Chapter 157: Acute Leukemias

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KEY CONCEPTS

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1. Acute leukemias are the most common malignancies in children and the leading cause of cancer-related death in patients younger than 20 years.

2. Several risk factors correlate with prognosis for acute lymphoblastic leukemia (ALL). Poor prognostic factors include high white blood cell (WBC) count at presentation, very young or very old age at diagnosis, delayed remission induction, and presence of certain cytogenetic abnormalities (eg, Philadelphia chromosome positive [Ph^+]).

3. For children with ALL, remission induction therapy includes vincristine, a corticosteroid, and asparaginase, with or without an anthracycline. For adults with ALL, vincristine, prednisone, anthracycline, and asparaginase are used.

4. All patients with ALL require prophylactic therapy to prevent CNS disease because of the high risk of central nervous system (CNS) relapse. The choice for therapy includes a combination of cranial irradiation, intrathecal chemotherapy, or high-dose systemic chemotherapy with drugs that cross the blood-brain barrier.

5. Long-term maintenance therapy for 2 to 3 years is essential to eradicate residual leukemia cells and prolong the duration of remission. Maintenance therapy consists of oral methotrexate and mercaptopurine, with or without monthly pulses of vincristine and a corticosteroid.

6. Disease-free survival is lower in adults with ALL and has been attributed to greater drug resistance, poor tolerance with subsequent nonadherence, and possibly less-effective therapy. This population is also more likely to have Ph^+ ALL, which is associated with a worse outcome, but the use of tyrosine kinase inhibitors (TKIs) has improved treatment results.

7. Several poor prognostic factors for adult acute myeloid leukemia (AML) include older age, organ impairment, extramedullary disease, and certain cytogenetic and molecular abnormalities.

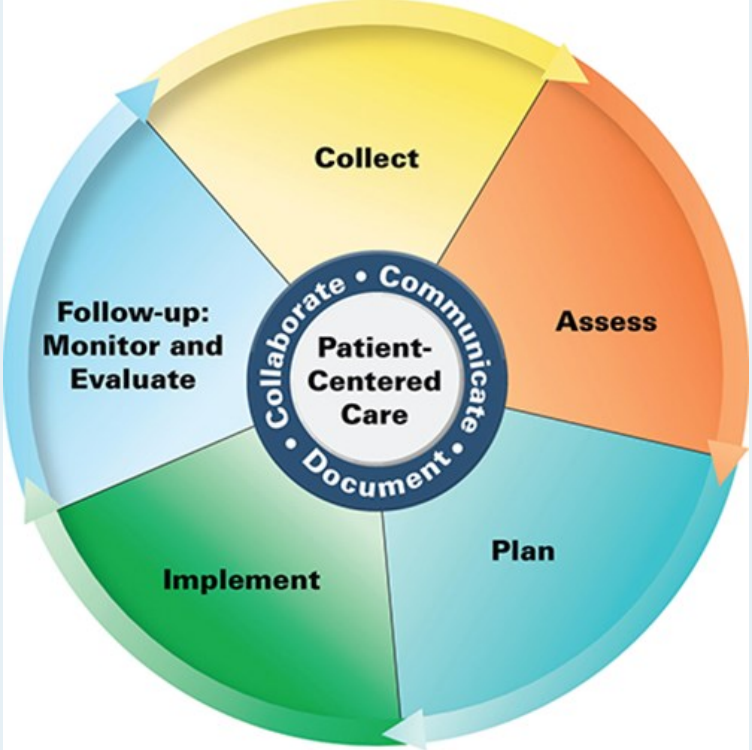
8. Treatment of AML usually includes therapy with an anthracycline and cytarabine. Postremission therapy is required in all patients and consists of either consolidation chemotherapy with or without maintenance therapy, or hematopoietic stem cell transplantation (HSCT). Novel oral therapies that inhibit FMS-related tyrosine kinase (FLT-3), isocitrate dehydrogenase (IDH1 and IDH2), and B-cell leukemia/lymphoma (BCL-2) have emerged in the AML treatment landscape.

9. Treatment of acute promyelocytic leukemia (APL) consists of induction therapy, consolidation, and maintenance therapy. Induction includes tretinoin and an anthracycline; consolidation therapy consists of two to three cycles of anthracycline-based therapy; maintenance consists of pulse doses of tretinoin, mercaptopurine, and methotrexate for 2 years.

10. Hematopoietic growth factors can be safely and effectively used with myelosuppressive chemotherapy for acute leukemias. They reduce the risk of serious infections, hospital length of stay, and treatment delays but do not prolong disease-free or overall survival.

PATIENT CARE PROCESS

Patient Care Process for Ph^+ Adult Lymphoblastic Leukemia



Collect

- Patient characteristics (eg, age, gender, pregnancy status)
- Patient medical history (personal and family)
- Social history (eg, tobacco/marijuana, ethanol use)
- Current medications including OTCs and herbal products
- Confirmation of histological diagnosis
- Objective data
    - Complete blood count (CBC) with differential, platelets
    - Hepatic function tests
    - Basic chemistry panel
    - DIC panel: D-dimer, fibrinogen, PT, PTT
    - Tumor lysis panel (uric acid, potassium, calcium, phosphate)
    - Hepatitis B/C serologies, HIV, CMV status

- ABO blood typing
- Human leukocyte antigen (HLA) typing

- Molecular/cytogenetic information

Assess

- Tumor lysis syndrome risk
- Risk for Hepatitis B reactivation (CD20+ monoclonal antibody)
- Central venous access device
- Echocardiogram or MUGA scan (anthracycline component in ALL therapy)
- Chemotherapy consent (willingness for intrathecal chemotherapy)
- Chemotherapy-induced nausea/vomiting risk
- Hemodynamic stability (eg, systolic blood pressure <90 mm Hg, heart rate >110 bpm, O_2 sat <90%, respiratory rate)
- Presence of active bleeding or bleeding risk factors
- Testicular disease (males)
- Dental evaluation
- Presence of Ph^+ disease
- Emotional status (eg, presence of anxiety, depression)
- Health insurance/prescription drug coverage (e.g. hospitalization, BCR-ABL inhibitor)

Plan

- Comprehensive patient education regarding treatment plan
- Drug therapy regimen including multiagent chemotherapy (IV, IT) with corticosteroids and TKI (eg, Hyper-CVAD + rituximab + dasatinib)
- Monitoring parameters including efficacy (eg, circulating blasts, platelets, trilineage hematopoiesis) and safety (eg, signs and symptoms of bleeding, serum creatinine); frequency and timing of follow-up
- Implement supportive care measures (transfusions, hematopoietic growth factors)
- Infection prophylaxis (antifungal, antiviral, *Pneumocystis jirovecii*)
- Referrals to other providers when appropriate
- Initiate donor search for future allogeneic HSCT
- Provide and document discharge summary and patient education

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence with tyrosine kinase inhibitor (i.e. dasatinib)

- Schedule clinic follow-up visits

Follow-up: Monitor and Evaluate

- Response assessment (monitor for minimal residual disease [RT-PCR or next generation sequencing to detect BCR-ABL1]) after completion of induction
- PET scans for extramedullary disease if applicable
- Repeat echocardiogram or MUGA scan if applicable
- Physical examination every 1 to 2 months within the first year following completion of therapy
- Referral to Cancer Survivorship clinic

**Collaborate with patient, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

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Watch the video "Valerie Shares Her Story for AML Awareness Month" (https://www.youtube.com/watch?v=8_CD1Yt1-2k). In this Cancer Care video, patient Valerie shares her journey with AML while she underwent treatment at the MD Anderson Cancer Center. After you watch this video, answer the following questions:

1. What are the signs/symptoms of a newly diagnosed AML patient?
2. What economic challenges does Valerie mention? What are some ongoing initiatives to reduce cancer disparities?
3. Discuss the AML treatment options for induction therapy (pediatric, 18-60, ≥60 years old population).
4. When should an AML patient consider a hematopoietic stem cell transplant?

INTRODUCTION

The leukemias are heterogeneous hematologic malignancies characterized by unregulated proliferation of the blood-forming cells in the bone marrow. These immature proliferating leukemia cells (blasts) physically "crowd out" or inhibit normal cellular maturation in bone marrow, resulting in anemia, granulocytopenia, including neutropenia, and thrombocytopenia. Leukemic blasts may also infiltrate various tissues such as lymph nodes, skin, liver, spleen, kidney, testes, and the central nervous system (CNS).

Leukemia is historically classified based on the cell of origin and cell line, and as acute or chronic based on differences in clinical presentation, rapidity of progression of the untreated disease, and response to therapy. The four major leukemias are acute lymphoblastic (or lymphocytic) leukemia (ALL), acute myeloid (or myelogenous) leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid (or myelogenous) leukemia (CML). Undifferentiated immature cells that proliferate autonomously characterize acute leukemias. Chronic leukemias also proliferate autonomously, but the cells are more differentiated and mature. If untreated, acute leukemia is fatal within weeks to months.

EPIDEMIOLOGY

[1] About 26,710 new cases of acute leukemia—20,050 cases of AML and 6,660 cases of ALL were diagnosed in the United States in 2022, accounting for about 1.5% of the total number of cancers diagnosed. The incidence has been relatively stable for two decades. An estimated 13,100 deaths per year,

representing about 2% of all cancer deaths, are caused by acute leukemias.[1]

Leukemia is the leading cause of cancer-related deaths in persons younger than 20 years.[2] It is the leading cause of cancer death for males aged 20 to 39 years, but it is an uncommon cause of cancer-related death for both genders after the age of 40 years. Among adults, acute and chronic leukemias occur at equal rates. More than 90% of the cases of acute and chronic leukemia occur in adults. AML accounts for most cases of acute leukemia in adults and occurs with increasing frequency in older patients.[1]

Despite the low incidence, acute leukemias are the most common malignancy in persons younger than 20 years, accounting for nearly 30% of all childhood malignancies. About 75% of children with leukemia have ALL and most of the remaining cases are AML.[1] Conversely, AML represents about 80% of acute leukemias in adults while only 20% of cases are ALL. Pediatric ALL is about 30% more common in males than in females, peaks at 1 to 4 years of age, and is almost twice as likely to affect Caucasian children than African American children.[2] Geographically, the highest rates of ALL have been identified in the Western portion of the US region.[3] Acute leukemia during the first year of life (infant leukemia) slightly favors ALL over AML.

ETIOLOGY

The exact cause of acute leukemias is unknown. A multifactorial process involving genetics, environmental and socioeconomic factors, toxins, immunologic status, and viral exposures is likely. Infectious and genetic factors have the strongest associations. In pediatric ALL, many environmental factors have been associated with the disease: exposure to ionizing radiation, toxic chemicals, herbicides and pesticides; maternal use of contraceptives, diethylstilbestrol, or cigarettes; parental exposure to drugs, diagnostic radiographs, alcohol consumption, coffee and cola consumption, or chemicals before and during pregnancy; and chemical contamination of groundwater.[4,5] Some studies have reported that high birth weight is a risk factor for ALL. Ionizing radiation and benzene exposure are the only environmental risk factors strongly associated with ALL or AML. Some studies have reported an association between electromagnetic fields of high-voltage power lines and the development of leukemia, but larger studies could not confirm this association. In most patients who develop leukemia, a cause cannot be identified.

PATHOPHYSIOLOGY

Normal hematopoiesis consists of multiple well-orchestrated steps of cellular development. Pluripotent stem cells undergo differentiation, proliferation, and maturation, to form the mature blood cells seen in the peripheral circulation. These pluripotent stem cells initially differentiate into two distinct stem cell pools. The myeloid stem cell gives rise to six types of blood cells (erythrocytes, platelets, monocytes, basophils, neutrophils, and eosinophils). Lymphoid stem cells differentiate into natural killer cells, B-lymphocytes, and T-lymphocytes. Leukemia may develop at any stage and within any cell line.

Two features are common to both AML and ALL. First, both arise from a single leukemic cell that expands and acquires additional mutations, culminating in a monoclonal population of leukemia cells. Second, there is a failure to maintain a relative balance between proliferation and differentiation, so that the cells do not differentiate past a particular stage of hematopoiesis. Cells (lymphoblasts or myeloblasts) then proliferate uncontrollably. Proliferation, differentiation, and apoptosis are under genetic control, and leukemia can occur when the balance between these processes is altered.

AML likely arises from a defect in the pluripotent stem cell or a more committed myeloid precursor, resulting in partial differentiation and proliferation of immature precursors of the myeloid blood-forming cells. In older patients, trilineage leukemia occurs, suggesting that the cell of origin is probably a stem or very early progenitor cell. In younger patients, a more differentiated progenitor becomes malignant, allowing some granulocytic and erythroid populations to mature. These two forms of AML exhibit different patterns of resistance to chemotherapy, with resistance more evident in older adults with AML. ALL is a disease characterized by the proliferation of immature lymphoblasts. In this type of acute leukemia, the defect is probably at the level of the lymphoid stem cell or an early lymphoid precursor.

Leukemic cells have growth and survival advantages over normal cells, leading to a “crowding out” phenomenon in the bone marrow. This growth advantage is not caused by more rapid proliferation than normal cells. It may be caused by factors produced by leukemic cells that either inhibit normal cellular proliferation and differentiation or reduce apoptosis compared with normal blood cells.

Specific genetic alterations that lead to leukemia continue to be elucidated. Genetic defects may include (a) activation of a normally suppressed gene

(protooncogene) to create an oncogene that produces a protein product that signals increased proliferation; (b) loss of signals for the blood cell to differentiate; (c) loss of tumor suppressor genes that control normal proliferation; and (d) loss of signals for apoptosis. Most normal cells are programmed to die eventually through apoptosis, but the appropriate programmed signal is often interrupted in cancer cells, leading to continued survival, replication, and drug resistance. Signal transduction, RNA transcription, cell-cycle control factors, cell differentiation, and programmed cell death may all be affected.[6,7]

LEUKEMIA CLASSIFICATION

In 2016, the World Health Organization (WHO) revised the current classification system for myeloid neoplasms (Table 157-1).[8] This classification system incorporates not only morphologic findings, but also genetic, immunophenotypic, cytochemical, and clinical features. With the recent discoveries of mutations involved in AML, the revised classification system expanded the prognostic significance of mutations such as c-KIT, FLT-3, CEBPA, NPM1, IDH, WT1, and TET2 in AML subtypes.

TABLE 157-1

World Health Organization Classification of Acute Myeloid Leukemia and Related Neoplasms

Acute myeloid leukemia (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 t(1;22)(p13.3;q13.3); RBM15-MKL1
AML with BCR-ABL1
AML with biallelic mutations of CEBPA
AML with mutated RUNX1
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
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome

PML, promyelocytic leukemia, RARα, retinoic acid receptor-α.

