Acute Leukemia

28

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Leukemias are an uncommon and heterogeneous group of diseases characterized by infiltration of the bone marrow, blood, and visceral organs by neoplastic cells of the hematopoietic system. Leukemias generally stem from the myeloid or lymphoid hematopoietic lineages and occur as acute or chronic disease. This chapter will focus on the acute leukemias, namely, acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). Acute leukemia is diagnosed by the discovery of ≥20% blasts in the peripheral blood or bone marrow, although such stringent cutoffs may not accurately define the biology of the disease.

Advances in the understanding of the molecular drivers of these diseases have led to further classification into subgroups, which can give prognostic information and, in some cases, may allow for the use of targeted treatment approaches. This classification is based on integrated results of morphology, immunohistochemistry, immunophenotyping by flow cytometry, cytogenetics (karyotyping), FISH, and molecular studies of mutations shown in Fig. 28.1.

Acute Myeloid Leukemia

AML, arising from hematopoietic precursors of the nonlymphoid compartment, is the most common acute leukemia in adults, with an annual incidence of 4.3/100,000. The frequency increases with age, with a median age at diagnosis of 70 years. Approximately 2.8/100,000 people are expected to die of AML each year, and only 27.4% of patients are alive at 5 years after diagnosis.

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Clinical Features, Workup, and Diagnosis

Patients with AML commonly present with symptoms that reflect underlying bone marrow failure. This causes symptoms reflecting anemia, such as pallor, fatigue, weakness, palpitations, or dyspnea on exertion. Symptoms of thrombocytopenia, including ecchymoses, petechiae, epistaxis, and prolonged bleeding after minor injury may also be seen. While patients may be found to be neutropenic, major infections are uncommon at diagnosis. Patients may also have systemic symptoms, including anorexia, weight loss, and low-grade fevers. Hepatomegaly or splenomegaly may be seen in approximately one-third of patients.

The initial evaluation of AML should focus on both the characteristics of the disease and the comorbidities of the patient. A bone marrow biopsy and aspiration should be performed to evaluate the blast percentage (see Fig. 28.2 for a representative marrow). Additionally, the disease should be evaluated on factors including cytogenetic or molecular abnormalities, antecedent myelodysplasia, or prior exposure to cytotoxic chemotherapy, as such an assessment offers prognostic information and may change therapy.

Some patients may present with disseminated intravascular coagulation (DIC), especially those with acute promyelocytic leukemia. As such, evaluation of the platelet count, prothrombin time, activated partial thromboplastin time, and serum fibrinogen should be part of the initial evaluation.

Hyperleukocytosis, i.e., the presentation of a high white blood cell count usually greater than $>100 \times 10^9$/L, is seen in approximately 5% of patients. Hyperleukocytosis can lead to leukostasis, a symptomatic rise in the blast count which leads to decreased tissue perfusion, due to increases in blood viscosity and cytokine release from high cellular metabolic activity. Leukostasis is a medical emergency and can manifest with CNS, pulmonary, or other symptoms due to leukostatic plugs preventing adequate tissue oxygenation. CNS manifestations include blurred vision, papilledema, retinal hemorrhages, dizziness, slurred speech, stupor, delirium, or intracranial hemorrhage. Pulmonary symptoms may include tachypnea, hypoxia,

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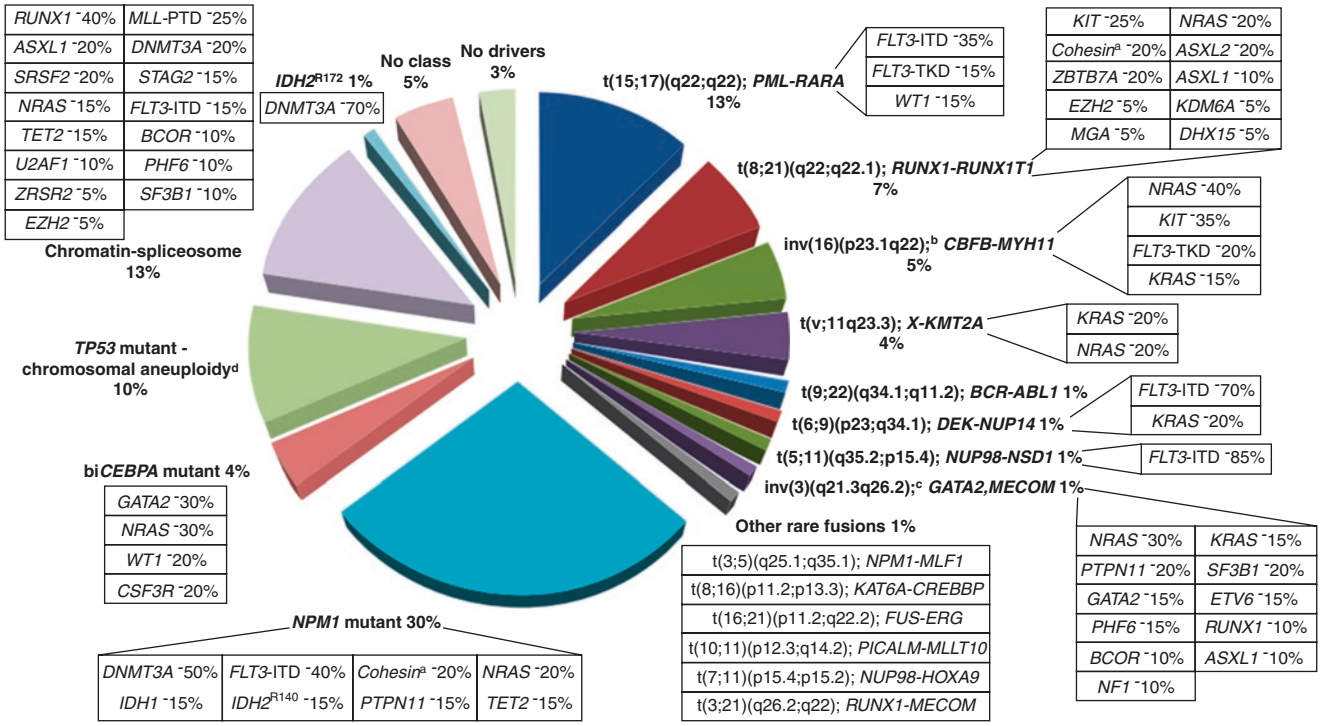

