 15.3%) and had a longer median overall survival (9.3 versus 5.6 months) and event-free survival (2.8 versus 0.7 months) than patients who received conventional salvage chemotherapy. Another oral selective *FLT3* inhibitor, quizartinib, was similarly tested in a randomized phase 3 trial (QuANTUM-R) in adults with primary refractory or early relapsed AML with *FLT3*-ITD. Quizartinib was associated with a statistically significantly longer median OS (6.2 versus 4.7 months) compared to an investigator's choice of conventional salvage chemotherapy. However, the drug did not obtain FDA approval, with concerns related to both marginal clinical benefit and toxicity in comparison with more intensive salvage regimens.

The oral inhibitors of mutant *IDH1* and *IDH2*, ivosidenib and enasidenib, respectively, were approved by the FDA as monotherapies for patients with relapsed/refractory *IDH*-mutant AML. In nonrandomized studies, use of these small molecule inhibitors yielded CR/CRh rates of 25% to 40%, with a median duration of response of around 9 months for these responders. Results from randomized trials are awaited to evaluate the efficacy of these *IDH* inhibitors relative to standard salvage chemotherapy regimens. Ongoing trials are also underway for *IDH* inhibitors in combination with other targeted agents as well as cytotoxic chemotherapy.

Acute promyelocytic leukemia

Acute promyelocytic leukemia is a subtype of AML characterized by a balanced reciprocal translocation resulting in the fusion of the *PML* gene on chromosome 15 with the *RARA* gene on chromosome 17. APL exists in hypergranular (typical) and microgranular forms. In hypergranular APL, the promyelocytes are strongly myeloperoxidase-positive and have bilobed or kidney-shaped nuclei. The cytoplasm has densely packed, large granules, and characteristic cells (faggot cells) containing bundles of Auer rods may be found in most cases (Figure 19-2). Cases of microgranular APL have predominantly bilobed nuclei, are strongly myeloperoxidase-positive, and often have a very high leukocyte count and doubling time. APL is generally characterized by low expression or absence of HLA-DR, CD34, CD117, and CD11b. Patients with APL are categorized as having low- (or low-intermediate) or high-risk disease based on a WBC at presentation of $\leq 10,000/\mu\text{L}$ versus $>10,000/\mu\text{L}$.

The incorporation of anthracyclines in the 1970s, all-*trans* retinoic acid (ATRA) in the 1980s, and the front-line use of ATRA in combination with chemotherapy, have pushed the CR rate over 90% with cures in 80% of patients with APL. Today, even better results are obtained using combination treatment with ATRA and arsenic trioxide (ATO), with no need for additional chemotherapy in low-risk patients and only minimal additional chemotherapy in high-risk patients.

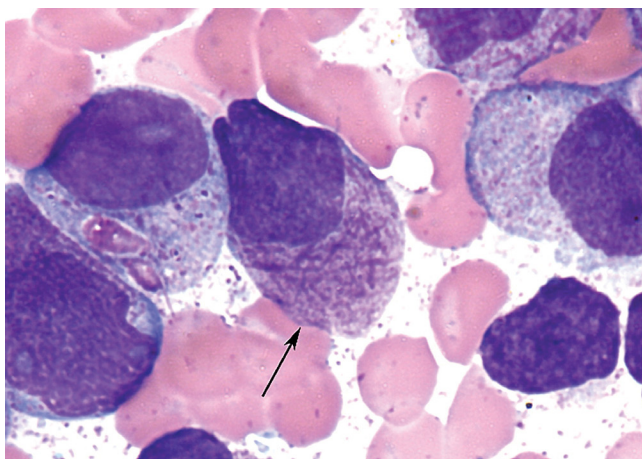
Still, while APL has seen incredible success over the last decades, there are still issues remaining in this disease that must be addressed. Most importantly, a patient with suspected initial diagnosis of APL should be hospitalized immediately and must be managed as a medical emergency. That is because patients with APL commonly