ALL is classified based on lymphoblast analysis. Immunophenotype is determined by flow cytometry that analyzes specific antigens, known as clusters of differentiation (often abbreviated “CD”), present on the cell surface. Although no leukemia-specific antigens have been identified, the pattern of cell-surface antigen expression reliably distinguishes between lymphoid and myeloid leukemia. The immunophenotype defines the cell of origin. The major phenotypes are mature B-cell, precursor B-cell, and T-cell disease, but the WHO classifies ALL as either B lymphoblastic or T lymphoblastic. About 80% of childhood ALL derives from precursor B cells and about 15% from T cells; the remainder is from mixed lineage or mature B cells. T-cell ALL is more common in teenage males. In adults, about 75% of ALL is B-cell lineage and 25% is T-cell lineage ALL.

Leukemias may also be described by cytogenetic abnormalities. Chromosome alterations include numerical (hyperdiploidy and hypodiploidy) and structural abnormalities due to exchanges of genetic information within (inversion) or between (translocation) chromosomes. Unique translocations can identify specific subtypes of acute leukemia. The most common translocation in adult ALL, occurring in 25% of patients, is the t(9;22) or Philadelphia chromosome positive (Ph^+), which causes fusion of the BCR signaling protein to the ABL nonreceptor tyrosine kinase, resulting in constitutive tyrosine kinase activity. Acute promyelocytic leukemia (APL) is characterized by a specific translocation between chromosomes 15 and 17: t(15;17). Molecular tests may be used to identify products of specific translocations, such as promyelocytic leukemia (PML) retinoic acid receptor-α (RARα) in APL and *AML1-ETO* and *CBFβ/MYH 11* in other subtypes of AML.

Several factors can affect the cytogenetics of AML in adults. First, in about 5% of patients, simultaneous blood and marrow samples demonstrate

normal cytogenetics versus abnormal cytogenetics, respectively. Second, central cytogenetic analysis is done in multicenter trials because of variability in specimen examination. Some patients have a normal karyotype on standard review, but carry fusion genes, which are identical to those of translocations or inversions.[8] These insertions of very small chromosome segments do not alter chromosome morphology but may affect outcome.

CLINICAL PRESENTATION

At presentation, common signs and symptoms result from malignant cells that replace and suppress normal hematopoietic progenitor cells and infiltrate into extramedullary spaces. Patients with acute leukemia often present with symptoms related to complications of pancytopenia (eg, anemia, neutropenia, and thrombocytopenia) which include fatigue, infections, gingival bleeding, ecchymoses, and epistaxis.

In addition to clinical presentation, laboratory and pathology evaluations are required for a definitive diagnosis of leukemia. An abnormal complete blood count (CBC) is usually the diagnostic test that initiates a leukemia workup. Although leukemic blast cells may be present on the peripheral blood smear, they are not diagnostic of leukemia because there are other explanations for why immature blast cells may be present in peripheral blood. The most important diagnostic test is a bone marrow biopsy and aspirate, which is submitted to hematopathology for numerous evaluations, including flow cytometry, cytogenetics, and immunophenotyping. A lumbar puncture is performed to determine if there are blasts in the CNS. Unlike ALL, AML is less commonly associated with CNS involvement. A chest radiograph or computed tomography is performed to screen for a mediastinal mass (most common in T-cell disease). The results of these evaluations help to determine the patient's prognosis and therapeutic plan.[9]

CLINICAL PRESENTATION: Acute Leukemias

General

- Recent history of vague symptoms such as tiredness, lack of exercise tolerance, weight loss, and "feeling unwell," but in no obvious distress.

Signs and Symptoms

- Common: Patients with anemia present with pallor, malaise, palpitations, and fatigue. Patients with low platelet count present with bruising, ecchymoses, and petechiae. Temperature is often elevated and may be caused by disease or infection. Patients may have bone pain from hyperactive bone marrow.
- Other possible symptoms include epistaxis, dyspnea on exertion, seizures, or headache. Splenomegaly, hepatomegaly, or lymphadenopathy is common in patients presenting with ALL, but painless testicular enlargement and rarely, small, blue-green collections of leukemia cells under the skin (chloromas) may also be present. Patients with AML may present with gum hypertrophy and bleeding.

Laboratory Tests

- Complete blood count with differential. Anemia (<7 g/dL [70 g/L; 4.34 mmol/L]) is normochromic and normocytic (without a compensatory increase in reticulocytes). Thrombocytopenia (severe, <20,000 cells/mm^3 [20 × 10^9/L]) is present in 28% of ALL and 50% of AML cases. Patients can present with leukopenia or leukocytosis; about 20% of patients will present with a WBC count ≥50,000 cells/mm^3 (50 × 10^9/L) and 53% of ALL and 20% of AML cases with a WBC <10,000 cells/mm^3 (10 × 10^9/L). Even patients with elevated counts can be considered functionally neutropenic.
- Uric acid may be elevated because of rapid cell turnover and is more common in patients presenting with elevated WBC count and with ALL.
- Electrolytes: potassium and phosphate may be elevated with a compensatory decrease in calcium, more common with ALL.
- Coagulation (more common with AML): elevated prothrombin time, partial thromboplastin time, D-dimers; hypofibrinogenemia.

Other Diagnostic Tests

- Bone marrow aspirate and biopsy: send for morphologic examination, cytochemical staining, immunophenotyping, and cytogenetic (chromosome) analysis. Molecular testing for FMS-like tyrosine kinase 3 (FLT3), nucleophosmin (NPM1), and CCAAT/enhancer binding-protein α (CEBPA), mutations is warranted for suspected AML.
- All adults with ALL should have a screening lumbar puncture performed to assess CNS involvement. Screening in patients with AML is not routine and depends on multiple factors at presentation including symptoms, WBC count, and morphology that includes monocytic disease.
- All pediatric patients with acute leukemias will receive a diagnostic lumbar puncture and intrathecal chemotherapy at that time (intrathecal is usually performed on day 1 of induction chemotherapy for ALL and within the first week of induction for AML patents).

ACUTE LYMPHOBLASTIC LEUKEMIA

Risk Classification

2 Several clinical and biological features at diagnosis are associated with response to treatment, as measured by the complete remission rate, duration of remission, and long-term survival. The patient's response to initial therapy is strongly associated with response to treatment. Identifying these risk factors allows the clinician to better understand the disease and personalize treatment according to the risk of disease recurrence (ie, risk-adapted therapy). For example, if a patient has many clinical and laboratory features that are associated with a favorable response to antineoplastic therapy (standard risk), the clinician may give less-intensive therapy to reduce the risk of long-term adverse effects. Conversely, if a patient is unlikely to respond well to standard therapy (high-risk or very-high-risk disease), the clinician may give more intensive antineoplastic therapy. The factors can

be grouped as follows: patient characteristics at diagnosis, leukemic cell features at diagnosis, and patient response to initial therapy.

The National Cancer Institute (NCI) developed an ALL-risk stratification to create a standard for comparison in children.[10] Induction therapy is initially selected based on this classification, which divides children into standard- or high-risk categories based on age and initial WBC count (Table 157-2a). Age remains an independent predictor of outcome with children aged 1 to 9 years having the best event-free survival, possibly due to a more frequent favorable cytogenetics in this age group.[11] Age and WBC count has limited prognostic importance in T-cell ALL.[10] The presence of CNS disease at diagnosis is associated with a higher relapse rate. About 2% of males have testicular disease at diagnosis, but not all cooperative groups classify this as an adverse prognostic factor. Male ALL patients have a slightly worse prognosis.[12]

TABLE 157-2a

National Cancer Institute Risk Classification for Pediatric Acute Lymphoblastic Leukemia

Risk Group	Standard Risk	High Risk
Age (years)	1–<10	<1 or ≥10
WBC count (× 10^3 cells/mm^3 or × 10^9/L)	<50	≥50
Karyotype	No t(9;22) or t(4;11)	t(9;22) or t(4;11)

WBC, white blood cell.

Data from Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996;14:18-24.

Cell surface and immunophenotype classify childhood ALL into B-cell (85%) or T-cell (15%). T-cell ALL patients are often male, African American, older, and less likely to be Hispanic than B-cell ALL. T-cell ALL generally presents with higher WBC counts and has mediastinal lymph node and CNS involvement. Historically, survival for T-cell ALL was inferior to B-cell ALL, but this difference has narrowed with more intensive therapy.[10] Several cytogenetic abnormalities are associated with prognosis. Favorable outcomes are associated with the presence of trisomy of chromosomes 4 and 10, high hyperdiploidy (chromosome number >50 and DNA index >1.16), and the *ETV6-RUNX1* cryptic translocation, t(12;21).[13] Unfavorable or poor prognostic genetic factors are hypodiploidy (chromosome number <44), MLL rearrangement, BCR-ABL1, Ph-like ALL, CRLF2 rearrangement, intrachromosomal amplification of chromosome 21, and IKZF1 alterations (common in Ph-positive and Ph-like ALL).[10] Ph-like ALL can have translocations similar to BCR/ABL (ie, fusions including ABL1 [non-BCR], ABL2, CSF1R, and PDGFRB) or defects in the Janus kinase (JAK) pathway. The most common cytogenetic abnormalities in B-cell ALL are hyperdiploidy (25%), ETV6-RUNX1 (25%), MLL (5%), hypodiploidy (1%-5%), and Ph-positive (4%).[13]

The strongest prognostic factor for ALL is response to therapy. Previous predictors for early response to treatment were response to the first week of glucocorticoid therapy and evaluation of marrow blasts following 1 to 2 weeks of induction therapy. Minimal residual disease (MRD) quantification at the end of induction has become the most important prognostic factor. Molecular measurement of subclinical MRD by either flow cytometry or polymerase chain reaction detects leukemic cells not visible on morphologic examination to assess treatment response and detect relapse. This technique detects one leukemia cell per 10^4 to 10^5 normal cells. The goal is to have MRD less than 0.01% at the end of remission induction therapy. Children with higher levels have a 3 to 5 times greater risk of treatment failure and death.[10]

The Children's Oncology Group uses a risk- and response-based classification of childhood ALL (Fig. 157-1). This classification system uses the NCI-risk assignment to initially categorize patients into standard- or high-risk groups (see Table 157-2a). Following induction therapy, the risk is reclassified based on completeness of response to therapy, the presence or absence of cytogenetic abnormalities, and CNS involvement (Table 157-2b). Patients are then reclassified as low risk, standard risk, high risk, or very-high risk (see Fig. 157-1). Patients who are initially high risk do not have their therapy reduced, but may have it intensified to very high risk.

FIGURE 157-1

Risk and response classification of childhood acute lymphoblastic leukemia.

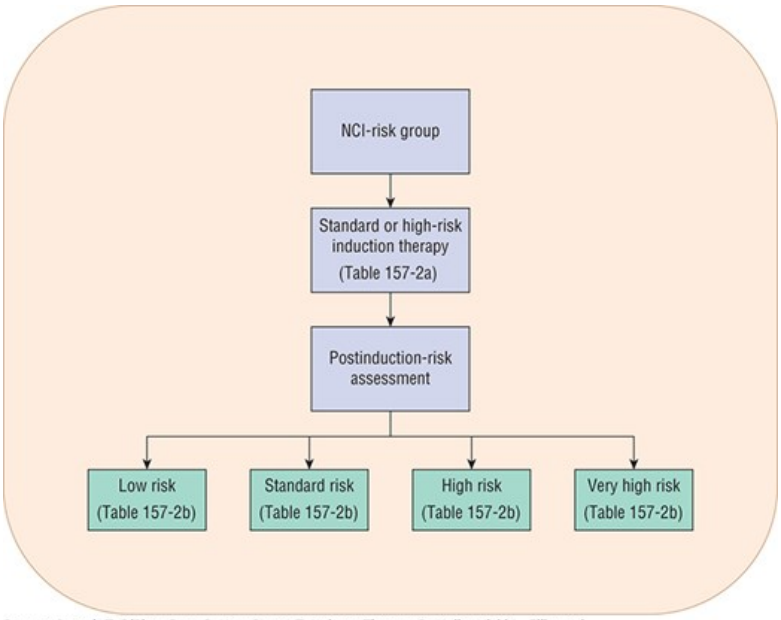


TABLE 157-2b

Pediatric Precursor B-Cell Acute Lymphoblastic Leukemia Risk Classification

	Low	Standard			High Risk			Very High Risk		
NCI Risk	**SR**	**SR**	**SR**	**SR**	**SR**	**HR (age <13)**	**SR**	**HR**	**HR (age >13)**	**Any**
Favorable Genetics	Yes	Yes	No	Yes	No	Any	No	Any	Any	Any
Unfavorable Characteristics	None	None	None	None	None	None	None	None	None	Yes
Day 29 Marrow MRD	<0.01%	<0.01%	<0.01%	>0.01%	<0.01%	>0.01%	<0.01%	>0.01%	<0.01%	Any

HR, high risk; MRD, minimal residual disease; NCI, National Cancer Institute; SR, standard risk.

Note: See Table 157-2a for criteria used to categorize patients into initial risk categories.

Data from Schultz KR, Pullen DJ, Sather HN, et al. Blood. 2007;109:926-935.

Children are classified as low risk and will have therapy reduced if they have trisomy 4 and 10 or the *ETV6-RUNX1* cryptic translocation with less than 0.01% MRD on day 29 bone marrow samples and do not have CNS or testicular disease. Children with testicular disease, MRD greater than or equal to 0.01% on day 29, or who received steroids before diagnosis have postinduction therapy intensified and are classified as high risk. Childhood precursor B-ALL with more than five WBCs and blasts present in the cerebrospinal fluid (CSF), Ph^+ disease, hypodiploidy, $iAMP_{21}$, induction failure, or *MLL* gene rearrangement have therapy intensified and are considered very high risk. Infant ALL, trisomy 21, or childhood T-cell ALL have unique risk classification schemas.[13] Relapse occurs in 15% to 20% of children with ALL. Factors associated with prognosis include time to relapse (ie, shorter time), immunophenotype (ie, T cell), and site of relapse (ie, bone marrow disease). If relapse occurs following the completion of primary treatment, the likelihood of cure is about 50%. If a patient relapses during therapy, only 20% to 30% are cured.[10]

Treatment—Acute Lymphoblastic Leukemia

Desired Outcomes

The short-term goal for ALL treatment is to rapidly achieve a complete clinical and hematologic remission (CR), defined as the disappearance of all physical and bone marrow evidence (normal cellularity with less than 5% blasts) of leukemia, with restoration of normal hematopoiesis. After a CR is achieved, the goal is to maintain the patient in continuous CR. A child is generally considered cured after being in continuous CR for 5 years.