Fig. 28.1 Frequency of prognostically relevant molecular and cytogenetic subgroups of AML from the 2017 European Leukemia Network (ELN) guidelines [4]

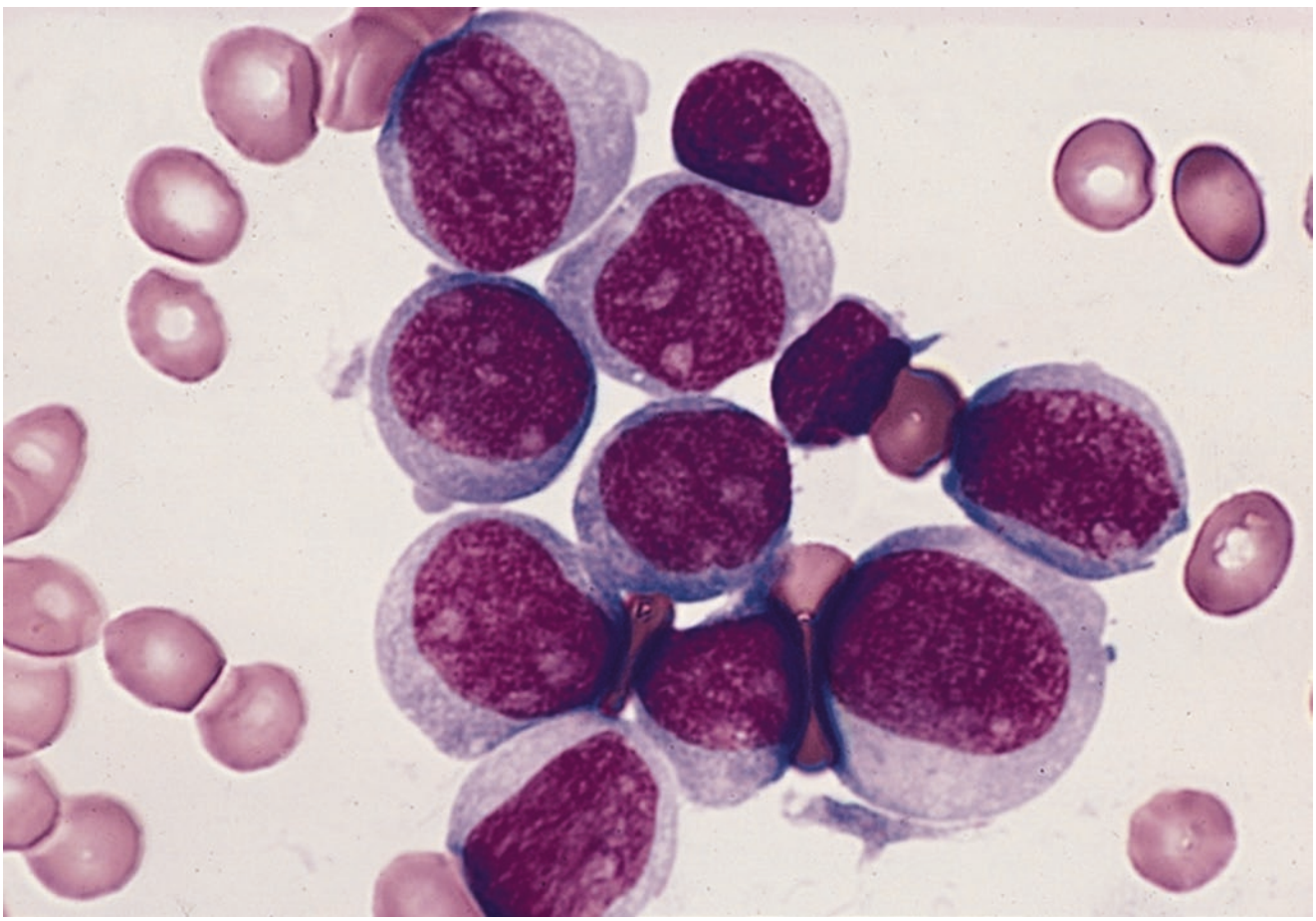

Fig. 28.2 Myeloid blasts in bone marrow. (Used from The Armed Forces Institute of Pathology)

cyanosis, dyspnea, and pulmonary infiltrates. When both neurologic manifestations and respiratory failure are present, patients have a predicted mortality rate of 90% by 1 week from diagnosis. Male patients may also experience priapism.

Leukostasis is acutely treated by lowering the white blood cell count (cytoreduction). This can be done with hydroxyurea, an antimetabolite which can drop the WBC by up to 80% within 24–48 h. As leukostasis is a medical emergency, hydroxyurea is commonly reserved for asymptomatic patients with hyperleukocytosis, and a more rapid approach may be chosen for those with symptomatic leukostasis. Such a rapid approach may include initiation of induction chemotherapy, with the understanding that this may induce rapid cellular lysis and precipitate tumor lysis syndrome. Induction chemotherapy may decrease the WBC count by 24 h and may be an effective strategy for rapid cytoreduction. Mechanical removal of excess WBCs can also be performed using a technique known as leukapheresis. Leukapheresis involves the placement of a large-bore central venous catheter, such as a dialysis catheter, that will allow for the withdrawal of blasts from the circulation. The effects of leukapheresis on mortality are controversial, and several sessions may be required to improve patient symptoms and lower the WBC. Given the risks involved in catheter placement and the lack of directed treatment at the underlying cause, leukapheresis should be used as an adjunct or a bridge to leukemia-directed therapy.