present with a complex coagulopathy with consumptive coagulation with thrombocytopenia as well as primary and secondary fibrinolysis. Resulting intracerebral and pulmonary hemorrhages, for which patients need to be carefully evaluated and monitored, are the most common causes of death before and early after treatment initiation. Thrombotic complications may also occur. Because early deaths are the main cause of death in APL, treatment with ATRA (at 45 mg/m^2 per day in 2 divided doses) should be initiated even before diagnosis confirmation (via routine karyotyping, FISH for $t(15;17)$, or PCR testing for the *PML/RARA* fusion transcript) as it can correct this coagulation disorder within days. Supportive measures to treat the coagulopathy are critical and include transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh frozen plasma to maintaining fibrinogen concentrations above 100 to 150 mg/dL, platelet counts above 30 to $50 \times 10^9/\text{L}$, and the international normalized ratio below 1.5.

Neoplastic promyelocytes have the unique ability to undergo differentiation with exposure to ATRA. Differentiation syndrome (DS) is a complication during induction caused by the effects of differentiating agents (ATRA and ATO) on leukemic blasts. Hyperleukocytosis frequently accompanies DS and may precede the clinical manifestations of DS. DS leads to a systemic inflammatory response-syndrome-like process. The most common problem seen with DS is acute respiratory distress caused by diffuse interstitial pulmonary infiltrates, which appear as a pleural effusions and pulmonary infiltration on chest imaging. Other features that may occur with DS are weight gain, edema, fevers, acute renal failure, pericardial effusions, and hyperbilirubinemia. Severe DS can be fatal, and patients with a WBC count greater than $5 \times 10^9/\text{L}$ at diagnosis are at increased risk for early mortality.

The use of prophylactic steroids in an ATO- and ATRA-based induction approach is recommended as a strategy to decrease the risk of severe DS. Additional agents to prevent DS are used in patients presenting with leukocytosis, or patients who develop leukocytosis. In the APL0406 trial (a study of patients with low-risk APL), patients whose WBC count exceeded $10 \times 10^9/\text{L}$ after ATRA/ATO initiation received hydroxyurea to reduce the peripheral WBC count. This approach appeared effective as no deaths from DS occurred on the ATRA/ATO arm. It is therefore recommended that hydroxyurea be started if the WBC count rises over $10 \times 10^9/\text{L}$. Patients who present with an elevated WBC count are at higher risk for DS. The APML4 protocol, which included high-risk patients, used up-front idarubicin partly to prevent

Figure 19-2 A faggot cell. Source: ASH Image Bank/Peter Maslak.



hyperleukocytosis and DS. In this trial no patients, including those with high-risk disease, died from DS. Thus, based on WBC count, adjusting induction therapy with an anthracycline is recommended for patients with high-risk disease. However, hyperleukocytosis that occurs during the treatment of standard-risk APL should be managed with hydroxyurea, reserving anthracycline use for resistant cases. Should DS occur despite these measures, rapid administration of dexamethasone (10 mg twice daily) at the earliest manifestation of DS with continuation until symptoms resolve, and for at least 3 days, can be lifesaving.