Successful treatment of ALL was first developed in children. Cure rates in children have risen from less than 10% with treatments used in the 1960s to current rates of about 90%.[10] The reason for this improvement lies primarily in improved scheduling of existing drugs, as relatively few new drugs have come to the market since the 1960s. MRD is a strong predictor of relapse in ALL. Children with low-risk disease have a 5-year event-free survival of more than 95%. The 5-year event-free survival for average-risk disease is 90% to 95%. The 5-year event-free survival is nearly 90% for high-risk childhood B-precursor and T-cell ALL. Children with very-high-risk disease have a 5-year event-free survival of less than 80%.[14] Response to treatment is determined by intrinsic drug sensitivity and the patient's pharmacogenomics and pharmacodynamics, treatment received, and treatment adherence.

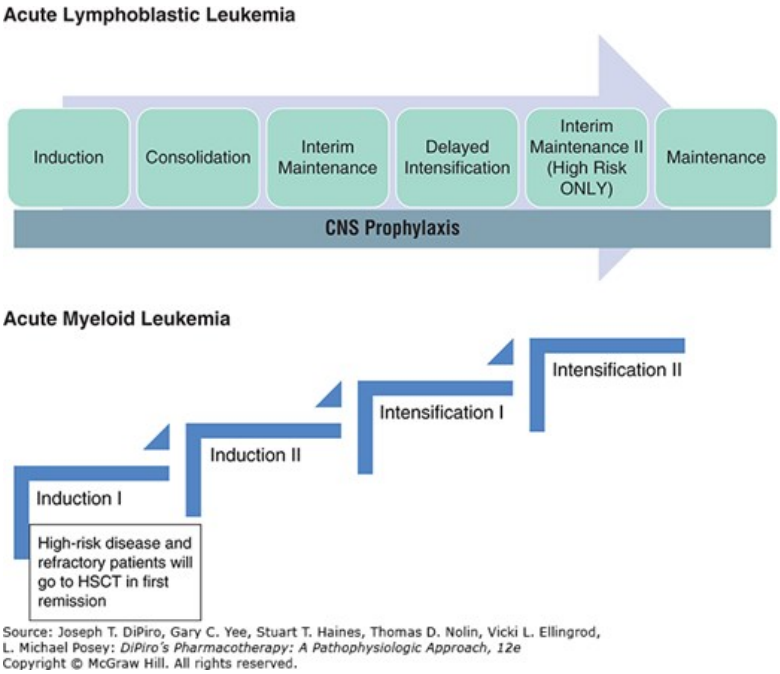
Although treatment response with adult ALL is worse than those with childhood ALL, recent use of aggressive chemotherapy in adult ALL has increased the initial CR rate after induction therapy from 60% to 85%. Long-term event-free survival in this population, however, remains low (between 30% and 40%) because a higher proportion of adults present with high-risk disease. CR rates and event-free survival depend on several poor prognostic factors and certain types of ALL are associated with a very poor outcome.

Treatment Phases

Therapy for childhood ALL is divided into five or six phases: (a) induction, (b) consolidation therapy, (c) interim maintenance, (d) delayed intensification, (e) interim maintenance II, and (f) maintenance therapy (Fig. 157-2). CNS prophylaxis is a mandatory component of ALL treatment regimens and is administered longitudinally during all phases of treatment. The total duration of treatment is 2 to 3 years.[13,15]

FIGURE 157-2

Treatment phases for acute leukemias.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Induction

3 The goal of induction is to rapidly induce a CR. The CR rate is about 98% for standard-risk children treated with vincristine, a glucocorticoid (dexamethasone or prednisone), and pegaspargase.[10] Many treatment protocols include daunorubicin in induction (four-drug induction) for high-risk or very-high-risk ALL. Most children achieve a CR in 4 weeks. Those who have positive MRD at day 29 receive intensified therapy. About 2% to 3% of children fail induction therapy and have a 10-year survival rate of 32%.

Prednisone has been the primary glucocorticoid used in pediatric ALL regimens but has been replaced with dexamethasone in most standard-risk protocols due to its longer duration of action and higher CSF penetration.[16] Dexamethasone improves event-free survival and decreases the risk of CNS relapse, but increases the risk of osteonecrosis, mood alteration, steroid myopathy, hyperglycemia, and infections.[16,17] Adolescents (older than 10 years) are particularly prone to osteonecrosis and receive prednisone instead of dexamethasone to minimize this adverse drug reaction.[12] Patients with Down syndrome also receive prednisone because they have increased infections and mortality with dexamethasone.[18]

Asparaginase has historically been available in three forms. L-Asparaginase (no longer manufactured in the United States) and pegaspargase are isolated from *Escherichia coli,* while Erwinia asparaginase is isolated from *Erwinia chrysanthemi.* Erwinia asparaginase is generally utilized in the setting of an allergic reaction to *E. coli* asparaginase. Erwinia asparaginase is given intramuscularly or intravenously. Erwinia asparaginase intravenously may require more frequent administration every 48 hours or the need for nadir serum asparaginase activity if every 72 hour dosing is required (ie, Monday, Wednesday, and Friday administration).[19] Asparaginase erwinia chrysanthemi (recombinant)-rywn is a new asparaginase product on the market. The dose is vastly different from Erwinia asparaginase.[20] An additional novel asparaginase product calaspargase pegol-mknl has also been developed.[21] Pegaspargase is pegylated *E. coli* asparaginase; pegylation prolongs its duration of activity and allows it to be given less frequently. Pegaspargase is used in most protocols and is preferred over L-asparaginase because of fewer intramuscular injections, decreased antibody formation, and superior response rates. Pegaspargase is also approved for IV administration.[22] The addition of asparaginase and an anthracycline to vincristine and prednisone improves remission rates from 85% to 95%.[15]

Asparaginase products are the antineoplastic agents used in ALL which are most likely to cause hypersensitivity reactions. Depending on the type of asparaginase used and the presence of a co-administered steroid, 8% to 42% of patients may develop hypersensitivity reactions to asparaginase.[23] Hypersensitivity reactions to pegaspargase may have a delayed onset (when administered intramuscularly) and prolonged duration, sometimes requiring hospitalization.[24] *Erwinia* asparaginase is only used for patients who are allergic to pegaspargase. Because *Erwinia* asparaginase has a short half-life, it must be administered more frequently. A single dose of pegaspargase is replaced by six doses of *Erwinia* asparaginase, given three times per week.[25]

Patients may develop silent inactivation, also known as subclinical hypersensitivity, in which they develop neutralizing antibodies that can rapidly inactivate asparaginase, but without developing a clinical hypersensitivity reaction. Silent inactivation can be detected by therapeutic monitoring of asparaginase activity. If inadequate asparaginase activity is detected, a therapeutic switch from pegaspargase to *Erwinia* asparaginase can be made to optimize activity and outcomes. The use of therapeutic drug monitoring to optimize the dosing of asparaginase has also been demonstrated in clinical trials.[26]

Central Nervous System Prophylaxis

4 Central nervous system prophylaxis is incorporated throughout all phases of therapy. The rationale for CNS prophylaxis is based on two observations. First, many antineoplastic agents do not readily cross the blood-brain barrier. Second, results from early clinical trials showed that most patients with ALL experienced CNS relapse.[10] These observations indicate that the CNS is a potential sanctuary for leukemic cells and undetectable leukemic cells are present in the CNS in many patients at the time of diagnosis, while only 3% of children have detectable CNS involvement at diagnosis.[11]

The goal of CNS prophylaxis is to eradicate undetectable leukemic cells from the CNS while minimizing neurotoxicity and late effects. Once CNS relapse has occurred, patients are at increased risk of bone marrow relapse and death from refractory leukemia. Initial trials of childhood ALL in the 1960s established craniospinal irradiation as the standard for prevention of CNS relapse. However, this approach is associated with long-term sequelae including neuropsychological deficits, precocious puberty, osteoporosis, decreased intellect, thyroid dysfunction, brain tumors, short stature, and

obesity. Subsequent trials showed that irradiation may be replaced by frequent administration of intrathecal chemotherapy in children with ALL. Some centers may treat children with CNS disease at diagnosis or very-high-risk disease with cranial radiation. The use of CNS irradiation and early intensified intrathecal chemotherapy has decreased the rate of CNS relapse to less than 5%.[12]

The CNS prophylaxis regimen is selected based on efficacy, toxicity, and risk of CNS disease. Intrathecal chemotherapy, cranial irradiation, dexamethasone, and high-dose IV methotrexate or cytarabine can be used to treat or prevent CNS disease. At least 80% of children with newly diagnosed ALL are treated without cranial radiation.[10] Risk factors for CNS relapse include male sex, hepatomegaly, T-cell phenotype, CNS2 disease (the presence of leukemic blasts in a CSF sample that contains less than 5 WBC/mm^3 [5×10^6/L]), age younger than 2 years or older than 6 years, and a bloody diagnostic lumbar puncture.[14,27] Intrathecal therapy consists of methotrexate and cytarabine, given either alone or in combination. When given together, hydrocortisone is commonly added (triple intrathecal therapy) to decrease the incidence of arachnoiditis. Triple intrathecal therapy is typically reserved for children with refractory CNS disease. For standard-risk ALL, triple intrathecal therapy decreased CNS relapse rates by 30% as compared to intrathecal methotrexate but had no effect on event-free survival and worsened overall survival.[27] Liposomal cytarabine given intrathecally can induce remission of CNS disease but is associated with arachnoiditis and other CNS-related adverse effects.[28]

Patients with T-cell leukemia have an increased incidence of CNS disease and usually receive systemic therapy that penetrates the CNS such as high-dose methotrexate. Patients with T-cell disease have lower methotrexate polyglutamate accumulation in leukemic blasts and therefore were expected to require higher doses of methotrexate intravenously. The Capizzi methotrexate regimen, which consists of low escalating doses of methotrexate without leucovorin rescue plus pegaspargase, was superior to high-dose methotrexate with leucovorin rescue in 90% of patients receiving cranial radiation therapy.[29]

Consolidation Therapy

Consolidation therapy is initiated after a CR has been achieved and refers to continued intensive antineoplastic therapy to eradicate clinically undetectable disease to secure (consolidate) the remission. Regimens usually incorporate either non–cross-resistant drugs that are different from the induction regimen, or more dose-intensive use of the same drugs.

Randomized trials show that consolidation therapy improves patient outcomes in children, but its benefit in adults is less clear. The relative benefit of individual components of treatment regimens is difficult to demonstrate because of the overall complexity of therapy in ALL. Standard consolidation lasts 4 weeks and usually consists of vincristine, mercaptopurine, and intrathecal methotrexate. In children, the intensity of consolidation therapy is personalized based on the child's initial risk classification and response to induction therapy. Children with high-risk disease receive intensified consolidation that includes the addition of pegaspargase, cyclophosphamide, and low-dose cytarabine to standard therapy.[10,13] Children with testicular disease usually receive radiation during this phase of therapy if a complete clinical response in the testes is not achieved by the end of induction. Patients with T-cell leukemia also receive nelarabine, a prodrug of ara-G that preferentially accumulates in T-lymphoblasts as ara-guanosine triphosphate (GTP), during consolidation and throughout the remainder of their treatment course because it improves event-free survival when it is added to an intensified-therapeutic backbone.[30]

Reinduction (Interim Maintenance and Delayed Intensification)

One or two interim maintenance phases separated by a high-intensity delayed intensification cycle can be added to maintain remission and decrease cumulative toxicity (Fig. 157-2). Interim maintenance is given to all ALL patients. Standard-risk patients receive one interim maintenance cycle that includes IV methotrexate (low dose that escalates over the course of the cycle) and vincristine while high-risk patients receive interim maintenance which includes vincristine, high-dose methotrexate, and mercaptopurine. High-risk patients receive a second interim maintenance after delayed intensification which is similar to standard-risk interim maintenance but adds asparaginase. Delayed intensification is similar for both standard- and high-risk patients and includes vincristine, glucocorticoid, doxorubicin, asparaginase, cyclophosphamide, cytarabine, and thioguanine.[11,12,15] ALL patients previously received one interim maintenance and two delayed intensification cycles. Delayed intensification with dose intensification improved event-free survival and decreased late relapses for high-risk childhood ALL, but there was no additional benefit for the second delayed intensification cycle. Children on the intensified arms of the study received significantly more antimicrobial drugs, blood products, and parenteral nutrition but had no increase in treatment-related mortality.[31] These phases use an augmented schedule and chemotherapy dose that reduces tumor burden and prevents the emergence of drug resistant clones.[12]

Maintenance Therapy

5 Maintenance therapy provides long-term drug exposure to slowly dividing cells, allows the immune system time to eradicate leukemia cells, and promotes apoptosis (programmed cell death). The goal of maintenance therapy is to further eradicate residual leukemic cells and prolong remission duration. Although maintenance therapy is clearly beneficial in childhood ALL, the benefit in adults has only been demonstrated.

Maintenance therapy usually consists of daily mercaptopurine and weekly methotrexate for 12-week courses, at doses that produce mild myelosuppression, with monthly pulses of vincristine and a steroid.[10,31] Since male children treated for 2 years versus 3 years have a slightly higher risk of late relapse (excluding isolated testicular relapse), some centers treat female children for 2 years while males receive maintenance for a total of 3 years of therapy.[11] The most recent Children's Oncology Group trial requires 2 years of therapy for male and female children.

Mercaptopurine and oral methotrexate are available as tablets and as an FDA-approved commercially available oral suspension. It was previously recommended that mercaptopurine be taken at night and administered on an empty stomach without concomitant milk products. It was thought xanthine oxidase in milk products would inactivate the drug and circadian rhythm would affect absorption. However, red cell thioguanine levels are not influenced by coadministration of food or dairy, timing of administration or whether the tablet is swallowed whole, crushed, or chewed. Therefore, previous recommendations may hinder drug adherence.[32] Interpatient variability in the adherence and systemic exposure to oral methotrexate and mercaptopurine is an important determinant of the effectiveness and toxicity of maintenance therapy. Children with an adherence rate less than 95% with mercaptopurine have a 2.7-fold higher risk of suffering a relapse.[33] Factors associated with nonadherence include single-parent household, adolescence, lower socioeconomic status, and Hispanic ethnicity.[34] To account for the interpatient variability, most clinicians will titrate the dose of these agents to achieve adequate myelosuppression.[11] Some clinicians overcome variable bioavailability and poor adherence issues by administering methotrexate IV or intramuscularly. The importance of these pharmacokinetic issues in adults is not well defined.