While CNS disease is less common with AML than it is with ALL, certain patients are at higher risk. Those with symptoms suggestive of CNS disease, monocytic differentiation, a high white blood cell count (>40,000/μL) at presentation, extramedullary disease, high-risk acute promyelocytic leukemia, or mixed-phenotype acute leukemia should undergo a lumbar puncture at first remission.

For patients who present with extramedullary disease without bone marrow involvement, commonly called myeloid sarcoma, PET/CT should be performed to evaluate for additional sites of disease.

Initial Evaluation for AML

- Thorough history and physical exam, including evaluation of performance status
- CBC with platelets and differential
- Peripheral smear evaluation
- Serum chemistries and liver function tests
- Disseminated intravascular coagulation (DIC) panel (D-dimer, fibrinogen, PT/aPTT, platelets)
- Tumor lysis syndrome (TLS) labs (serum lactate dehydrogenase (LDH), uric acid, potassium, phosphate, calcium)
- Bone marrow analysis with aspirate and morphology review, cytogenetics/FISH, flow cytometry, myeloid mutation panel, Rapid IDH1, IDH2, and FLT3 mutational analysis
- Urinalysis
- Hepatitis B/C, HIV, CMV antibody testing
- Pregnancy testing in females
- Fertility counseling
- Evaluation of cardiac function (e.g., transthoracic echocardiogram)
- Head imaging and LP if concern for CNS involvement
- PET/CT if concern for CNS or other extramedullary involvement

Classification

The classification of AML has evolved from the previous French-American-British (FAB) system, which was based on morphology alone, to the World Health Organization system, which incorporates cytogenetics, immunophenotypic analysis, and molecular abnormalities.

In this schema, AML is diagnosed with presence of 20% blasts detected in the peripheral blood or bone marrow. The WHO does identify certain clonal cytogenetic abnormalities, namely, t(15;17), t(8;21), and inv(16), whose presence should be considered diagnostic of AML, regardless of the percentage of blasts detected.

Details of risk stratification by the 2016 WHO classification schema are presented in Table 28.1

Risk Stratification

Cytogenetics are the most important prognostic factor in predicting rate of remission, risk of relapse, and overall survival outcomes. Patients with t(8;21) and inv(16) without a *c-kit*

Table 28.1 WHO classification of myeloid neoplasms and acute leukemia [6]

WHO Myeloid Neoplasom and Acute Leukemia Classification
Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML). *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis

(continued)

Table 28.1 (continued)

WHO Myeloid Neoplasom and Acute Leukemia Classification
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRS*, or *FGFR1*, or with *PCM1-JAk2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood
Myeloid neoplasms with germ line predisposition
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with I(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
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
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

Table 28.2 ELN risk stratification by genetics [4]

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3-ITD* or with *FLT3*-ITD^{low}
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q2l.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype, monosomal karyotype ll
	Wild-type *NPM1* and *FLT3*-ITD^{high}
	Mutated *RUNX1*
	Mutated *ASXL1*
	Mutated *TP53*

mutation and those with t(15;17) are thought to have favorable-risk disease, based on the 2017 European Leukemia Network (ELN) guidelines. Adverse-risk disease is seen in patients with cytogenetic abnormalities including complex karyotype (≥3 cytogenetic abnormalities), monosomal karyotype (the presence of a monosomy in addition to a second monosomy or other cytogenetic abnormality), and −5/del(5q); −7; t(6;9); t(v;11q23); t(9;22); inv(3). Intermediate-risk classification is applied to patients with t(9;11), trisomy 8, normal cytogenetics, or other cytogenetic changes not otherwise defined.

Molecular data are also being used to risk stratify patients, and this field is rapidly evolving. Based on the 2017 ELN guidelines, patients with mutated *NPM1* without *FLT3*-ITD and those with biallelic mutations in *CEBPA* are considered favorable risk. Those with wild-type *NPM1* and *FLT3*-ITD^{high} or with mutated *RUNX1*, *ASXL1*, or *TP53* are considered adverse-risk. With the advent of myeloid genomic testing being incorporated into the standard of care, further studies are likely to identify additional mutational profiles that are of prognostic significance (Table 28.2).

Treatment

Induction

The intent of induction chemotherapy is to achieve remission to gain initial control over the disease, as well as to restore

normal hematopoiesis. The choice of induction therapy is influenced by individual characteristics of both the patient and the disease.

Standard induction regimens utilize cytarabine in combination with an anthracycline. The anthracycline daunorubicin has been studied more commonly than idarubicin, although both have been found to have comparable remission rates. Mitoxantrone is an anthracenedione and has also been studied in combination with cytarabine for induction therapy but is more commonly used in pediatric regimens.

For patients 60 years of age or younger, cytarabine 100 mg/m^2 administered as a continuous IV infusion for 7 days in combination with daunorubicin 90 mg/m^2 daily for 3 days ("7 + 3") is a commonly used regimen. Daunorubicin 90 mg/m^2 was compared to 45 mg/m^2 in patients 60 years and younger and was shown to produce a higher rate of complete remissions and longer overall survival without a significant increase in cardiotoxicity.

For patients over 60 years of age, daunorubicin at a dose of 60 mg/m^2 in combination with cytarabine is considered a standard "7 + 3" regimen for those who are fit and wish to undergo induction therapy. Some European studies suggest that the addition of a purine analog (cladribine or fludarabine) to an induction regimen can improve overall survival; however, this has not been adopted as standard practice in the United States.