Treatment approaches for APL

The approach to treatment of APL differs based on the perceived disease risk. For both low-risk and high-risk disease, however, treatment with ATRA/ATO nowadays forms the backbone of therapy. That is even though combination regimens with ATRA and an anthracycline (with or without cytarabine) induce remissions in >90% of patients, and long-term cures are achieved in >70% to 80% of patients. Still, ATRA/ATO is preferred over ATRA/anthracycline-based induction therapy in low-risk APL because it offers a survival benefit when used for newly diagnosed patients as it produces very high rates of durable remissions with low rates of hematologic toxicity and avoids the use of genotoxic chemotherapeutics, with a near 100% survival at 4 years in 1 large, randomized trial. For patients with high-risk disease, there are currently 2 potential treatment approaches, namely ATRA/ATO with the addition of some cytoreductive chemotherapy (most typically, an anthracycline or GO) or ATRA plus chemotherapy. Anthracyclines and GO have been used, because APL cells are exquisitely sensitive to these agents. These agents lower the WBC count and therefore directly treat the APL, minimize the risk of DS, and are used in the up-front treatment for high-risk APL. 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/m² for 3 days) or idarubicin (12 mg/m² 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. Patients presenting with high-risk disease treated with ATRA/anthracycline-based induction may benefit from intermediate-dose cytarabine or HiDAC during either induction or consolidation. Of note, some protocols for high-risk APL have also incorporated prophylactic intrathecal chemotherapy, though it is not known if this therapy is needed in the era of ATO-based approaches. With the many choices available and the

very good outcomes reported, it is highly recommended that patients should be treated with 1 regimen consistently throughout their treatment course and that components not be mixed, for example: induction from 1 regimen and consolidation from another.

The persistence or reappearance of *PML-RARA* fusion-gene transcripts in patients with APL is highly predictive of overt relapse. However, while frequent monitoring by RT-PCR has been integrated into many clinical trials, routine PCR monitoring is no longer recommended in low-risk patients treated with ATRA/ATO who are PCR negative after completion of consolidation therapy given the extreme rarity of relapse. On the other hand, because early treatment intervention may afford better outcomes, monitoring should be offered to other patients, most notably high-risk patients, for up to 3 years.

Depending on the time to relapse, ATO with or without ATRA can be considered (because APL may regain sensitivity) as can GO and ATRA/idarubicin. There is currently no standard approach to relapsed APL with the widespread use of ATO in newly diagnosed patients and the rarity of recurrence. However, another attempt with ATRA/ATO is often recommended if it has been at least 6 months since the last exposure. In addition, autologous stem cell transplantation can be considered for patients in second complete molecular remission. Allogeneic stem cell transplantation is reserved for patients who are not able to attain a complete molecular remission or who are in second relapse.

KEY POINTS

- APL is a unique subtype of AML that is exquisitely sensitive to ATRA, anthracyclines, arsenic trioxide, and gemtuzumab ozogamicin.
- ATRA should be started immediately if the diagnosis of APL is suspected.
- APL may be complicated by a life-threatening coagulopathy or differentiation syndrome.
- In patients treated with ATRA/ATO induction, prophylactic steroids should be used to prevent differentiation syndrome. Should differentiation syndrome occur, patients should be promptly treated with dexamethasone (10 mg twice daily) for at least 3 days.
- Cure rates are high in APL.

Pediatric AML

Pediatric AML accounts for approximately 20% of children diagnosed with leukemia in the United States.

Although there are overlapping molecular features, the genomic landscape of pediatric AML varies significantly from adult-onset AML. Oncogenic translocations are much more frequently observed in pediatric cases, especially in infants and young children. *KMT2A* gene rearrangements are identified in 25% of childhood AML cases, including approximately 50% of infant AML cases. Moreover, certain molecular subtypes, such as *CBFA2T3-GLIS2*-driven AML, are uniquely specific to very young children with AML. Mutations commonly seen in adult-onset AML such as *DNMT3A* and *IDH1/2* are extremely uncommon in pediatric AML, whereas Ras-pathway mutations are much more commonly observed among children.