Genetic polymorphisms may affect drug metabolism, receptor expression, drug transport, drug disposition, and pharmacologic response. Pharmacogenomic polymorphisms are an important determinant of mercaptopurine toxicity. Thiopurine methyltransferase (TPMT) is the predominant inactivating enzyme for thiopurines in hematopoietic tissues. About 10% of the population has intermediate TPMT activity because of heterozygous polymorphisms in the gene encoding for TPMT, and 1 in 300 has extremely low activity because of homozygous presence of this TPMT polymorphism. Patients with low activity (homozygous mutant TPMT genotype) require a tenfold dose reduction and frequency change to three times weekly instead of daily. Heterozygous or intermediate metabolizers will require an initial dose reduction of 30% to 80% if the dose is 75 mg/m^2/day or greater. If the mercaptopurine dose is less than 75 mg/m^2/day, then dose reduction may not be recommended.[35] TPMT testing is now a standard of care at many institutions and treatment dosing is adjusted to minimize toxicity without compromising anti-leukemic outcomes. A coding variant in nudix hydrolase 15 (NUDT15) is another important determinant of thiopurine toxicity. NUDT15 encodes a nucleoside diphosphatase that dephosphorylates active thiopurine metabolites, which prevents them from incorporating into DNA and minimizes their cytotoxicity. If a patient has defective NUDT15 alleles, active thiopurine metabolites can accumulate and cause toxicity.[36]

Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Ph$^+$ ALL has historically been treated as very-high-risk disease, which includes the use of a four-drug induction regimen with continuous imatinib mesylate, a tyrosine kinase inhibitor (TKI) that inhibits BCR-ABL kinase, throughout all phases of treatment. This targeted therapeutic approach results in a 5-year overall survival of 70%. The results for patients receiving chemotherapy with imatinib were similar to those receiving hematopoietic stem cell transplantation (HSCT).[37] Imatinib is incorporated into childhood treatment trials for Ph$^+$ ALL in Europe and the United States. Dasatinib shows improved event-free and overall survival compared to imatinib-treated patients with pediatric Ph$^+$ ALL.[38,39] Ph-like ALL is more common in the adolescent and young adult age group (ie, 15-39 years). TKIs (dasatinib), JAK inhibitor (ruxolitinib), and mTOR inhibitors (sirolimus and everolimus) are being investigated for Ph-like ALL.[12,15]

Acute Lymphoblastic Leukemia in Adolescents and Young Adults

Although ALL is relatively uncommon in adolescents and young adults (15-39 years old [AYA]), the outcomes are generally worse than for childhood ALL.[13] The number of AYA patients with ALL has doubled since 1975 and it is estimated to be about 1,200 new diagnoses per year since 2006. In the last

decade, about 50% of AYA patients with ALL survived 10 years. ALL in AYA has a higher frequency of T-cell immunophenotype and a lower frequency of the t(12;21)(p13;q22) cryptic translocation responsible for hyperdiploidy and the *ETV6-RUNX1* fusion gene; and increased incidence of Ph^+ ALL, intrachromosomal amplification of chromosome 21, and Ph-like ALL which occurs most frequently in the AYA population. Thirteen studies have compared outcomes of AYA patients treated with either pediatric or adult regimens. Pediatric-inspired regimens had better outcomes reported in 12 of the 13 studies. Event-free survival rates ranged from 60% to 77% with pediatric regimens versus 32% to 72% with adult regimens, with an overall survival rate of 27% to 80% versus 10% to 74% for pediatric and adult regimens, respectively. Treatment outcomes for AYA patients undergoing related or unrelated HSCT were compared to similar patients treated with pediatric chemotherapy regimens. Patients treated with chemotherapy alone had a similar relapse rate but significantly less treatment-related mortality. The AYA patients treated with chemotherapy had a significantly higher 4-year survival rate.

The toxicity of chemotherapy regimens is a vital consideration when treating the AYA population. Pediatric regimens do not usually require hospitalization and have a low potential for cardiotoxicity, infertility, and carcinogenesis while adult regimens often require hospitalization for neutropenic fever and other infectious complications. Pediatric chemotherapy regimens are associated with an overall increase in both life years and quality-adjusted life years (QALYs) following the initial stages of treatment. Based on mental health and quality-of-life surveys, depression, anxiety, and posttraumatic stress disorder were present in one-third of AYA patients. Adherence is more problematic in the AYA population due to education, employment, various relationships, and insurance. Oral chemotherapy agents are a large portion of treatment in pediatric regimens while adult regimens often require inpatient therapy, thus affecting school or employment. Both require reliable access to transportation.[40]

Acute Lymphoblastic Leukemia in Adults

6 Risk stratification for adult patients depends on age and Philadelphia chromosome status. The National Comprehensive Cancer Network (NCCN) guidelines recommend different strategies for AYA (15-39 years), adults (40-65 years), and older adults (≥65 years) with substantial comorbidities.[41] The most common treatment regimens use a four-drug induction regimen consisting of an anthracycline, vincristine, an asparaginase, and a corticosteroid. These regimens produce high CR rates (>70%), but the long-term event-free survival is unsatisfactory.[42] Poorer outcomes in adults have been attributed to differences in cytogenetic abnormalities, greater drug resistance, higher risk of treatment-related adverse drug reactions with subsequent nonadherence, and possibly less-effective therapy. Several different regimens are considered appropriate first-line therapies in adults including the Cancer and Leukemia Group B (CALGB) 8811 (Larson regimen), Eastern Cooperative Oncology Group (ECOG) 2903, or Linker regimen.[41] Some studies suggest that high-dose methotrexate and cytarabine alternating with fractionated cyclophosphamide plus vincristine, doxorubicin, and dexamethasone (hyper-CVAD) may improve response and survival in adults with ALL. Many cases occur in patients older than 65 years, and the response to therapy and durability of response in this subgroup is less than in other populations. Treatment-related mortality rates during remission induction therapy are also higher in this population.[42]

While the overall incidence of Ph^+ disease is 25% in adults, the incidence rises to over 40% in adults older than 50 years. Historically, patients with Ph^+ ALL had a poor prognosis, with 1-year survival of about 10% without an allogeneic HSCT.[42] As compared with historical control patients treated with standard chemotherapy alone, the addition of BCR-ABL TKI-based therapy to chemotherapy is associated with an increased CR rate and overall survival.[43-46] TKIs should be incorporated early in the Ph^+ ALL patient and continuous dosing has demonstrated superior outcomes compared to pulse or intermittent dosing strategies. For patients older than 65 years or those with poor performance status, remission induction regimens may include a BCR-ABL TKI (imatinib, dasatinib, bosutinib, or nilotinib) combined with corticosteroids.[41]

The emergence of resistance to BCR-ABL TKIs provides a challenge in patients relapsing after treatment. Point mutations within the ABL kinase domain and the activation of alternative signaling pathways due to SRC kinase have been identified. A patient's specific mutation analysis should be considered when a specific TKI is selected in the relapsed or refractory setting. Second- and third-generation TKIs have demonstrated activity in patients with imatinib-resistant Ph^+ ALL, but ABL mutations such as T315I, V299L, and F317L have demonstrated resistance to dasatinib. Ponatinib is the only BCR-ABL TKI available with known activity against T315I mutations. With the emergence of more potent inhibitors that can induce sustained remissions, studies evaluating the need for intensive chemotherapy are ongoing.[47]

In adults with B-cell ALL, about 50% have leukemic cells that express CD20. CD20 expression is associated with decreased CR rates, higher risk of relapse, and shorter overall survival.[48] The addition of rituximab to hyper-CVAD results in a higher CR rate (70% vs 38%) and longer overall survival

(75% vs 47%) as compared with hyper-CVAD alone.[49] Ofatumumab, a more potent second-generation anti-CD20 monoclonal antibody, was also added to hyper-CVAD and produced CR and MRD negativity rates of 98% and 93%, respectively.[50]

HSCT plays an important role in the treatment of adult patients with ALL. For patients with ALL who have a CR after induction therapy, consolidation with allogeneic HSCT should be considered if a human leukocyte antigen (HLA)-matched sibling or matched unrelated donor is available. After HSCT, patients with Ph^+ ALL should continue with standard maintenance therapy that includes a TKI. Allogeneic HSCT should be considered for patients with Philadelphia chromosome negative (Ph^-) disease who have MRD after induction therapy if a matched donor is available. Allogenic HSCT is preferred over autologous HSCT because of lower disease relapse rates.[51]

Relapsed Acute Lymphoblastic Leukemia

About 20% of children with ALL will relapse, but about 40% will experience long-term overall survival following relapsed treatment regimens.[10] In adults, about 30% to 60% of patients will relapse despite aggressive consolidation and maintenance chemotherapy.[52] The most common site for relapse is the bone marrow, although relapses can occur in the CNS, testicles, or multiple sites. Patients who have completed treatment and remained in remission for longer periods are more likely to achieve remission again.[11,41]

Clofarabine, a purine antimetabolite, is an option for patients with second or later relapses, but the duration of response is short. Single-agent clofarabine is associated with hepatotoxicity, prolonged myelosuppression, and febrile neutropenia.[53] Nelarabine, a T-cell-specific purine nucleoside analog, is approved to treat T-cell ALL who have relapsed disease following at least two prior therapies.[54] The drug is being evaluated in the frontline setting.[55] Adverse drug reactions such as severe peripheral and sensory neurotoxicity, severe somnolence, and seizures have occurred with nelarabine.[54]

Blinatumomab is approved for relapsed or refractory B-cell precursor ALL and in first or second CR with minimal residual disease (MRD) greater than or equal to 0.1%. As a bispecific T-cell engager (BiTE), blinatumomab binds to both CD19, an antigen present throughout B-cell development, and CD3, a T-cell receptor. By linking CD19 and CD3, blinatumomab enables a cascade of events resulting in lysis of CD19 cells.[56] Blinatumomab can induce a CR and achieve MRD negativity in adult and pediatric patients with relapsed or refractory ALL. In a randomized Phase 3 clinical trial, patients receiving blinatumomab had improved overall survival as compared to standard chemotherapy.[57] Blinatumomab has a short half-life and therefore must be administered as a continuous infusion for 28 days of a 6-week cycle. Adverse drug reactions occur in most patients, ranging from mild, reversible symptoms such as fever and rigors to more severe toxicities including neurotoxicity, infections, and cytokine release syndrome.[56]

Inotuzumab ozogamicin, an antibody-drug conjugate targeting CD22, received FDA approval in 2017 for relapsed or refractory B-cell ALL.[58] In a Phase 3 clinical trial, inotuzumab ozogamicin had significantly higher CR rates (80.7% vs 29.4%) compared to a standard chemotherapy group in patients with relapsed or refractory ALL. Positive responses occurred in patients with heavy disease burden and Ph^+ disease.[59] In a pediatric study, inotuzumab ozogamicin was evaluated in 51 children who received therapy in a compassionate use program. A CR was achieved in 67% of patients with overt marrow disease with most responders having MRD negativity.[60] Inotuzumab ozogamicin is associated with hepatotoxicity (including veno-occlusive disease [ie, sinusoidal obstruction syndrome]) and increased non-relapse mortality for patients who proceed to HSCT.[59]

Chimeric antigen receptor (CAR) T-cell therapy is a therapeutic option for ALL patients without other curative options. This novel therapeutic modality involves genetically engineered T cells that express CARs directed against CD19, resulting in T cells targeting leukemic cells that express CD19. In August 2017, the FDA-approved tisagenlecleucel, a CD19-directed autologous T-cell immunotherapy, for treatment of patients up to 25 years of age with B-cell ALL that is refractory or in second or later relapse.[61] An impressive 81% of children and young adults had a CR, many of which were durable.[62] The enthusiasm over CAR T-cell therapy based on its activity must be balanced by its significant adverse events and cost. Serious adverse drug reactions of CAR T-cell therapy include hypogammaglobulinemia, encephalopathy, seizures, and cytokine release syndrome (CRS), ranging from mild, flu-like symptoms to multiorgan system failure.[63] A single infusion of tisagenlecleucel is estimated to cost $475,000.[64] In October 2021, the FDA approved brexucabtagene autoleucel, an autologous anti-CD19 CAR T-cell therapy for adult patients with relapsed or refractory B-cell precursor ALL. In the ZUMA-3 trial, 83% of patients achieved a CR following brexucabtagene autoleucel. Adverse drug reactions were frequent with Grade ≥3 CRS and neurologic events occurring in 31% and 38% of patients, respectively.[65]

Allogeneic HSCT has traditionally been the treatment of choice for early bone marrow relapse (continuous CR less than 36 months) while children who relapse more than 36 months after completion of initial therapy have traditionally received chemotherapy alone.[10] The American Society for Transplantation and Cellular Therapy (ASTCT) guidelines recommend allogeneic HSCT for both standard- and high-risk ALL patients in first CR (CR1).[51] This recommendation is based on a meta-analysis of randomized trials that reported significantly reduced all-cause mortality with allogeneic HSCT in CR1 when compared to autologous HSCT.[66] For older patients, reduced-intensity conditioning (RIC) nonmyeloablative transplants may produce similar outcomes with less treatment-related morbidity and mortality.[67]

The decision for pediatric patients with relapsed ALL depends on the time from diagnosis to relapse and MRD at the end of reinduction. Patients who relapse <18 months since diagnosis are considered to have a *very early* relapse; these patients usually relapse while receiving their initial therapy. *Early* relapse occurs 18 months to 3 years; these patients relapse during maintenance or soon after finishing therapy. *Late* relapse occurs greater than 3 years from the start of their initial treatment. Patients are considered low risk if they have a late B-ALL marrow relapse with an end of reinduction marrow MRD <0.1% or late isolated extramedullary relapse with an end of reinduction MRD <0.1%. Intermediate risk patients have a late B-ALL marrow relapse with an end of reinduction MRD greater than or equal to 0.1% or late isolated extramedullary relapse with an end of reinduction RMD greater than or equal to 0.1%. Finally, high-risk patients have an early B-ALL marrow or isolated extramedullary relapse or T-ALL relapse. All patients receive the same four-drug reinduction regimen. Based on the end of reinduction MRD and risk stratification, patients may receive more chemotherapy for a total of 2 years, blinatumomab and HSCT, or continued reinduction cycles and HSCT. If a patient does not achieve MRD less than 0.01%, HSCT is not considered and alternative strategies such as investigational trials should be considered.[14]

ACUTE MYELOID LEUKEMIA

Risk Classification

Risk stratification for AML is based on patient-related and disease-related factors that influence a patient's likelihood of responding to drug therapy.[6] Early identification of these risk factors allows clinicians to personalize treatment according to the risk of disease recurrence. A key prognostic factor for AML is age. Patients aged 60 years and older have significantly worse outcomes than their younger counterparts. Older patients have differences in tumor biology which confers resistance and patient characteristics (eg, impaired performance status) that reduce treatment tolerance. Other unfavorable prognostic factors in adult AML include multidrug-resistance gene expression, WBC greater than 100,000 cells/mm^3 (100×10^9/L) and therapy-related AML.[68] Patients who develop "secondary" leukemia after treatment of another malignancy (ie, therapy-related AML) usually have a very poor response to antileukemic chemotherapy. Patient factors such as where patients received treatment, educational level, and cohabitation status may also affect treatment-related mortality.[69,70]

The genetic analysis includes karyotyping and molecular mutational profiling and provides important prognostic information (Table 157-3). For example, patients with core-binding factor with t(8;21)(q22;q22) or inv(16)(p13;q22)/t(16;16)(p13;q22) treated with a cytarabine-based regimen have a relatively favorable prognosis. Adults and children with chromosomal deletions such as 3q[abn(3q)] or 5q[del(5q)], monosomies of chromosome 5 or 7(−5/−7) have a poor prognosis with standard chemotherapy for AML and may be candidates for experimental treatments. About 40% of cases have a normal karyotype.[68] Molecular markers such as FMS-like tyrosine kinase 3 (FLT3), nucleophosmin 1(NPM1), c-KIT, DNA (cytosine-5)-methyltransferase (DNMT3), CEBPA, and isocitrate dehydrogenase 1 and 2 (IDH 1/2) can provide prognostic information and guide postremission therapy.[71]

TABLE 157-3

AML Risk Status According to Cytogenetics and Molecular Abnormalities

Risk	Cytogenetics	Molecular Abnormalities
Favorable	Inv(16) t(8;21) t(15;17)	NPM1 mutation in the absence of FLT3-ITD or presence of FLT3-ITD^{low} Biallelic CEBPA mutation
Intermediate	Cytogenetics abnormalities not classified as favorable or poor t(9;11)	Core binding factor with KIT mutation Mutated NPM1 and FLT3-ITD^{high} WT-NPM1 without FLT3-ITD^{low}
Poor risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q, -7, 7q- 11q23 Inv(3) t(6;9) t(9;22)	Normal cytogenetics with FLT3-ITD Mutated TP53 Mutated RUNX1 Mutated ASXL WT-NPM1 and FLT3-ITD^{high}

AML, acute myeloid leukemia; ASXL, additional sex combs; FLT-3-ITD, FMS-like tyrosine kinase 3 internal tandem duplication; NPM1, nucleophosmin; RUNX1, Runt-related transcription factor 1; TP53, tumor protein.