In recent years, induction chemotherapy regimens have begun to change for certain populations. For elderly adults who are unfit or do not wish to undergo treatment with intensive chemotherapy, initial therapy may include the combination of venetoclax with low-dose cytarabine. Patients who have a therapy-related myeloid neoplasm or who have AML with myelodysplasia-related changes may be candidates for treatment with liposomal daunorubicin and cytarabine, known as CPX-351. Finally, patients with *FLT3* mutations may benefit from the addition of midostaurin to their induction and consolidation regimens.

Consolidation

Post-remission therapy, known as consolidation, is also necessary – patients who do not receive post-induction therapy may relapse within 6–9 months. The choice of consolidation therapy may depend on the patient's risk stratification. Patients who have so-called favorable-risk disease may be treated with high-dose cytarabine alone, commonly given as 3 g/m^2 IV every 12 hours on days 1, 3, and 5 with G-CSF support, although bone marrow transplantation can be considered in certain cases. Those with intermediate- or adverse-risk disease may have a higher risk of relapse and should strongly consider consolidative treatment with an allogeneic hematopoietic cell transplant (HCT), with or without additional chemotherapy (such as high-dose cytarabine) given prior to HCT.

CNS Disease

Leptomeningeal disease is somewhat infrequent in AML, especially as compared to ALL, and occurs in <3% of AML cases. As such, lumbar puncture (LP) is not usually performed as part of the routine diagnostic workup. For patients who present with symptoms such as headache, confusion, altered sensorium, etc., initial head imaging (i.e., CT or MRI) should be performed to rule out intracranial hemorrhage or the presence of a mass lesion prior to an LP. If the imaging and LP are negative, patients can be clinically followed for symptoms with repeat evaluation as warranted by clinical status. If the LP is positive, IT chemotherapy should be given concurrently with standard induction. Generally, IT chemotherapy (e.g., with cytarabine, methotrexate, or a regimen that incorporates both) is given twice weekly until blasts are cleared from the CNS and then weekly for an additional 4–6-week period. The CNS should again be assessed in the post-induction setting with additional IT therapy given as appropriate.

For patients in whom imaging detects a mass lesion or parenchymal involvement, needle aspiration may be considered to confirm the diagnosis. If confirmed, the patient may be offered radiation therapy followed by IT chemotherapy. HIDAC, which penetrates the blood-brain barrier and can be used as both systemic and CNS-directed therapy or focused IT therapy, should not be given concurrently with cranial irradiation as this may increase neurotoxicity.

Response Criteria

As per the WHO [6], response to therapy is categorized as follows:

- Complete response (CR): ANC >1000/μL, platelets ≥100,000/μL, no residual evidence of extramedullary disease, and transfusion independence
- Complete response with incomplete count recovery (CR_i): <5% bone marrow blasts, transfusion independence but with a persistent cytopenia (either ANC <1000/μL or thrombocytopenia <100,000/μL.
- Cytogenetic CR – normal cytogenetics in those with previous abnormalities
- Molecular CR (APL and Ph+ ALL only) – qPCR negative
- Partial remission (PR): 50% decrease in the blast percentage, with a blast percentage of between 5% and 25%, not meeting criteria for any type of CR
- Relapse: Reappearance of leukemic blasts in the peripheral blood, the finding of >5% bone marrow blasts, or recurrence of extramedullary disease

Minimal Residual Disease

Minimal residual disease (MRD) is the presence of leukemic cells in the bone marrow after treatment which can be

detected by flow cytometry or molecular testing. The role of MRD in the prognosis and treatment of AML is still under study. Current data suggest that patients who are MRD positive after treatment are more likely to relapse, even after HCT. Studies are underway to determine what strategies may be effective in eradicating MRD.

Acute Promyelocytic Leukemia

APL is an aggressive subtype of AML with distinct morphological and clinical features. It is cytogenetically characterized by the presence of translocation t(15;17), which leads to the production of a *PML-RARα* fusion gene. The fusion transcript also is detected and monitored by qPCR to document disease burden, with a goal of achieving molecular remission with treatment.

Historically, APL has been associated with a high early death rate related to coagulopathy that is often seen at presentation. It has also been described as occurring as therapy-related disease after treatment with topoisomerase II inhibitors and/or radiation. Despite its aggressive nature, treatment of APL is now leading to cure rates of up to 99% without bone marrow transplantation.

Treatment for APL is chosen based on stratification by WBC, with ≤10,000 cells/μL considered low risk and levels above this threshold considered high risk. Low-risk disease is treated with induction therapy that incorporates all-trans retinoic acid (ATRA), which can induce differentiation of APL blasts and reverse the coagulopathy commonly seen with this disease. The most common regimen, published by LoCoco et al. in NEJM in 2013, uses ATRA and arsenic trioxide (ATO) for both induction and consolidation therapy, with long-term follow-up studies showing persistent response rates of as high as 99% in low-risk patients. Patients with high-risk disease are treated with a combination regimen that includes ATRA and an anthracycline, such as ATRA with daunorubicin and cytarabine or ATRA with idarubicin and ATO.

Patients who are thought to have APL based on morphology, presence of coagulopathy or disseminated intravascular coagulation, or immunophenotype should be started on ATRA without awaiting confirmation of the diagnosis. If APL is not confirmed by cytogenetics or FISH, ATRA can be discontinued in favor of alternative therapy; however, a delay in initiating therapy for a patient with APL may be fatal.