Akin to adult-onset AML, frontline treatment regimens for childhood AML rely on intensive cycles of anthracycline- and cytarabine-based chemotherapy, with event-free survival rates generally ranging between 50% and 60%. The use of allogeneic HCT in first remission for patients with high-risk cytogenetic or molecular features varies among consortia given conflicting data of benefit. In the Children's Oncology Group (COG) AAML0531 study, the addition of GO to standard chemotherapy demonstrated significantly significant improvements in EFS and relapse risk in patients with high CD33 expression. This led to FDA approval of GO for children with newly diagnosed CD33-positive AML in 2020. The subsequent COG AAML1031 study investigated the addition of sorafenib for patients with high allelic ratio *FLT3* ITD. The 3-year EFS was 57.5% for patients treated with sorafenib versus 34.3% for those treated without ($P = 0.007$). The ongoing COG AAML1831 study is evaluating the use of liposomal daunorubicin and cytarabine (CPX-351) compared to standard induction in an effort to improve outcomes and reduce anthracycline related cardiotoxicity rates. Furthermore, patients with *FLT3* mutations receive the type 1 inhibitor gilteritinib as an effort to further improve outcomes for this molecular subset of patients.

Children with Down syndrome have a 150-fold increased risk of developing myeloid leukemia before the age of 5 years. Myeloid leukemia of Down syndrome (ML-DS) typically presents as acute megakaryoblastic leukemia and is characterized by mutations of the *GATA1* gene. These truncating mutations of *GATA1* lead to the condition of transient abnormal myelopoiesis (TAM), a clonal disorder which can present with elevated blasts and signs such as hepatosplenomegaly but can also be clinically silent. Progression from TAM to ML-DS occurs through the acquisition of additional mutations which often involve cohesion family members

or epigenetic regulators. Outcomes for ML-DS with the use of cytarabine-based therapy with reduced anthracycline dosing are favorable with event-free survival rates approaching 90%.

Children with relapsed AML are generally treated with salvage chemotherapy regimens followed by allogeneic HCT. Length of first remission as well as molecular features have been established as prognostic factors for outcomes of relapse therapy. Numerous salvage chemotherapy regimens have been studied; however, they have mostly been relatively small single-arm studies, limiting the ability to compare and standardize approaches. A recent study of CPX-351 in 37 evaluable children with AML in first relapse led to an overall response rate of 81%. This has led to the evaluation of CPX-351 in frontline therapy in the ongoing COG AAML1831 study. In striking contrast to adult-onset AML, which has seen the approval of numerous targeted agents over the past 5 years (Table 19-3), there has been little progress made for childhood AML. Gemtuzumab ozogamicin, FDA-approved in 2017, is the only targeted agent approved for children with relapsed disease. Unique challenges for drug development in this population include tumor rarity as well as significant disease heterogeneity. However, it is imperative that novel targeted therapies and immunotherapies are studied through national and international consortia to develop improved therapeutic modalities for the substantial percentage of children with relapsed AML.

Genetics of AML predisposition

Constitutional predisposition to AML is increasingly recognized and a component of the WHO classification schema. There are several autosomal dominant and recessive syndromes conferring risk to developing AML. Constitutional aberrations in copy number, transcription factors, ribosomal genes, telomere maintenance complex genes, the Fanconi pathway, DNA damage pathway, Ras/MEK pathway, immune modulators, epigenetic regulators, and cell cycle pathway predispose to MDS/AML (Table 19-4). While age is a significant risk factor for AML, certain AML/MDS predisposing syndromes tend to occur in different decades of life. The interplay of treatment and predisposition in general is an increasing area of understanding and particularly relevant to MDS/AML. Identifying individuals with AML predisposition is clinically relevant in understanding prognosis, therapeutic vulnerabilities and sensitivities, donor considerations, long-term follow-up and family planning. Examples