Data from Dohner H, Estey E, Grimwade D, et al. Blood. 2017;129:424-447. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 3.2021. Accessed November 15, 2021.

Two major types of FLT3 mutations have been identified—internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations. Patients with FLT3-ITD mutations have shorter remission durations and worse survival outcomes.[71,72] FLT3-ITD mutations occur in about 15% of older patients and 25% of patients younger than 60 years.[73] *NPM1* mutations occur in about 30% of patients with AML, even in patients with normal karyotype, and commonly coexists with FLT3. They are associated with a higher CR and reduced relapse risk as compared to patients without the mutation. c-KIT mutations have been observed in about 20% of patients with core-binding factor AML and are associated with decreased duration of CR and overall survival.[69,74] CEBPA mutations occur in about 10% of patients with AML. The most common CEBPA mutation, a biallelic (double) mutation, is associated with improved prognosis.[8] IDH1/2 mutations occur in <10% of patients and its effect on prognosis is unclear.[69]

Prognostic factors associated with pediatric AML include response to the first course of remission induction therapy, cytogenetics, and molecular genetics. Poor prognostic factors include monosomy 7, age older than 10 years, black race, internal tandem duplications of FLT3, *MLL* gene rearrangements, and a diagnosis of AML secondary to prior chemotherapy or radiation therapy. Conversely, inversion of chromosome 16, trisomy 21, CBF-AML, *PML-RARA*, *NPM1*, biallelic CEBPA, and *RUNX1-RUNX1T1* fusion transcript t(8;21) are associated with a favorable outcome.[75]

TREATMENT—ACUTE MYELOID LEUKEMIA

Desired Outcomes

The short-term goal of treatment for AML is to rapidly achieve a complete clinical and hematologic remission. In the absence of a CR, a rapid and fatal outcome is inevitable. After a CR is achieved, the goal is to maintain the patient in continuous CR.[72,73] The occurrence of leukemic relapse in the bone

marrow significantly reduces the likelihood of cure. Upon relapse, available clinical trials, additional chemotherapy, or best supportive care should be pursued depending on the patient's clinical status.[72] Most patients who will die from acute leukemia die within the first 6 years. Survival curves tend to plateau after that time, and patients alive without disease are considered to be cured of their leukemia.

With recent advances in antineoplastic therapy and supportive care, 20% to 40% become long-term survivors. Overall, the median duration of remission is 1 to 2 years.[74] In contrast to ALL, effective therapies utilized in AML result in severe and often prolonged myelosuppression. As a result, patients with AML, particularly patients older than 60 years, are at greater risk for treatment-related fatal infectious and bleeding complications.

Treatment Phases

Therapy for AML is divided into two phases: (a) induction and (b) postremission therapy (eg, consolidation, intensification) (Fig. 157-2).

Induction

As with ALL, the goal of remission induction for AML is to rapidly induce a CR, defined as the disappearance of all clinical and bone marrow evidence (normal cellularity more than 20% with less than 5% blasts) of leukemia, with restoration of normal hematopoiesis (neutrophils more than or equal to 1,000 cells/mm^3 [1×10^9/L] and platelets more than 100,000 cells/mm^3 [100×10^9/L]). Partial remission is a significant response to treatment (a decrease of at least 50% of blasts). Evidence of residual disease in the bone marrow (5%-25% blasts) is considered a treatment failure requiring additional therapy. The definition of CR has several categories, including CR (morphologic CR with restoration of normal hematopoiesis), CR with incomplete hematological recovery (CRi), cytogenetic CR ([CRc] patient with normal cytogenetics in which cytogenetics were previously abnormal), and molecular CR ([CRm] molecular studies negative). A bone aspirate/biopsy should be obtained 14 to 21 days after the start of induction therapy to assess for response.[72]

A CR is achieved in 60% to 85% of adults aged 60 years or younger. Compared to ALL, however, the CR rate is lower with AML. Because the CR rate in AML is related to the intensity of the remission induction regimen, the drugs used in AML are given at doses that uniformly cause severe myelosuppression (except tretinoin). One reason for the lower CR rate in AML as compared to ALL is the inability to give optimal doses of chemotherapy because of marrow toxicity. With continued improvement of supportive care, more intensive treatment regimens are given to reduce the high rate of leukemic relapse and increase the proportion of long-term survivors. Most patients achieve a CR after one or two courses of chemotherapy. Patients who require additional chemotherapy to achieve a CR have been reported to have a poor prognosis, even if remission is ultimately achieved.

The most active single agents in AML are the anthracycline antibiotics (daunorubicin, doxorubicin, and idarubicin), mitoxantrone, and the antimetabolite cytarabine. The standard therapy for the treatment of adult AML has not changed in several decades. The most common regimen ("7+3") combines daunorubicin administered as a short infusion of 60 to 90 mg/m^2/day on days 1 to 3, along with cytarabine administered as a continuous 24-hour infusion of 100 to 200 mg/m^2/day on days 1 to 7.[6,72] The CR rate with the 7+3 regimen is 65% to 75% in patients aged 18 to 60 years. Several trials have attempted to improve on conventional 7+3 therapy, but have shown no improvement by (a) increasing cytarabine to 10 days, (b) shortening cytarabine to 5 days, (c) substituting doxorubicin, idarubicin, or mitoxantrone for daunorubicin, (d) adding other agents such as etoposide, thioguanine, or topotecan, or (e) increasing cytarabine to higher doses (2 g/m^2 every 12 hours for 8-12 doses).[72] The most recent change to the standard 7+3 regimen is to increase the daunorubicin dose. Adults younger than 60 years with AML who were randomized to receive higher daunorubicin dosages (90 mg/m^2/day on days 1-3) in combination with 7 days of standard-dose cytarabine (100 mg/m^2/day) had a significantly higher CR rate (71% vs 57%) and longer median overall survival (23.7 vs 15.7 months) as compared with those who received the standard 7+3 regimen of daunorubicin (45 mg/m^2/day on days 1-3) and cytarabine. However, on subgroup analysis, the survival benefit with high-dose daunorubicin was restricted to patients with favorable or intermediate-risk cytogenetics and those younger than 50 years.[76]

Idarubicin and mitoxantrone have been evaluated as alternatives to daunorubicin in combination with standard-dose continuous infusion cytarabine. Trials in younger patients reported improved CR rates with these newer anthracyclines (idarubicin) or anthracenediones (mitoxantrone), and one trial reported prolonged survival. Among older adults, the CR rate and overall survival are not different among the different anthracyclines or anthracenediones.[74] Therefore, the anthracycline of choice for the standard 7+3 regimen is daunorubicin or idarubicin (12 mg/m^2) and many centers adopt idarubicin or higher doses of daunorubicin into the induction regimen in younger AML patients.

Based on experimental tumor models that showed a steep dose-response curve for cytarabine, higher cytarabine doses have been evaluated to increase its antileukemic activity. The decision to give high-dose cytarabine during induction depends on the treatment plan for postremission or consolidation therapy. In a study of patients aged 15 through 60 years with AML, the cytarabine dose (conventional dose versus high-dose) in the remission induction regimen (with both cohorts receiving daunorubicin and etoposide) was evaluated in a treatment protocol that did not include high-dose cytarabine as consolidation.[77] Patients who received high-dose cytarabine had higher remission rates and longer overall survival, particularly in patients younger than 46 years. A retrospective study conducted by the European Group for Blood and Marrow Transplantation reported that the cytarabine dose administered during induction and/or consolidation does not influence the outcome in patients who ultimately received allogeneic or autologous HSCT.[78] These data suggest that high doses of cytarabine during induction may not be needed in patients who receive HSCT as postremission therapy. In summary, the role of high-dose cytarabine during induction remains controversial. If used during induction, high-dose cytarabine is more appropriate in younger patients than in older patients because of poor tolerance by older patients. In addition, it may be an option in patients unable to tolerate anthracyclines.

A novel remission induction option has emerged for patients with poor prognosis AML. In August 2017, the FDA granted regular approval to a liposome-encapsulated combination of daunorubicin and cytarabine (CPX-351) to treat adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes.[79] Approval was based on an open-label phase 3 trial of newly diagnosed high-risk AML patients aged 60 to 75 years who were randomized to receive the standard 7+3 regimen or CPX-351 for one to two cycles of induction followed by similar consolidation. The CPX-351 induction course consisted of 100 units/m^2 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin) administered as a 90-minute infusion on days 1, 3, and 5. Patients who received CPX-351 had significantly higher CR rates (37.3% vs 25.6%) and overall remission rates (47.7% vs 33.3%) as compared to those receiving the standard 7+3 regimen.[80] Adverse drug reactions associated with CPX-351 include hemorrhagic events, febrile neutropenia, rash, fatigue, and increased risk of infections. Since CPX-351 includes daunorubicin, cardiotoxicity remains a concern and clinicians should monitor cardiac function.[79]

Another recent addition to remission induction therapy is gemtuzumab ozogamicin, which was withdrawn from the US market in 2010 because no survival benefit and increased treatment-related mortality were observed in the pivotal trial. Subsequent trials evaluated lower doses of gemtuzumab ozogamicin.[81] In a Phase 3 trial, patients were randomized to receive daunorubicin (60 mg/m^2 days 1-3) and cytarabine (200 mg/m^2 days 1-7) with or without gemtuzumab ozogamicin (days 1, 4, and 7) for the treatment of adults with newly diagnosed *de novo* AML. Patients in the gemtuzumab ozogamicin group had significantly longer median event-free survival (17.3 vs 9.5 months) as compared with those in the daunorubicin and cytarabine group, but also a higher risk of grade 3 or higher adverse drug reactions (infection, hemorrhage, veno-occlusive disease, and thrombocytopenia).[82]

Several small molecule FLT3 inhibitors have been developed and are changing the AML treatment landscape.[83] Midostaurin is an oral multitargeted TKI that is active against FLT3. In a large phase 3 trial, patients younger than 60 years with AML and an *FLT3* mutation were randomly assigned to receive standard remission induction with daunorubicin and cytarabine plus either midostaurin or placebo. Patients who remained in remission after consolidation therapy received either midostaurin or placebo as maintenance therapy. Patients in the midostaurin arm had a significant improvement in overall survival (74.7 vs 25.6 months).[84] Midostaurin is administered days 8 to 21 of each cycle of induction chemotherapy and during each consolidation cycle.[85]

The NCCN guidelines recommend the standard 7+3 regimen for AML patients younger than 60 years. Younger patients with intermediate-risk disease cytogenetics with *FLT3*-mutant disease should receive 7+3 therapy combined with midostaurin. Patients with therapy-related AML should receive standard 7+3 as remission induction, but CPX-351 administered on days 1, 3, and 5 for one cycle is a recommended alternative option.[72]

Older patients (more than or equal to 60 years) who are not candidates for intensive remission induction therapy should be offered venetoclax, an oral BCL-2 inhibitor, once daily with ramp-up dosing with a hypomethylating agent such as azacitidine or decitabine.[72,86] Azacitidine and decitabine are pyrimidine nucleoside analogs of cytidine that inhibit DNA methylation. While each agent has shown promising results versus conventional chemotherapy and best supportive care, the agents have not been compared to each other in trials.[86,87] Azacitidine is usually given IV or SQ for 7 days while decitabine is given IV for 5 days. Cycles are repeated every 28 days. Median overall survival was increased 4 months with azacitidine compared to standard induction chemotherapy (10.4 vs 6.5 months).[88] These agents are generally well-tolerated with the most significant adverse drug reaction being myelosuppression. Best supportive care includes the use of blood product transfusion support.

Other options for older patients who are not candidates for intensive remission induction therapy include gemtuzumab ozogamicin in CD33-positive patients and IDH inhibitors for patients with IDH1/2 mutations.[72] A single remission induction course of gemtuzumab on days 1 and 8 improves overall survival as compared to best supportive care.[89] Ivosidenib (IDH1 inhibitor) and enasidenib (IDH2 inhibitor) are both FDA-approved for relapsed/refractory AML.[90] These agents are evaluated in combination with hypomethylating agents in the frontline setting. A novel oral hedgehog pathway inhibitor, glasdegib, is approved in combination with low-dose cytarabine for patients ≥75 years who cannot tolerate intensive remission induction therapy.[91]

The NCCN guidelines recommend venetoclax, in combination with decitabine or azacytidine, in AML patients ≥60 years who are not candidates for intensive induction therapies.[72] Venetoclax is associated with tumor lysis syndrome (TLS), and patients should have a WBC <25,000 cells/mm^3 (25×10^9/L) prior to initiation.[92] Clinicians should provide prophylactic strategies such as hydration and anti-hyperuricemic therapies and monitor blood chemistries (uric acid, potassium, phosphorus, and calcium).