Treatment with ATRA may induce what is known as differentiation syndrome, heralded by fever, shortness of breath, hypoxemia, and pleural or pericardial effusions. Patients with high-risk disease (WBC >10,000/μL) should receive steroid prophylaxis, and patients who develop differentiation syndrome should be treated with dexamethasone 10 mg every 12 hours, and ATRA should be temporarily held. Treatment with ATO can cause QT prolongation, requiring EKG and electrolyte monitoring.

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia, sometimes called acute lymphocytic leukemia, is a clonal, neoplastic disease of immature lymphocytes derived from either B- or T-cell lineage. ALL is the most common malignancy in childhood (3–4/100,000) with a peak incidence occurring between 2 and 3 years of age and most cases occurring before age 10. The incidence of adult ALL is much lower, at about 1.7/100,000 people annually in the United States (Fig. 28.3).

Clinical Features, Workup, and Diagnosis

As with acute myeloid leukemia, patients may present with nonspecific symptoms. Adults with ALL may sometimes initially complain of fatigue, B-symptoms (e.g., fevers, chills, night sweats, and weight loss), dyspnea, easy bruising, bleeding, or petechiae. Bone pain can be seen but is more common in children. Approximately 20% of patients may present with lymphadenopathy, splenomegaly, and possibly hepatomegaly. Patients who complain of perioral or chin numbness, headache, confusion, or cranial nerve abnormalities should be evaluated for leptomeningeal disease.

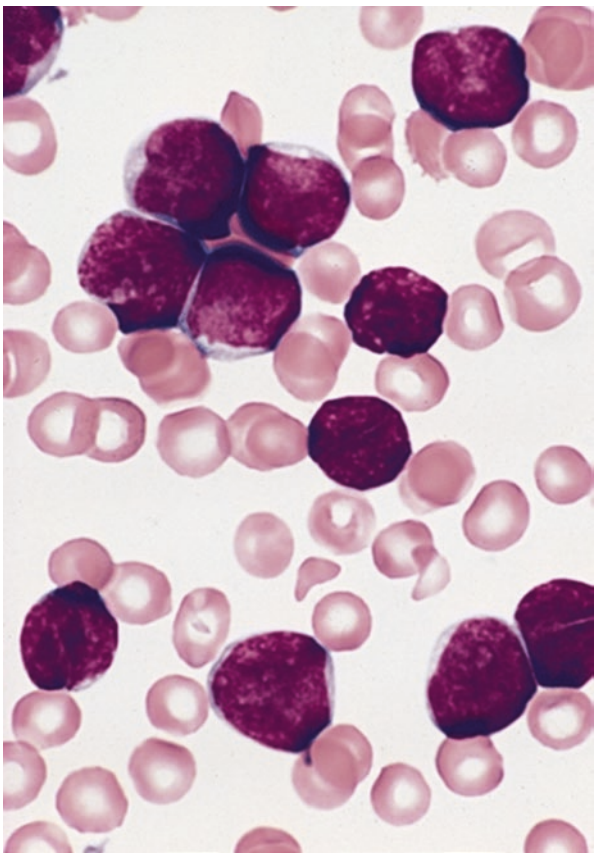

Fig. 28.3 Acute lymphoblastic leukemia. (Used from The Armed Forces Institute of Pathology)

Patients may present with an elevated white blood cell count, with a WBC >30,000/μL for B-lineage and >100,000/μL T-lineage disease being adverse prognostic factors, and evaluation of the peripheral blood smear may show circulating lymphoblasts. In cases with an elevated white blood cell count and symptoms including dyspnea, hypoxemia, confusion, visual changes, tinnitus, gait instability, somnolence, or fever, leukostasis should be considered – although this is less commonly seen than in AML. Some patients also present with thrombocytopenia, which may manifest as purpura, menorrhagia, mucosal bleeding, or even retinal hemorrhage.

Workup for the disease includes a history and physical exam, laboratory studies, imaging studies where appropriate, evaluation for opportunistic infections, and fertility counseling, and should be tailored to each individual case.

Initial Evaluation for ALL

- Thorough history and physical exam, including evaluation of performance status
- CBC with platelets and differential
- Peripheral smear evaluation
- Serum chemistries and liver function tests
- Disseminated intravascular coagulation (DIC) panel (D-dimer, fibrinogen, PT/aPTT, platelets)
- Tumor lysis syndrome (TLS) labs [serum lactate dehydrogenase (LDH), uric acid, potassium, phosphate, calcium]
- Bone marrow analysis with aspirate and morphology review, cytogenetics/FISH, flow cytometry, and gene fusion panel
- Urinalysis
- Hepatitis B/C, HIV, and CMV antibody testing
- Pregnancy testing in females
- Evaluation of testicular involvement in male patients
- Fertility counseling
- Evaluation of cardiac function (e.g., transthoracic echocardiogram)
- CNS imaging as appropriate
- Lumbar puncture as per treatment protocol (diagnostic LP commonly performed at time of first intrathecal treatment)

Acute lymphoblastic leukemia is considered to be the same entity as lymphoblastic lymphoma, as per the 2016 WHO guidelines. The distinction between the two is that the bone marrow is involved with 20% lymphoblasts or greater in acute lymphoblastic leukemia, whereas the disease is restricted to a mass lesion involving nodal or extranodal sites with minimal or no involvement in the blood or bone marrow in lymphoblastic lymphoma. As such, a bone marrow biopsy and aspiration is necessary to confirm the diagnosis.

Flow cytometry is also used to classify ALL into three immunophenotypic subgroups, namely, precursor B-cell ALL, mature B-cell ALL, and T-cell ALL. A representative photomicrograph of precursor B-cell ALL cells in the bone marrow is shown in Fig. 28.3. In addition, cytogenetic and molecular studies are often sent at diagnosis from a bone marrow sample to assist in risk stratification and choice of an optimal treatment regimen.