Table 19-4 AML/MDS cancer predisposition genes

Genetic aberrancy		Molecular testing and diagnostic evaluation
Copy number	Trisomy 21, mosaic trisomy 8	Karyotype/microarray
Transcription factors	<i>CEBPA, GATA2, MECOM/EVI1, MRTFA, RUNX1, TET2</i>	Sequencing
Ras/MEK	<i>CBL, NF1, PTPN11</i>	Sequencing
Constitutional mismatch repair deficiency	<i>MSH2, MSH6, PMS2, MLH1</i> (biallelic)	Sequencing
Ribosomal pathway	<i>DNAJC21, SBDS</i>	Sequencing
Telomeropathy	<i>DKC1, TERT, TERC, RTEL, TINF2, ACD1</i>	Sequencing and telomere lengths
DNA damage	<i>ATM, FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FANCN, FANCO, FANCP, FANCO, FANCR, FANCS, FANCT, FANCU, FANCV, ERCC6L2, KDM1A, TP53</i>	Sequencing and chromosomal breakage
Other	<i>SAMD9, SAMD9L, WAS, CSF3R, MBD4, DDX41, ANKRD26, BLM</i>	Sequencing

of therapeutic vulnerabilities and sensitivities are most extreme for individuals with Fanconi anemia and telomere syndromes. In regard to transplant planning, it is additionally important to identify shared constitutional mutations among siblings who may be potential donors.

Bibliography

American Cancer Society. Key statistics for acute myeloid leukemia (AML). Available at: <https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html>.

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391-2405.

Bachas C, Schuurhuis GJ, Reinhardt D, et al. Clinical relevance of molecular aberrations in paediatric acute myeloid leukaemia at first relapse. *Br J Haematol*. 2014;166:902-910.

Berman E, Little C, Gee T, et al. Reasons that patients with acute myelogenous leukemia do not undergo allogeneic bone marrow transplantation. *N Engl J Med*. 1992;326:156-160.

Bhatnagar N, Nizery L, Tunstall O, et al. Transient abnormal myelopoiesis and AML in Down syndrome: an update. *Curr Hematol Malig Rep*. 2016;11:333-341.

Bolouri H, Farrar JE, Triche T Jr, et al. The molecular landscape of pediatric acute myeloid leukemia reveals recurrent structural alterations and age-specific mutational interactions. *Nat Med*. 2018;24:103-112.

Brown AL, Hahn CN, Scott HS. Secondary leukemia in patients with germline transcription factor mutations (*RUNX1, GATA2, CEBPA*). *Blood*. 2020;136:24-35.

Burke MJ, Wagner JE, Cao Q, et al. Allogeneic hematopoietic cell transplantation in first remission abrogates poor outcomes associated with high-risk pediatric acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2013;19:1021-1025.

Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in

all risk groups (AML17): results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2015;16(13):1295-1305.

Cho BS, Min GJ, Park S, et al. Haploidentical vs matched unrelated donor transplantation for acute myeloid leukemia in remission: a prospective comparative study. *Am J Hematol*. 2021;96:98-109.

Conneely SE, Rau RE. The genomics of acute myeloid leukemia in children. *Cancer Metastasis Rev*. 2020;39:189-209.

Cooper TM, Absalon MJ, Alonzo TA, et al. Phase I/II study of CPX-351 followed by fludarabine, cytarabine, and granulocyte-colony stimulating factor for children with relapsed acute myeloid leukemia: a report from the Children's Oncology Group. *J Clin Oncol*. 2020;38:2170-2177.

Corces-Zimmerman MR, Hong WJ, Weissman IL, Medeiros BC, Majeti R. Preleukemic mutations in human acute myeloid leukemia affect epigenetic regulators and persist in remission. *Proc Natl Acad Sci USA*. 2014;111(7):2548-2553.

Cornelissen JJ, Blaise D. Hematopoietic stem cell transplantation for patients with AML in first complete remission. *Blood*. 2016;127:62-70.

Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. 2019;33:379-389.

Cortes JE, Khaled S, Martinelli G, et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:984-997.

Creutzig U, Reinhardt D, Diekamp S, et al. AML patients with Down syndrome have a high cure rate with AML-BFM therapy with reduced dose intensity. *Leukemia*. 2005;19:1355-1360.

Dalle JH. HCT for Fanconi anemia in children: factors that influence early and late results. *Bone Marrow Transplant*. 2008;42(suppl 2):S51-S53.