All adult patients who present with CNS symptoms or asymptomatic monocytic disease should have a diagnostic lumbar puncture and should be treated for disease if it is positive. Methotrexate or cytarabine should be administered intrathecally twice a week until clearance of leukemic blasts from the CSF, and then weekly for 4 to 6 weeks. Continued secondary prophylaxis is recommended following treatment for CNS disease.[72]

Postremission Therapy

Although most adults with AML achieve a CR, the duration of remission is short (6-9 months) if no further treatment is given. Relapse is presumably a consequence of the presence of residual, but clinically undetectable, leukemic cells after remission induction therapy. The goal of intensive postremission therapy is to eradicate these residual leukemic cells and prevent the emergence of drug-resistant disease. The need for postremission therapy is based on postmortem analysis and cell kinetic data suggesting that nearly 10^9 residual leukemic cells remain after effective remission induction therapy. Strategies evaluated as postremission therapy include (a) low-dose, prolonged maintenance therapy, (b) short-course intensive chemotherapy-alone regimens, and (c) high-dose chemotherapy followed by allogeneic or autologous HSCT.

In the treatment of AML, intensive postremission therapy is referred to as consolidation therapy. Results of randomized controlled trials in adults clearly show that intensive postremission therapy following remission induction therapy prolongs survival versus no therapy, although the exact duration of postremission therapy is controversial.[6,74]

The intensity of postremission therapy is important. In a large CALGB trial, all patients who achieved a CR after standard 7+3 induction were randomized to receive one of the three cytarabine-based consolidation regimens: 100 mg/m^2/day or 400 mg/m^2/day as a continuous 24-hour infusion, or 3,000 mg/m^2 every 12 hours on days 1, 3, and 5. For adults younger than 60 years, the probability of remaining in CR after 4 years was significantly higher in patients who received high-dose cytarabine (25% vs 29% vs 44%, respectively). Older patients had lower response rates in all arms and did not benefit from the higher cytarabine doses, probably because they could not tolerate the high-dose regimen. Dose-limiting neurotoxicity in the high-dose arm was more common in older patients and those with impaired renal function.[93]

High-dose cytarabine is an essential component of postremission therapy, particularly if it is not used in induction therapy. However, many questions remain, such as the optimal dose (g/m^2), number of doses per cycle, and number of cycles of high-dose cytarabine. Among patients with core-binding factor AML, defined as the presence of either t(8;21) or inv(16), multiple cycles are beneficial. The NCCN guideline recommends three to four cycles of high-dose cytarabine for adults younger than 60 years with favorable cytogenetics. Patients with intermediate-risk cytogenetics should receive three to four cycles of high-dose cytarabine or proceed directly to a matched sibling or alternative donor HSCT.[72] For those patients with FLT3-positive AML, midostaurin on days 8 to 21 should be added to high-dose cytarabine.[83,84] Gemtuzumab ozogamicin, in combination with daunorubicin and cytarabine, is an option for patients with CD33-positive, intermediate-risk cytogenetics AML.

If the patient is 60 years of age or older, standard-dose cytarabine with or without an anthracycline for one to two cycles, a reduced-dose high-dose cytarabine regimen (1-1.5 g/m^2/day for 4-6 doses) for one to two cycles, continuation of low-intensity therapy such as azacitidine or decitabine, or enrollment in a clinical trial is recommended. The reduced dose of high-dose cytarabine in older patients is related to their reduced ability to tolerate cytarabine and the higher risk of neurotoxicity. Patients with high-risk cytogenetics, underlying MDS, or secondary AML should either be enrolled in a clinical trial or be referred for either a matched sibling or alternative donor allogeneic HSCT.[72]

After remission is achieved, maintenance therapy with oral azacitidine (days 1-14 of a 28-day cycle) is recommended for patients <60 years old with intermediate or unfavorable cytogenetics.[72] In a Phase 3 trial of patients >55 years old who were in CR1, oral azacitidine improved overall survival (24.7 vs 14.8 months) as compared to placebo. Common grades 3/4 adverse drug reactions associated with oral azacitidine are neutropenia and thrombocytopenia.[94]

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic HSCT is the most aggressive postremission therapy in the management of AML. This treatment approach is controversial, specifically the appropriateness, timing, treatment design, and donor selection.

The antileukemic activity of allogeneic HSCT is based on the administration of pretransplant high-dose chemotherapy and the development of a posttransplant immune-based antileukemic response. The immune-based response, referred to as a graft-versus-leukemia (GVL) effect, often accompanies the graft-versus-host disease (GVHD) reaction. Evidence for the immune-based benefit of allogeneic HSCT is based on the observation of consistently lower relapse rates with allogeneic HSCT as compared to autologous or syngeneic HSCT. This potential benefit of allogeneic HSCT can be offset by the risk of posttransplant complications such as GVHD, sinusoidal obstruction syndrome, graft failure, and infections.

Allogeneic HSCT was first evaluated as a treatment modality for AML in refractory patients, but because of initial success in small numbers of patients, it has also been evaluated as intensive-postremission therapy in AML patients in first or subsequent remission.[95] Transplant-related mortality following HLA-matched sibling allogeneic HSCT ranges from 10% to 25%. However, these data are based on studies of HSCT with HLA-identical sibling donors. With increasing use of matched unrelated donors and umbilical cord blood as donor sources, transplant-related mortality of allogeneic transplants continues to be evaluated. With the availability of more effective immunosuppressive and antibiotic regimens, transplant-related mortality has decreased and survival has increased.[96]

Allogeneic HSCT from an HLA-matched sibling donor for AML patients in CR1 results in long-term event-free survival in 43% to 55% of patients. Although the results vary, some of the studies show longer event-free survival and lower relapse rates with allogeneic HSCT in AML in CR1 as compared to chemotherapy-alone postremission regimens. Single center prospective trials have not shown an overall survival advantage for allogeneic HSCT in all patients with AML CR1. Meta-analyses of clinical trials comparing allogeneic HSCT to other consolidation strategies in CR1 show that allogeneic HSCT does provide an overall survival advantage for patients with intermediate- and high-risk AML. The ASTCT recommends allogeneic HSCT for AML patients who are in CR1 with intermediate- or high-risk disease and CR2 patients.[51]

Myeloablative allogeneic HSCT is generally restricted to patients younger than 60 years, which limits the number of patients eligible for treatment of a disease that primarily affects older adults. Non-myeloablative transplantation (NMT) uses RIC preparative regimens and is now being used in AML patients, particularly in older patients and those with comorbid illnesses that would limit their eligibility for conventional allogeneic HSCT.[97] NMT is designed to provide enough immunosuppression in the preparative regimen to allow for engraftment of donor cells and depends primarily on the development of a GVL effect as a means to treat and prevent relapse of AML. The procedure is well tolerated in a wide age range of patients, with low rates of regimen-related toxicity. In a large study of 1,637 patients who received NMT, age was not associated with outcome.[98] Registry data of patients aged 70 years or older (89% received NMT) reported that 2-year overall survival significantly improved between 2000-2007 and 2008-2013 (26% vs 39%).[99]

Given that only 30% of patients have an HLA-matched sibling donor, matched unrelated donor HSCT is also an option for children and younger adults with AML. This approach is associated with improved survival, but the risk of transplant-related mortality is higher than in patients undergoing HLA-matched sibling allogeneic HSCT. A large observational study of matched unrelated donor transplants indicates that overall survival, nonrelapse mortality, and relapse rate have improved over the last two decades.[100]

Autologous Hematopoietic Stem Cell Transplantation

Compared to allogeneic HSCT, autologous HSCT has the advantages of a lower risk of posttransplant complications because of lack of immunosuppression and GVHD, and more broad applicability because of a lack of donor limitations and fewer age restrictions. Although the preparative regimen still provides antileukemic activity, autologous HSCT is associated with a higher risk of relapse because of a lack of a GVL effect

and potential tumor contamination with autologous stem cells. The ASTCT does not recommend autologous HSCT in pediatric patients.[51] Autologous HSCT is an alternative option in adults, particularly in low-risk patients but should not be pursued in patients with high-risk cytogenetics.[51,101] The NCCN guideline does not recommend autologous HSCT outside the setting of a clinical trial.[72]

Postremission Therapies

Several randomized trials in AML patients in CR1 have compared outcomes following allogeneic HSCT, autologous HSCT, or intensive consolidation chemotherapy.[101] In most trials, eligible patients based on age and donor availability received an allogeneic HSCT and the remaining patients were randomized between autologous HSCT and chemotherapy alone. The effect of stem cell source (bone marrow or peripheral blood) on event-free and overall survival has been evaluated in several trials. The ASTCT recommends bone marrow grafts with myeloablative conditioning regimens given comparable survival with a lower risk of chronic GVHD. Peripheral blood may offer improved leukemia-free survival for patients who receive RIC, but additional prospective trials are needed.[96]

The decision to transplant is often based on the cytogenetic risk category.[69] Allogeneic HSCT is the treatment of choice in patients with high-risk cytogenetics because they do poorly with conventional chemotherapy or autologous HSCT. Patients with favorable-risk cytogenetics should not proceed to transplant in CR1, as neither autologous nor allogeneic HSCT is superior to conventional chemotherapy. The optimal treatment of choice in patients with intermediate-risk cytogenetics is not clear and is based on the availability of a matched-related donor and clinician preference. Despite recommendations that patients with intermediate-risk cytogenetics should receive HSCT in CR1, a recent study reported only 27% of patients in a European study proceeded to transplant at CR1.[102]

For patients 60 years and older, additional consolidative chemotherapy or immediately proceeding to HSCT is recommended if the patient has achieved a CR1 and is deemed a suitable transplant candidate. The NCCN guideline recommends NMT rather than a myeloablative transplant in this patient population. For the AML patient who relapses early after induction therapy, if a sibling or matched unrelated donor is available, then allogeneic HSCT is the primary reinduction therapy because conventional chemotherapy offers little benefit. If the relapse occurs late, then HSCT may be used as postremission consolidation after reinduction therapy. In those patients who achieve remission with an intensive regimen but experience significant toxicities, the use of maintenance hypomethylating agents (eg, decitabine or azacitidine) every 4 to 6 weeks until progression is an option.[72]

Acute Myeloid Leukemia in Children

AML comprises about 20% of leukemias in children and adolescents. Most cases of AML in children arise *de novo* but AML is associated with trisomy 21, Fanconi anemia, dyskeratosis congenital, Schwachman-Diamond syndrome, and Kostmann syndrome. Secondary AML is extremely rare in children and is associated with alkylating agents, topoisomerase inhibitors and radiation therapy.[12] AML patients are classified as low risk or high risk based on molecular and cytogenetic markers and response to therapy. Examples of low-risk cytogenetic and molecular markers (ie, favorable prognostic markers) are PML-RARA, inv(16), RUNX1, CEBPα, and NPM1 and examples of high-risk markers (unfavorable prognostic markers) are monosomy 5, monosomy 7, KMT2A (MLL), FLT3/ITD with allelic ratio greater than 0.1%, and rearrangement or loss of ETV6.[103] The CR rate in pediatric AML is high at about 90%, with an event-free and overall survival of 45% and 65%, respectively. Unfortunately, relapse occurs in nearly half of pediatric AML patients. Even in low-risk children, the relapse rate is about 35%. Children with high-risk genetic features are at highest risk of relapse and only one in three are alive at 3 years.

Therapy for AML in children includes one to two cycles of induction therapy followed by two to three cycles of consolidation therapy. The number of cycles varies by protocol. Induction therapy with cytarabine and an anthracycline is standard. Etoposide is often included in induction but its contribution to efficacy is unclear.[104] Gemtuzumab ozogamicin was FDA-approved for newly diagnosed CD33-positive AML patients aged 1 month and older. It has been incorporated into the standard backbone in Children's Oncology Group trials of children with newly diagnosed AML.[105] Consolidation therapy or intensification phases of treatment involve the use of high-dose cytarabine in combination with an anthracycline and etoposide.[13] Maintenance therapy has no role in pediatric AML (see Fig. 157-2). Intrathecal chemotherapy for CNS prophylaxis is routinely used, but the optimal regimen is unknown and varies by protocol.[75] Cranial radiation is only used for patients with refractory CNS disease.

Certain patients may be eligible to receive an HSCT as consolidation therapy instead of continued chemotherapy. The use of HSCT in CR1 rather than waiting until relapse/CR2 is controversial. Most trials recommend consolidation with chemotherapy for favorable-risk patients. The role of HSCT in

unfavorable or high-risk patients has been utilized in recent childhood AML studies upfront.[106]

Relapsed or Refractory Acute Myeloid Leukemia

Treatment of relapsed or refractory AML is a therapeutic challenge despite the emergence of novel agents and the increasing number of available donors for HSCT. The most common cause of treatment failure in AML patients receiving chemotherapy alone or undergoing HSCT is relapse. In addition, many patients, particularly older patients, have refractory disease as defined by the inability to achieve a CR after two courses of induction therapy. In most cases, the preferred method of treatment for relapsed or refractory disease is HSCT if patients can tolerate it. Unfortunately, most patients receive salvage chemotherapy because only a small percentage of relapsed or refractory adult patients will be eligible for HSCT, particularly allogeneic HSCT because of age and donor restrictions.

Commonly used salvage chemotherapy regimens include FLAG-IDA (fludarabine, cytarabine, idarubicin, and granulocyte colony stimulating factor), MEC (mitoxantrone, etoposide, cytarabine), and GCLAC (clofarabine, high-dose cytarabine, and priming granulocyte colony stimulating factor). These regimens are associated with CR rates of 40% to 65% in younger patients and significant toxicity.[107] Patients who achieve a CR2 should pursue an allogeneic HSCT since this modality is the only potentially curative therapy. Allogeneic HSCT should be performed when a patient is in CR to allow for a robust GVL effect.