Immunophenotypic Characterization

In adults, approximately 75% of ALL cases evolve from B-cells. The immunophenotype of early precursor B-cell ALL is characterized by the presence of terminal deoxynucleotidyl transferase (TdT), the expression of CD19/CD22/CD79a, and the absence of CD10 or surface immunoglobulins.

The immunophenotype of precursor B-cell ALL is characterized by the presence of CD10, CD19, CD22, and CD79a, as well as the presence of cytoplasmic immunoglobulins.

Mature B-cell ALL has an immunophenotype that is positive for surface immunoglobulins and clonal lambda or kappa light chains and is negative for TdT.

CD20 expression can be seen in approximately 50% of adult B-cell ALL cases and is most commonly seen in the mature B-cell subtype.

T-cell ALL typically presents with an immunophenotype of cytoplasmic or cell surface CD3, in addition to variable expression of CD1a/C2/CD5/CD7 and expression of TdT. Around 30–50% of the cells may also express CD52.

Early T-cell precursor (ETP) ALL is seen in about 2% of adult ALL and was traditionally associated with poor clinical outcomes. ETP ALL is usually characterized by the absence of CD1a/CD8, weak expression of CD5, and expression of one or more myeloid or stem cell markers, including CD34, CD33, CD11b, CD117, HLA-DR, CD13, and CD65. ETP was previously thought to have a poorer prognosis, but more recent data suggest that outcomes for these patients may be no worse than for patients with other subtypes of ALL, if they are treated effectively.

A subset of acute leukemias are of ambiguous lineage and are considered to be "mixed phenotype" acute leukemias (MPAL). These leukemias have features of both AML and ALL and can be treated based on their molecular characteristics (e.g., TKIs can be used in the presence of a t(9;22)).

Chromosomal and Molecular Changes

Table 28.3 below outlines some of the most common chromosomal and molecular abnormalities seen in 2016 WHO classification of ALL.

Table 28.3 2016 WHO classification of ALL [6]

B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.30);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural kilter (NK) cell lymphoblastic leukemia/lymphoma

Numerical changes in chromosomes are common in this disease. Hypodiploidy (<46 chromosomes), pseudodiploidy (46 chromosomes with other structural abnormalities), and hyperdiploidy (>50 chromosomes) are frequently seen. Hyperdiploidy confers a favorable prognosis unless the patient is near triploidy; low hypodiploidy and pseudodiploidy/complex karyotype (≥5 cytogenetic abnormalities) notably both have a poor prognosis.

Table 28.4 (below) further describes the common chromosomal and molecular abnormalities seen in ALL. Translocation t(9;22), also called a Philadelphia chromosome, leads to a BCR-ABL1 gene fusion product and is seen commonly in B-cell ALL in adults, occurring in about 25% of cases. This gene fusion product encodes a tyrosine kinase which is constitutively active and interferes with signaling pathways such as RAS. Philadelphia chromosome positivity can indicate a poorer prognosis and can also affect the choice of therapy, as discussed below.

Detection of a Philadelphia chromosome-like phenotype, in which the gene expression profile is similar to that seen in Ph-positive B-ALL but without the presence of a translocation t(9;22), also carries an unfavorable prognosis – one study of adult patients found a 5-year event-free survival of 22.5%. Philadelphia-like ALL may involve a mutation of the Ikaros (*IKZF1*) gene, but mutations in genes such as *ABL1*, *ABL2*, *EPOR*, *JAK2*, *PDGFRβ*, *EBF1*, *FL2*, *IL7R*, *NTRK3*, and *SH2B3* have also been found to generate this phenotype.

The presence of a translocation t(12;21) defines an *ETV6-RUNX1* fusion, also called *TEL-AML1*. This is the most common genetic abnormality noted in childhood ALL and is associated with a favorable prognosis (see Chap. 35). Translocation t(v;11q23) involves the mixed-lineage leukemia gene (*MLL*) which encodes a lysine methyltransferase and is therefore also known as *KMT2A*; translocations at this site portend a poor prognosis. Finally, translocation t(8;14) is associated with a mature B-cell phenotype and dysregulation of the c-myc proto-oncogene; it occurs in about 5% of ALL and confers a poor prognosis.

Table 28.4 Common chromosomal and molecular abnormalities in ALL [2]

Cytogenetics	Gene	Frequency in adults	Frequency in children
Hyperdiploidy (>50 chromosomes)	–	7%	25%
Hypodiploidy (<44 chromosomes)	–	2%	1%
t(9;22)(q34;q11): Philadelphia chromosome (Ph)	*BCR-ABL1*	25%	2–4%
t(12;21)(p13;q22)	*ETV6-RUNX1(TEL-AML1)*	2%	22%
t(v;11q23)[e.g., t(4;11), t(9;11)], t(11;19)	*KMT2A (MLL)*	10%	8%
t(1;19)(q23;pl3)	*TCF3-PBX1(E2A-PBX1)*	3%	6%
t(5;14)(q31;q32)	*IL3-IGH*	<1%	<1%
t(8;14), t(2;8), t(8;22)	*c-MYC*	4%	2%
t(1;l4)(p32;q11)	*TAL-1*[a]	12%	7%
t(10;l4)(q24;q11)	*HOX11(TLX1)*[a]	8%	1%
t(5;14)(q35;q32)	*HOX11L2*[a]	1%	3%
t(11;l4)(q11) [e.g., (pl3;q11), (p15;q11)]	*TCRα and TCRδ*	20–25%	10–20%
BCR-ABL1-like	*Various*[b]	10–30%	15%
ETP	*Various*[a]	2%	2%
Ikaros	*IKZF1*	25–35%	12–17%

[a]Abnormalities observed exclusively in T-cell lineage ALL; all others occur exclusively or predominately in B-cell lineage ALL
[b]See text for more details

Early T-cell precursor (ETP) lymphoblastic leukemia was also previously described to have a poor prognosis, with high rates of remission failure and hematologic relapse. Activating mutations in the cytokine receptor and RAS signaling pathways have been identified, including mutations in *NRAS*, *KRAS*, *FLT3*, *IL7R*, *JAK3*, *JAK1*, *SH2B3*, and *BRAF*. Inactivating mutations in genes that encode proteins required for normal differentiation, including *GATA3*, *ETV6*, *RUNX1*, *IKZF1*, and *EP300*, have also been described.