Daver N, Wei AH, Pollyea DA, Fathi AT, Vyas P, DiNardo CD. New directions for emerging therapies in acute myeloid leukemia: the next chapter. *Blood Cancer J*. 2020;10:107.

- DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383:617-629.
- DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378:2386-2398.
- Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
- Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373:1136-1152.
- Dores GM, Devesa SS, Curtis RE, et al. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood*. 2012;119:34-43.
- D'Souza A, Fretham C, Lee SJ, et al. Current use of and trends in hematopoietic cell transplantation in the United States. *Biol Blood Marrow Transplant*. 2020;26:e177-e182.
- Fuchs EJ, O'Donnell PV, Eapen M, et al. Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial. *Blood*. 2021;137:420-428.
- Godley LA. Germline mutations in MDS/AML predisposition disorders. *Curr Opin Hematol*. 2021;28:86-93.
- Godwin CD, Gale RP, Walter RB. Gemtuzumab ozogamicin in acute myeloid leukemia. *Leukemia*. 2017;31:1855-1868.
- Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116:354-365.
- Gurnari C, Fabiani E, Falconi G, et al. From clonal hematopoiesis to therapy-related myeloid neoplasms: the silent way of cancer progression. *Biology*. 2021;10(2):128.
- Harrison CJ, Hills RK, Moorman AV, et al. Cytogenetics of childhood acute myeloid leukemia: United Kingdom Medical Research Council Treatment trials AML 10 and 12. *J Clin Oncol*. 2010;28:2674-2681.
- Herold T, Rothenberg-Thurley M, Grunwald VV, et al. Validation and refinement of the revised 2017 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. *Leukemia*. 2020;34:3161-3172.
- Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol*. 2014;15:986-96.
- Ishikawa Y, Kawashima N, Atsuta Y, et al. Prospective evaluation of prognostic impact of KIT mutations on acute myeloid leukemia with RUNX1-RUNX1T1 and CBFB-MYH11. *Blood Adv*. 2020;4:66-75.
- Kelly MJ, Horan JT, Alonzo TA, et al. Comparable survival for pediatric acute myeloid leukemia with poor-risk cytogenetics following chemotherapy, matched related donor, or unrelated donor transplantation. *Pediatr Blood Cancer*. 2014;61:269-275.
- Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA*. 2009;301(22):2349-2361.
- Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36:2684-2692.
- Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *N Engl J Med*. 2013;369:111-121. *A randomized trial of non-chemotherapy-based treatment (ATRA + arsenic trioxide) versus traditional ATRA plus chemotherapy for newly diagnosed, low-risk APL showing similar outcomes and less hematologic toxicity. Longer follow-up shows better outcomes with ATRA plus arsenic, and this combination is now the standard treatment approach for patients with low-risk APL.*
- Masetti R, Bertuccio SN, Pession A, et al. CBFA2T3-GLIS2-positive acute myeloid leukaemia. A peculiar paediatric entity. *Br J Haematol*. 2019;184:337-347.
- Mayer RJ, Davis RB, Schiffer CA, et al; Cancer and Leukemia Group B. Intensive postremission chemotherapy in adults with acute myeloid leukemia. *N Engl J Med*. 1994;331(14):896-903. *A randomized study of three different cytarabine regimens in postremission therapy of AML. The benefit of HiDAC is limited to younger patients. HiDAC is suggested to be harmful to older patients.*
- McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. *Nat Rev Cancer*. 2017;17:513-527.
- Mehta PA, Ileri T, Harris RE, et al. Chemotherapy for myeloid malignancy in children with Fanconi anemia. *Pediatr Blood Cancer*. 2007;48:668-672.
- Meybodi MA, Cao W, Luznik L, et al. HLA-haploidentical vs matched-sibling hematopoietic cell transplantation: a systematic review and meta-analysis. *Blood Adv*. 2019;3:2581-2585.
- National Comprehensive Cancer Network. NCCN Guidelines for Treatment of Cancer by Site: Acute Myeloid Leukemia. National Comprehensive Cancer Network;2021.
- Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
- Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med*. 2012;366(12):1079-1089.
- Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381:1728-1740.
- Pollard JA, Alonzo TA, Brown PA, et al. Sorafenib in combination with standard chemotherapy for children with high allelic ratio FLT3/ITD+ AML improves event-free survival and reduces relapse risk: a report from the Children's Oncology Group Protocol AAML1031. *Blood*. 2019;134:292.
- Pollard JA, Loken M, Gerbing RB, et al. CD33 expression and its association with gemtuzumab ozogamicin response: results from the