In patients unfit to receive intensive salvage chemotherapy, less-aggressive therapies such as hypomethylating agents (azacitidine, decitabine) are options.[72] In a large multicenter retrospective study of hypomethylating agents in relapsed/refractory AML, 11% of patients achieved a CR with a median overall survival of 6.7 months.[108] Given these poor outcomes with current options, older or unfit patients with relapsed or refractory AML are encouraged to enroll in clinical trials.[72]

Several novel classes of agents are treatment options for relapsed or refractory AML including FLT-3 inhibitors (eg, midostaurin, gilteritinib), IDH (eg, enasidenib, ivosidenib), Hedgehog inhibitors (glasdegib), and BCL-2 inhibitors (venetoclax). Table 157-4 lists novel oral agents for AML. These agents are given either as single agents or combined with other agents such as low-dose cytarabine and hypomethylating agents. Immunotherapy approaches such as CAR T-cells, BiTEs, antibody-drug conjugates, and cell-based vaccines are being investigated in clinical trials.[109]

TABLE 157-4

Novel Oral Therapies for Acute Myeloid Leukemia

Agent	Class	Dosing	FDA Indication	Drug Interactions
Midostaurin	FLT3 inhibitor	50 mg PO twice daily with food	Newly diagnosed AML that is FLT3 mutation positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation	• Strong CYP3A4 inhibitors; consider alternative therapies • Avoid concomitant CYP3A4 inducers • CYP2B6, BCRP, OATP1B1 substrates; dose adjustment may be necessary
Gilteritinib	FLT3 inhibitor	120 mg PO once daily	Treatment of adult patients who have relapsed or refractory AML with an FLT3 mutation as detected by an FDA-approved test	• Strong CYP3A inhibitors; consider alternative therapies • Avoid concomitant

				P-gp and strong CYP3A inducers
Enasidenib	IDH inhibitor	100 mg PO once daily	Treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test	Decrease the dose of OATP1B1, OATP1B3, and BCRP substrates
Ivosidenib	IDH inhibitor	500 mg PO once daily with or without food	• Newly diagnosed with IDH1 mutation positive AML who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy • Relapsed or refractory AML IDH1 mutation positive	• Avoid concomitant CYP3A4 inducers • Avoid concomitant CYP3A4 substrates • Strong or moderate CYP3A4 inhibitors; reduce ivosidenib dose to 250 mg/day if given with strong CYP3A4 inhibitor • QTc prolonging drugs
Glasdegib	Hedgehog inhibitor	100 mg PO once daily	Treatment of newly diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy (in combination with low dose cytarabine)	• Avoid concomitant strong and moderate CYP3A4 inducers • Strong CYP3A4 inhibitors; consider alternative therapies • QTc prolonging drugs
Venetoclax	BCL-2 inhibitor	Day 1: 100 mg PO once daily Day 2: 200 mg PO once daily Day 3: 400 mg PO once daily Day 4 and beyond: 400 mg PO once daily of each 28-day cycle in combination with azacitidine or decitabine; 600 mg PO once daily of each 28-day cycle in combination with low-dose cytarabine	Treatment of newly diagnosed AML in adult patients who are ≥75 years old, or who have comorbidities that preclude use of intensive induction chemotherapy (in combination with azacitidine, or decitabine, or low-dose cytarabine)	• Avoid concomitant strong and moderate CYP3A4 inducers • Strong or moderate CYP3A inhibitors or P-gp inhibitors; adjust dosage of venetoclax • P-gp substrates, take 6 hours prior to venetoclax

Azacitidine	Nucleoside metabolic inhibitor	300 mg PO once daily on days 1 through 14 of each 28-day cycle	Treatment of adult patients with AML who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and are not able to complete intensive curative therapy	Coadministration with omeprazole increased azacitidine AUC by 19%

BCRP, breast cancer resistance protein; CYP, cytochrome P43550; P-gp, P-glycoprotein; OATP, organic anion-transporting polypeptide.

Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APL) is a subclass of AML that accounts for about 10% of all cases. APL is the most curable AML subtype, but its clinical presentation is associated with a high early death rate secondary to coagulopathy.[110] Most patients are diagnosed between the ages of 15 and 60 years, and the average age is 44 years.[72] Although the management of APL is complex, remission induction regimens produce CR rates exceeding 90% with 5-year event-free survival rates of 70% to 80%.[111] APL is clinically unique from the other subclasses because of the common occurrence of severe coagulopathy (characterized by disseminated intravascular coagulation) at diagnosis and during induction therapy, which frequently results in intracerebral hemorrhage. In APL, differentiation and maturation arrest are caused by alterations in the retinoic acid receptor (RAR) because of the translocation of chromosomes 15 and 17. The discovery of t(15;17) provides a cytogenetic marker of the disease and is predictive of response to differentiation therapy with tretinoin (commonly referred to as all-*trans* retinoic acid or ATRA). This translocation leads to a fusion protein of the *PML* gene on chromosome 15 and the RARα on chromosome 17.

Before the availability of tretinoin in the late 1980s, treatment of APL consisted of the same combination chemotherapy regimens used in the treatment of other subclasses of AML. Such standard regimens produced CR rates of 50% to 60% but were associated with high treatment–related mortality caused by hemorrhagic complications. The introduction of targeted therapy with tretinoin results in high CR rates with a lower risk of life-threatening bleeding complications. Arsenic trioxide targets the PML moiety, resulting in apoptosis, and is synergistic with tretinoin.[112] The initial WBC count at presentation is the most important prognostic factor in patients with APL. Risk stratification of patients at diagnosis based on WBC count has improved outcomes. Abnormal creatinine, increased peripheral blast count, and coagulopathy are risk factors associated with early death due to hemorrhage.[113]

Treatment Phases

Induction Therapy

Tretinoin, an oral vitamin A analog, is given orally in a dose of 45 mg/m^2/day, as a single dose or divided into two doses, after a meal. Tretinoin-based regimens achieve CR rates as high as 95% in APL patients within 1 to 3 months. Because tretinoin does not cross the blood-brain barrier, leukemic meningitis should be treated with conventional intrathecal chemotherapy.

Although it is not myelosuppressive, tretinoin therapy is associated with headache, skin and mucous membrane reactions, bone pain, nausea, and retinoic acid syndrome. When tretinoin is started, rapid onset of differentiation of promyelocytes occurs, which can lead to leukocytosis and retinoic acid syndrome. The retinoic acid syndrome (unexplained fever, acute respiratory distress, interstitial pulmonary infiltrates, pleural effusions, and weight gain) is now referred to as APL differentiation syndrome (or APL hyperleukocytosis syndrome) because it is associated with other treatment modalities in the management of APL. The syndrome is fatal in 5% to 29% of cases. A combination of chemotherapy with tretinoin induction decreases the risk of APL differentiation syndrome, and rapid initiation of dexamethasone 10 mg (0.2 mg/kg per dose in children) twice daily on development of symptoms decreases associated mortality.[113]

For newly diagnosed low-risk APL patients (WBC ≤10,000/mm^3 [10 × 10^9/L]), induction therapy should consist of tretinoin 45 mg/m^2 in two divided doses daily in addition to arsenic trioxide (ATO) 0.15 mg/kg IV daily until hematologic CR.[72] This “chemotherapy-free” strategy achieved an impressive 100% CR rate in a Phase 3 clinical trial. Furthermore, early mortality and hematological toxicities were significantly less with patients who received tretinoin + ATO compared to those who received tretinoin and chemotherapy.[113] For patients with adequate cardiac function, the combination of daily tretinoin and idarubicin 12 mg/m^2 on days 2, 4, 6, and 8 is also a recommended alternative regimen. Assessment of response to treatment of APL is

completed when the bone marrow has recovered after induction therapy. A 28- to 35-day bone marrow biopsy is recommended to document morphologic remission before consolidation.[72] ATO induces clinical remissions in APL through its induction of apoptosis and differentiation.

ATO therapy is associated with two specific adverse drug reactions. First, it can cause the APL differentiation syndrome, similar to tretinoin. Management is similar: corticosteroids at first signs of pulmonary distress or a rapidly rising WBC count. The second adverse drug reaction is prolonged QT_c interval. It is important to obtain a baseline 12-lead electrocardiogram before starting therapy with ATO and correct any electrolyte abnormalities, including potassium, calcium, and magnesium. Other medications known to prolong the QT_c interval should be avoided, if possible, during arsenic trioxide therapy. The QT_c interval should not exceed 500 ms at baseline, and if it increases to more than 500 ms during therapy, the patient should be reevaluated. ATO should not be restarted until the QT_c is less than 460 ms.

High-risk patients (WBC > 10,000/mm^3 [10×10^9/L]) represent about 30% of APL patients. They should proceed with induction therapy that consists of tretinoin in addition to an anthracycline. All of these regimens include tretinoin 45 mg/m^2/day until a CR is achieved, in combination with an anthracycline (either daunorubicin or idarubicin) or tretinoin plus ATO for patients unable to tolerate anthracycline therapy. Several induction regimens also contain cytarabine; similar CR rates are observed with daunorubicin or idarubicin.[72] APL cells are more sensitive to anthracyclines, possibly because of decreased P-glycoprotein expression. Gemtuzumab ozogamicin has been added to tretinoin and anthracycline combinations for high-risk patients but does not increase event-free or overall survival.[114]

Consolidation Therapy

Due to a high relapse rate, all APL patients should receive consolidation therapy. The NCCN guideline recommends ATO 5 days/week for 4 weeks every 8 weeks for four cycles in addition to tretinoin 45 mg/m^2/day for 2 weeks every 4 weeks for seven cycles in low-risk patients. If ATO is unavailable or contraindicated, low-risk patients should receive tretinoin in combination with an anthracycline in consolidation. In high-risk patients, consolidation therapy consists of multiple cycles of ATO and tretinoin. In patients who have ATO or tretinoin discontinued for toxicity, gemtuzumab ozogamicin may be given once every 4 to 5 weeks until 28 weeks have elapsed from the CR date. Intrathecal chemotherapy (methotrexate alternating with cytarabine) is recommended in high-risk patients during consolidation.[72]

Maintenance Therapy

Unlike other subtypes of AML, maintenance therapy is an important but controversial component of therapy for APL. Before the development of tretinoin, nonrandomized trials suggested a benefit of continuous low-dose methotrexate and mercaptopurine as maintenance therapy. Larger prospective randomized trials have demonstrated decreased relapse rates in patients who received maintenance therapy (either tretinoin or combination chemotherapy) and some trials have demonstrated increased event-free and overall survival. However, several large APL study (APL0406, UK AML17, and MD Anderson) protocols do not include maintenance therapy for patients in molecular remission at the end of consolidation.[114] The AIDA 0493 study evaluated four maintenance cohorts (intramuscular methotrexate and mercaptopurine, tretinoin, alternating chemotherapy with tretinoin, and observation) and reported a 12-year event-free survival of 69%, with no significant differences between cohorts. Some experts do not recommend the use of maintenance therapy, particularly in low-risk patients.[113,114] NCCN guidelines recommend that APL patients who achieve molecular remission after consolidation should receive maintenance therapy if indicated by treatment protocol.[72]

Relapsed Acute Promyelocytic Leukemia

The overall incidence of relapsed or refractory APL is 5% to 10%, with rates as high as 20% to 30% in high-risk disease. Most relapses occur in the first 3 years following induction therapy. ATO is the agent of choice for relapsed APL, and this agent serves as a backbone for treatment regimens. Multiple studies have reported CR rates of about 80%.[111]

Several regimens consisting of tretinoin, anthracyclines, ATO, high-dose cytarabine, and gemtuzumab ozogamicin are options for relapsed or refractory APL. For patients in early first relapse (<6 months), an anthracycline-based regimen is recommended for those patients with no prior anthracycline. Similarly, ATO should be integrated into the treatment regimen if the patient has not received prior ATO. For patients who relapse (≥6 months) following an ATO-containing regimen, ATO should be continued with tretinoin plus an anthracycline (or single dose of gemtuzumab ozogamicin).

Patients who achieve a hematologic and molecular remission after ATO therapy should proceed to autologous HSCT.[72] Outcomes with autologous HSCT depend on the patient's disease status at the time of transplant. Autologous HSCT in CR2 (vs CR1) is associated with lower overall survival, leukemia-free survival, and increased treatment-related mortality. Autologous HSCT has shown increased disease-free and overall survival as compared to allogeneic HSCT. In patients who present with bone marrow involvement by cytogenetics or molecular testing before transplant, an allogeneic HSCT should be pursued.[72,115]

Patient Monitoring

In comparison to non-APL AML, molecular and cytogenetic testing at the end of remission induction therapy in APL has no prognostic value. Clinicians should therefore not make decisions based on the presence or absence of any genetic abnormalities. Since terminal differentiation of blasts in APL requires more than 40 days, results of a bone marrow biopsy obtained at the end of remission induction can be misleading because insufficient time has elapsed to determine response. Molecular and cytogenetic response assessment should occur after the completion of consolidation treatment.

Detection of residual PML/RARα transcripts in the bone marrow at the end of consolidation therapy is strongly associated with subsequent hematologic relapse. Achievement of PML/RARα-negative status is associated with a higher probability of cure. This molecular technique allows the clinician to assess response to therapy and detect relapse earlier, which might prevent the development of overt disease recurrence and is associated with improved outcomes as compared with delaying treatment until overt morphologic relapse. Most experts recommend that APL patients be routinely evaluated with polymerase chain reaction for PML/RARα every 3 to 6 months for 2 years, and then every 6 months for 2 years.[72]

ROLE OF HEMATOPOIETIC GROWTH FACTORS IN ACUTE MYELOID LEUKEMIA

10 Hematopoietic growth factors have been evaluated in AML patients to enhance chemotherapy cytotoxicity, shorten the duration of neutropenia, and reduce the incidence and severity of infection following induction and consolidation chemotherapy. Most studies show limited benefit with the use of colony-stimulating factors as "priming" agents administered during remission induction therapy to recruit leukemia cells into the cycle to enhance susceptibility to cell-cycle–specific chemotherapy agents, leading to increased cell kill. The use of hematopoietic growth factors concurrently during chemotherapy administration is discouraged outside the setting of a clinical trial and is not recommended in the American Society of Clinical Oncology (ASCO) guidelines.[116]

Both filgrastim and sargramostim are FDA-approved to prevent neutropenic complications in adult AML patients receiving intensive chemotherapy. Since myeloid blast cells have receptors for granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, some experts were initially concerned that the use of these factors would stimulate regrowth of leukemia. Although subsequent studies have addressed these concerns, many clinicians do not initiate filgrastim until an initial remission is achieved. Growth factors are not recommended in APL patients during induction therapy because they can increase the risk of differentiation syndrome.[72]

Several randomized trials, primarily in older patients, show that filgrastim or sargramostim reduces the duration of neutropenia following AML-induction chemotherapy. The ASCO Guidelines for the Use of White Blood Cell Growth Factors consider the use of hematopoietic growth factors after initial induction therapy reasonable, with the understanding that the effects on length of hospitalization and incidence of severe infection are modest. Patients older than 55 years derive the greatest benefit, and use is appropriate in this population where more rapid marrow recovery might decrease the duration of hospitalization.[116] Hematopoietic growth factors have been evaluated in patients with AML, including sargramostim, filgrastim, and pegfilgrastim. Although pegfilgrastim is not FDA-approved for this indication, evidence supports its use in this setting. Multiple biosimilar products are available. Filgrastim-sndz was the first FDA-approved growth factor indicated in patients with AML receiving induction and consolidation therapy.[117] Filgrastim-aafi was approved to reduce the time of neutrophil recovery and duration of fever in AML patients.[118] The use of hematopoietic growth factors can also interfere with the interpretation of the day 14 bone marrow examination. Hematopoietic growth factors should be discontinued at least 7 days before a bone marrow aspirate and biopsy to avoid interfering with the interpretation of the results (ie, may see immature myeloid forms that would suggest residual disease).[72]

SUPPORTIVE CARE

The most common and significant adverse drug reaction of antileukemic agents is marrow suppression. Except for corticosteroids, tretinoin, asparaginase/pegaspargase, and vincristine, antineoplastic agents used to treat acute leukemia cause myelosuppression. During AML remission and postremission therapy, daily monitoring of the complete blood count and the absolute neutrophil count is necessary to determine when red cell and platelet transfusions are needed and when neutropenia occurs and resolves. Marrow hypoplasia from the myelosuppressive regimens usually reaches its lowest point (nadir) after 1 to 2 weeks of therapy and lasts for another 1 to 2 weeks. During this period of hypoplasia, infectious and bleeding complications are major causes of death in leukemic patients.