Other subtypes of T-ALL involve activating mutations in *NOTCH1*, which is associated with improved outcomes.

Patients with hereditary syndromes (including Down, Bloom, Klinefelter, and Fanconi) are predisposed to developing cytogenetic and molecular abnormalities that may lead to ALL. Additionally, patients exposed to ionizing radiation or radon may also be at an increased risk for developing the disease.

Risk Stratification

Children, Adolescents, and Young Adult Patients (up to 21 Years of Age)

Lower Risk
- Hyperdiploidy
- T(12;21) – *ETV6-RUNX1/TEL-AML1*
- Simultaneous trisomies of chromosomes 4, 10, and 17

Standard Risk
- Age 1–10 years
- WBC <50,000/μL

High Risk
- T-cell ALL
- Not meeting criteria for another category
- Extramedullary disease at diagnosis

Very High Risk (B-cell ALL only)
- Less than 1 year of age
- Philadelphia chromosome or *BCR-ABL1* fusion protein positivity
- Ph-like or *BCR-ABL1*-like gene signature
- Hypodiploidy (<44 chromosomes)
- *iAMP21*
- Failure to achieve remission with induction chemotherapy
- *MLL* rearranged disease

Adults

High Risk
- Age >35 years
- Elevated WBC at diagnosis (>30,000/μL for B-lineage and >100,000/μL T-lineage)
- Adverse cytogenetics: t(9;22), t(4;11), t(8;14), complex karyotype, low hypodiploidy, near triploidy
- Time to achieve CR >4 weeks
- Presence of minimal residual disease after induction and intensification

Treatment

Treatment for ALL usually consists of three phases: induction, consolidation, and maintenance therapy. Several different treatment regimens exist, and the choice of therapy depends on the patient's age and subtype of ALL, as well as physician preference and the patient's performance status and potential ability to tolerate certain agents (e.g., L-asparaginase). All treatment regimens incorporate prophylaxis and/or treatment for CNS disease.

Induction

Induction therapy is meant to debulk the tumor burden in the bone marrow. Most ALL induction therapy regimens are designed based on pediatric models (such as the one designed by the Berlin-Frankfurt-Münster group) and incorporate agents such as vincristine, anthracyclines, corticosteroids, and possibly cyclophosphamide and/or L-asparaginase. ALL cells are unable to synthesize the amino acid asparagine, and they require it from an exogenous source in order to proceed with protein translation. Asparaginase is utilized because it causes the rapid deamination of asparagine, depleting it from the serum and causing cell death. The agent must be used with caution, however, as it can cause LFT abnormalities, pancreatitis, hypercoagulability, and hypersensitivity reactions.

Consolidation

Consolidation therapy is given with the goal of eradicating residual disease that may persist after induction. In some regimens, the consolidation phase also includes an intensification phase, which can be considered a post-remission re-induction. Commonly used agents include high-dose methotrexate, 6-mercaptopurine, vincristine, cytarabine, corticosteroids, cyclophosphamide, and L-asparaginase.

In patients who are considered standard or high risk, allogeneic HCT should be considered as a consolidative therapy.

CNS Prophylaxis

Unlike AML, sanctuary site relapse is commonly seen in ALL. Therefore, periodic intrathecal chemotherapy, coupled with cycles of high-dose methotrexate, is administered starting during induction and continuing throughout consolidation and maintenance. Cranial irradiation is sometimes considered for adult patients who are not planning to undergo an allogeneic transplant. With CNS prophylaxis, the risk of relapse in this site decreases from 30% to 5%.

Maintenance

For patients who do not go on to a HCT, extended maintenance therapy can prevent disease relapse and has been shown to significantly improve overall survival in ALL patients. Commonly used agents included in maintenance may be omitted in patients with mature B-cell ALL, as these patients often have long-term remissions with short courses of intensive therapy, and relapses are rarely seen in this population beyond 12 months.

Tyrosine Kinase Inhibitor Therapy

BCR-ABL tyrosine kinase inhibitors are used in patients with Philadelphia chromosome-positive ALL. By inhibiting the kinase activity of the BCR-ABL protein product, these agents eliminate the constitutive downstream signaling that drives the malignancy. Both imatinib and dasatinib are reasonable options; however, the latter has increased potency in inhibiting signaling pathways, activity against various ABL kinase mutations, and greater penetration of the blood-brain barrier and therefore is commonly preferred.

In patients who do not wish to undergo intensive therapy, or are not candidates for it, TKI with corticosteroid therapy is a possible treatment option.

Anti-CD20 Therapy

Approximately 32% of patients with Philadelphia chromosome-negative precursor B-cell ALL express the CD20 antigen on the cell surface, although some estimates put this closer to 40–50%. Patients with CD20 expressing B-cell ALL may benefit with anti-CD20 monoclonal antibody therapy, e.g., rituximab. While other anti-CD20 antibodies, such as obinutzumab and ofatumumab, have been developed, they are not currently approved for use in ALL patients.