- randomized phase III Children's Oncology Group trial AAML0531. *J Clin Oncol*. 2016;34:747-755.
- Porter CC, Druley TE, Erez A, et al. Recommendations for surveillance for children with leukemia-predisposing conditions. *Clin Cancer Res*. 2017;23:e14-e22.
- Rollig C, Kramer M, Schliemann C, et al. Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia? *Blood*. 2020;136:823-830.
- Sanz MA, Fenaux P, Tallman MS, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. *Blood*. 2019;133:1630-1643.
- Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. *Blood*. 2014;123(18):2777-2782.
- Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2018;131(12):1275-1291.
- Stahnke K, Boos J, Bender-Gotze C, et al. Duration of first remission predicts remission rates and long-term survival in children with relapsed acute myelogenous leukemia. *Leukemia*. 1998;12:1534-1538.
- Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-731.
- Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377:454-464.
- Taub JW, Berman JN, Hitzler JK, et al. Improved outcomes for myeloid leukemia of Down syndrome: a report from the Children's Oncology Group AAML0431 trial. *Blood*. 2017;129:3304-3313.
- Tunstall-Pedoe O, Roy A, Karadimitris A, et al. Abnormalities in the myeloid progenitor compartment in Down syndrome fetal liver precede acquisition of GATA1 mutations. *Blood*. 2008;112:4507-4511.
- Uffmann M, Rasche M, Zimmermann M, et al. Therapy reduction in patients with Down syndrome and myeloid leukemia: the international ML-DS 2006 trial. *Blood*. 2017;129:3314-3321.
- Walsh MF, Chang VY, Kohlmann WK, et al. Recommendations for childhood cancer screening and surveillance in DNA repair disorders. *Clin Cancer Res*. 2017;23:e23-e31.
- Walsh M, Wu G, Edmonson M, et al. Incidence of germline mutations in cancer-predisposition genes in children with hematologic malignancies: a report from the Pediatric Cancer Genome Project [abstract]. *Blood*. 2014;124(21). Abstract 127.
- Wareham NE, Heilmann C, Abrahamsson J, et al. Outcome of poor response paediatric AML using early SCT. *Eur J Haematol*. 2013;90:187-194.
- Webb DK, Wheatley K, Harrison G, et al. Outcome for children with relapsed acute myeloid leukaemia following initial therapy in the Medical Research Council (MRC) AML 10 trial. MRC Childhood Leukaemia Working Party. *Leukemia*. 1999;13:25-31.
- Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383:2526-2537.
- Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135:2137-2145.
- Xiao H, Shi J, Luo Y, et al. First report of multiple CEBPA mutations contributing to donor origin of leukemia relapse after allogeneic hematopoietic stem cell transplantation. *Blood*. 2011;117:5257-5260.
- Xie M, Lu C, Wang J, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. *Nat Med*. 2014;20(12):1472-1478.
- Yoshida K, Toki T, Okuno Y, et al. The landscape of somatic mutations in Down syndrome-related myeloid disorders. *Nat Genet*. 2013;45:1293-1299.
- Zwaan CM, Kolb EA, Reinhardt D, et al. Collaborative efforts driving progress in pediatric acute myeloid leukemia. *J Clin Oncol*. 2015;33:2949-2962.