Other Targeted Therapies

The bi-specific T-cell engager blinatumomab targets CD19-positive cells and can be used in patients with relapsed/refractory Philadelphia chromosome-negative ALL. It is commonly used to induce an MRD-negative remission in patients who have achieved an MRD-positive CR. Side effects include fever, cytokine release syndrome, neurological toxicities, neutropenia, and infection.

The anti-CD22 antibody-drug conjugate inotuzumab ozogamicin is also used in patients with relapsed/refractory disease who express CD22 on their ALL cells. The most common adverse event associated with inotuzumab is hepatotoxicity, including sinusoidal obstruction syndrome (also known as veno-occlusive liver disease).

Cellular Therapy

Anti-CD19 chimeric antigen receptor T-cells (CAR T-cells) came into widespread use in 2017. Anti-CD19 CAR T-cells are developed by engineering a T-cell receptor with an extracellular domain targeted against CD19 and intracellular signaling domains of the T-cell receptor complex. This allows the T-cells to engage the CD19-positive ALL cells, which activates the T-cells and stimulates a cytotoxic response.

Tisagenlecleucel was the first anti-CD19 CAR T-cell therapy approved by the FDA for use in children and young adults with relapsed/refractory ALL in 2017. This product is an autologous CAR T-cell therapy which uses a patient's own cells. It was found to create durable, MRD-negative responses in patients with ALL, even in those who had relapsed after HSCT.

Supportive Care

Leukostasis

Patients with elevated WBC, usually >100,000/μL, may develop symptoms of leukostasis. These symptoms may include neurological symptoms such as numbness, tingling, decreased hearing, vision changes, and tinnitus, and pulmonay symptoms such as dyspnea, tachypnea, hypoxia, and cyanosis. Treatment in this situation should be individualized, but the approach may include administration of fluids (not blood products) and leukapheresis. For patients with an elevated WBC who are asymptomatic and who are not yet ready for induction therapy, hydroxyurea can be used for leukoreduction in AML, and steroids may be used in patients with ALL. APL patients with high WBC are not routinely treated with leukapheresis. See the previous discussion in this chapter regarding leukostasis in AML.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is defined by the Cairo-Bishop criteria as potassium >6 meq/L, phosphate >4.5 mg/dL, calcium <7 mg/dL, and uric acid >8 mg/dL. Standard prophylaxis includes hydration with diuresis and allopurinol. If TLS develops, standard treatment may include rasburicase, a recombinant urate oxidase enzyme that allows for the rapid enzymatic degradation of urate crystals. Institutional guidelines may vary on when to use rasburicase, but a mildly elevated uric acid level without other signs of ongoing TLS may not warrant the use of this costly medication. Additionally, patients should be screened for potential glucose-6-phosphate dehydrogenase deficiency prior to rasburicas administration, as methemoglobinemia may result from the production of hydrogen peroxide in the urate oxidase reaction in these patients.

Coagulopathy

Coagulopathy can occur at presentation in many leukemias, and thus all patients with acute leukemia should have a prothrombin time, activated partial thromboplastin time, fibrinogen, and platelet count (as part of the CBC) for screening. For patients with APL, platelets should be kept ≥50,000/μL, fibrinogen levels should be followed, and cryoprecipitate should be provided to maintain a level over 150 mg/dL, and PT and aPTT should be followed with treatment as appropriate.

Blood Product Support

Patients treated in the inpatient setting should receive leukocyte-depleted blood products. If possible, irradiation of blood products is also recommended to reduce infectious risk. While guidelines for inpatient management may vary across institutions, many transfuse packed RBCs for a hemoglobin <7 mg/dL to promote adequate tissue oxygenation and transfuse platelets for a count <10,000/μL to reduce the risk of spontaneous intracranial hemorrhage.

Opportunistic Infections and Neutropenic Fever

Patients who are neutropenic should be placed on viral and fungal prophylaxis given the high risk of opportunistic infections. Of note, posaconazole has been shown to significantly decrease fungal infections as compared to fluconazole or itraconazole. Isavuconazole is also gaining favor given fewer drug interactions and potentially less QT prolongation. Bacterial prophylaxis, for example, with levofloxacin, should be offered to patients who remain neutropenic in the outpatient setting. Prophylaxis should be continued until the ANC remains steadily above 1000/μL. Neutropenic fever should be treated as per local guidelines with the use of an antipseudomonal, broad-spectrum antibiotic, continued at least until the neutropenia has resolved. A rigorous infectious workup should also be pursued.

Fertility and Suppression of Menses

Patients of childbearing potential should be counseled on options for preserving fertility prior to chemotherapy initiation, if possible. Some female patients may require treatment to suppress menstruation, given the risks of hemorrhage with concurrent treatment-related thrombocytopenia. Conception should be avoided during treatment and patients should be counseled on this point.

Summary

Acute myeloid leukemia is a malignant proliferation of myeloid progenitor cells which can lead to symptoms of bone marrow failure, impaired immunity and infections, DIC, leukostasis, and CNS disease. Classification and risk stratification give information on prognosis and can change treatment recommendations. Patients are generally treated with induction therapy, most commonly using an anthracycline and cytarabine combination regimen, followed by consolidation, which may or may not include a bone marrow transplant. Acute promyelocytic leukemia is a subtype of AML which is driven by a *PML-RARα* fusion; the development of regimens incorporating all-trans retinoic acid (ATRA) has made this aggressive form of leukemia highly curable. Acute lymphoblastic leukemia is a clonal neoplastic malignancy of immature lymphocytes which more commonly presents with CNS disease. Classification and risk stratification are again important in these patients, who are treated with induction, consolidation, CNS-directed therapy, maintenance, and possibly tyrosine kinase inhibitor therapy and/or bone marrow transplantation. Supportive care measures are important to understand, as specialized treatment strategies exist for leukostasis, tumor lysis syndrome, and other complications seen with the acute leukemias.

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