Since typical signs and symptoms of infection may be absent in the neutropenic host, frequent monitoring of vital signs (particularly fever) and daily assessment are essential. Infection control strategies often include routine handwashing; dietary restrictions; reverse isolation and laminar-air flow rooms; fungal, *Pneumocystis*, and bacterial prophylaxis; and the empiric use of broad-spectrum antibiotics when fever occurs. A joint ASCO/IDSA guideline recommends antibacterial and antifungal prophylaxis in high-risk neutropenic patients (<100 cells/mm^3 [0.1×10^9/L] for 7 days). Furthermore, *Pneumocystis jirovecii* prophylaxis is recommended in patients receiving chemotherapy associated with >3.5% risk for pneumonia. Leukemia patients who are herpes simplex virus seropositive undergoing induction therapy should receive antiviral prophylaxis.[119,120] See Chapters 144 and 145 for more detailed discussion of infections in immunocompromised patients.

In children, short-term levofloxacin prophylaxis is recommended during intensive chemotherapy for acute leukemias (i.e. *de novo* AML, relapsed AML, secondary AML, ambiguous lineage leukemia treated on AML therapy and relapsed ALL) to reduce the risk of bacteremias. However, pediatric HSCT patients have not shown a significant reduction in bacteremia with levofloxacin prophylaxis. Levofloxacin prophylaxis in pediatric leukemia patients decreases the risk of febrile episodes but does not reduce the risk of severe infection or invasive fungal disease.[121] Infectious complications, especially fungi, are a major cause of morbidity and mortality. Therefore, primary antifungal prophylaxis with a mold active agent is strongly recommended for children with AML, undergoing allogeneic HSCT or receiving systemic treatment for GVHD.[122]

Acute leukemia patients, particularly those with an initial elevated WBC count, are at risk for tumor lysis syndrome (see Chapter 150). Measures to prevent the development of urate nephropathy from the rapid destruction of WBCs include allopurinol or rasburicase, and adequate hydration before and during chemotherapy. Rasburicase, a recombinant urate oxidase enzyme produced by genetic modification of *Saccharomyces cerevisiae*, catalyzes the enzymatic oxidation of uric acid into the inactive soluble metabolite, allantoin. In children, rasburicase more rapidly reduces uric acid levels in patients with aggressive malignancies as compared to allopurinol, and reduces the need for dialysis. Rasburicase has been evaluated in adults, and some studies show that fixed dosing produces equivalent outcomes to a weight-based, milligram per kilogram dosing strategy. Due to its high cost, rasburicase is usually limited to patients with ALL who have a high-WBC count or bulky extramedullary disease, aggressive lymphoma, or patients with AML with a high-presenting WBC. Most institutions also include an elevated uric acid as part of the criteria for use. Rasburicase has a rapid onset of action and long duration of action, so many institutions also limit its use to a single dose and allow repeat doses as needed. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to an increased risk of methemoglobinemia. Tumor lysis syndrome may result in hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and subsequent renal insufficiency.[123]

Hematologic support consists primarily of platelet and packed red blood cell transfusions. Platelet transfusions are often given for peripheral counts below 10,000 cells/mm^3 (10×10^9/L) or clinical signs of bleeding. Transfusions of packed red cells may also be indicated for a hemoglobin less than 8 g/dL (80 g/L; 4.96 mmol/L), fatigue, dyspnea, tachycardia, or chest pain. APL can release procoagulants that can cause disseminated intravascular coagulation, necessitating close monitoring and replacement of coagulation factors with cryoprecipitate.

EVALUATION OF THERAPEUTIC OUTCOMES

The development of a pharmaceutical care plan for a acute leukemia patient begins with information about the patient's diagnosis and prognosis. Long-term therapeutic goals for the patient may include long-term event-free survival, although palliative care is possible in some patients. The desired short-term outcome is the achievement of remission. Restoration of normal hematopoiesis and a repeat bone marrow biopsy that demonstrates no evidence of disease serve as documentation that remission has been achieved. After the appropriate postremission therapy has been completed, the patient may return monthly for 1 year, and then every 3 months, to check hematologic values. If no evidence of disease exists after 5 years from the diagnosis and the patient has been in continuous CR, the patient is considered cured.

Frequent monitoring of fevers, hematologic and chemistry laboratory values, microbiology reports, and the patient's physical condition are necessary to identify infection, risk of bleeding, and tumor lysis syndrome early. A coagulation screening panel will identify patients with ongoing disseminated

intravascular coagulation, a particular risk with APL.

Clinicians should provide patient education on acute and chronic toxicities of the chemotherapy administered and information regarding antibiotics, antiemetics, nutritional support, hematopoietic growth factors, and other supportive care issues. With the emergence of novel oral agents in the treatment landscape of AML, patients should receive institutional assistance to prevent financial toxicity given potential out-of-pocket expenses that can occur. Financial distress can impact drug therapy adherence, which could potentially impact clinical outcomes. Clinicians need to be actively engaged in assessing drug doses and any dose modifications for organ dysfunction.

Numerous late sequelae from leukemia therapy have been recognized and should be included in the monitoring plan after therapy is completed. Chapter e163 discusses the long-term consequences of HSCT. The Children's Oncology Group Long-Term Follow-Up Guidelines provide an additional resource for assessment and monitoring.[124]

CONCLUSION

Major scientific discoveries, particularly in the elucidation of molecular and genetic alterations, advanced diagnostic methodologies, and the emergence of novel therapeutics, have improved clinical responses and survival in acute leukemias. In ALL, multiagent chemotherapy with vincristine, corticosteroids, and an anthracycline followed by an allogeneic HSCT remains the standard of care for eligible candidates. Second- and third-generation TKIs in combination with chemotherapy have significantly improved survival in patients with Ph^+ ALL. The development of CAR T-cell therapies, in which a patient's T-cells are genetically programmed to recognize leukemic cells, have offered hope to patients with relapsed or refractory ALL. Childhood ALL requires multiple phases of therapy including CNS prophylaxis and most children treated today are cured of their leukemia. In adult AML, the historical induction therapy "7+3" continues to be used, but the FDA has approved nine new agents since 2017. Next-generation sequencing has identified frequently mutated genes including FLT3, NPM1, DNMT3A, IDH1/2, TET2, and others which are associated with prognosis. Novel therapies such as venetoclax, FLT3 inhibitors, IDH inhibitors, Hedgehog inhibitors, and novel anti-CD33 directed agents are changing the AML treatment landscape.

ABBREVIATIONS

ASTCT	American Society for Transplantation and Cellular Therapy
ASCO	American Society of Clinical Oncology
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
ATRA	all-*trans* retinoic acid
AYA	adolescents and young adults
BCL-2	B-cell lymphoma 2
BCR-ABL	breakpoint cluster region-Abelson protooncogene
BiTE	bi-specific T-cell engager
BMI	body mass index
CALGB	Cancer and Leukemia Group B

CAR	chimeric antigen receptor
CD	cluster of differentiation
CEBPA	CCAAT/enhancer binding-protein α
CNS	central nervous system
CR	complete remission
CR1	first complete remission
CR2	second complete remission
CRi	complete remission with incomplete hematological recovery
CRc	cytogenetic complete remission
CRm	molecular complete remission
CSF	cerebrospinal fluid
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
GTP	guanosine triphosphate
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
Hyper-CVAD	high-dose methotrexate and cytarabine alternating with fractionated cyclophosphamide plus vincristine, doxorubicin, and dexamethasone
JAK	Janus kinase
$iAMLP_{21}$	intrachromosomal amplification of chromosome 21
IDH	isocitrate dehydrogenase
ITD	internal tandem duplication
MDS	myelodysplastic syndrome
MLL	mixed lineage leukemia

MRD	minimal residual disease
m-TOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMT	nonmyeloablative transplant
NPM1	nucleophosmin 1
PETHEMA	Programa para el Estudio de la Terapeutica en Hemopatıa Maligna
Ph-	Philadelphia chromosome negative
Ph^+	Philadelphia chromosome positive
PML	promyelocytic leukemia
QALYs	quality adjusted life years
RAR*α*	retinoic acid receptor-α
RIC	reduced intensity conditioning
TET	ten-eleven translocation methylcytosine dioxygenase
TKD	tyrosine kinase domain
TKI	tyrosine kinase inhibitor
TPMT	thiopurine *S*-methyltransferase
WBC	white blood cell
WHO	World Health Organization
WT1	Wilms tumor 1

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SELF-ASSESSMENT QUESTIONS

1. TA is a 6-year-old male who presents to the ED with fatigue, easy bruising, and fever. His labs reveal a WBC 62,000 cells/mm^3 (62 × 10^9/L), Hb 7.0 g/dL (70 g/L; 4.34 mmol/L), Hct 21.0%, platelets 26,000/mm^3 (26 × 10^9/L), neutrophils 1%, lymphocytes 69%, monocytes 0%, eosinophils 0%, basophils 0%, blasts 30%. Upon peripheral flow cytometry being performed TA is found to have B-cell acute lymphoblastic leukemia (ALL). His ALL risk classification is considered:

   A. Low risk

   B. Standard risk

   C. High risk

   D. Very high risk

2. CP is a 9-year-old female admitted to the pediatric hematology/oncology floor with concern for leukemia. She has WBC 15,000 cells/mm^3 (15×10^9/L) on her CBC. Her bone marrow aspirate shows B-cell ALL. What chemotherapy agent would NOT be a component of her induction therapy for B-cell ALL?

   A. Dexamethasone

   B. Vincristine

   C. Daunorubicin

   D. Pegaspargase

3. AB is a 13-year-old male with newly diagnosed B-cell ALL. Which corticosteroid should be utilized in the treatment regimen for AB?

   A. Prednisone

   B. Dexamethasone

   C. Hydrocortisone

   D. Fludrocortisone

4. LK is an 8-year-old female who is being evaluated on day 32 of induction chemotherapy for B-cell ALL. Her original CBC on admission demonstrated: WBC 40,000 cells/mm^3 (40×10^9/L), Hb 6.8 g/dL (68 g/L; 4.22 mmol/L), platelets 26,000 cells/mm^3 (26×10^9/L), absolute neutrophil count (ANC) 400 cells/mm^3 (0.4×10^9/L), blasts 76%. Her cytogenetics were positive for *CRLF2* gene rearrangement and day 29 bone marrow has 0.5% lymphoblasts. What risk stratification is LK?

   A. Low risk

   B. Standard risk

   C. High risk

   D. Very high risk

5. Which agent is utilized in the first-line treatment of acute myeloid leukemia (AML)?

   A. Blinatumomab

   B. Inotuzumab ozogamicin

   C. Liposomal combination of daunorubicin and cytarabine (CPX-351)

   D. Brexucabtagene autoleucel

6. TS is a 19-year-old male who is to receive tisagenlecleucel for relapsed B-cell acute lymphoblastic leukemia (ALL). Which of the following toxicities is TS most likely to experience?

   A. Febrile neutropenia, encephalopathy, hypogammaglobulinemia

   B. Cardiotoxicity, pleural effusions, sinusoidal obstruction syndrome

   C. Differentiation syndrome, cardiotoxicity, rash

   D. Alopecia, cardiotoxicity, tumor lysis syndrome

7. Which of the following karyotypes or molecular mutation profiling represents favorable risk acute myeloid leukemia (AML)?

A. t(8;21) and NPM1 mutation without a FLT3 mutation

B. Normal cytogenetics with FLT3-ITD

C. Complex (≥3 clonal chromosomal abnormalities with a mutated TP53)

D. t(9;11) and core binding factor with KIT mutation

8. DL is a 40-year-old male with newly diagnosed AML. Cytogenetic analysis reveals abnormalities not classified as favorable or poor. He has a mutated NPM1 and FLT3-ITD. What would be the most appropriate induction treatment regimen?

A. Cytarabine 3 g/m^2 IV every 12 hours on days 1, 3, and 5

B. Cytarabine 100 mg/m^2/day continuous IV on days 1 through 7, daunorubicin 60 mg/m^2 IV on days 1 through 3, and midostaurin 50 mg PO daily on days 8 to 21

C. Cytarabine 100 mg/m^2/day continuous IV on days 1 through 7 and daunorubicin 90 mg/m^2 IV on days 1 through 3

D. Venetoclax 400 mg PO daily with low-dose cytarabine 20 mg/m^2 SQ daily on days 1 to 10

9. A 9-year-old female patient of Asian descent with ALL underwent genotyping prior to receiving therapy. The patient was determined to be TPMT (*3A/*3A; poor metabolizer) and NUDT15 (*3/*3; poor metabolizer). Which of the following agents is this patient at increased risk of toxicity for?

A. Brexucabtagene autoleucel

B. Cytarabine

C. 6-Mercaptopurine

D. Methotrexate

10. TC is a 56-year-old male who presents with fatigue and lymphadenopathy. His WBC count is 15,000 cells/mm^3 (15 × 10^9/L), Hb 8.1 g/dL (81 g/L; 5.03 mmol/L), platelets 75,000 cells/mm^3 (75 × 10^9/L), absolute neutrophil count (ANC) 2500 cells/mm^3 (2.5 × 10^9/L), and blasts 15%. The patient is diagnosed with B-cell acute lymphoblastic leukemia (ALL). Cytogenetic analysis reveals t(9:22). His induction chemotherapy treatment regimen should include which of the following?

A. Cytarabine 100 mg/m^2/day continuous IV on days 1 through 7 and daunorubicin 60 mg/m^2 IV on days 1 through 3

B. Hyper-CVAD + dasatinib 140 mg/day

C. Inotuzumab ozogamicin 0.8 mg/m^2 day 1, 8, and 15

D. Rituximab + dasatinib 140 mg/day

11. Tumor lysis syndrome is characterized by which of the following?

A. Hypocalcemia, hypouricemia, hyperkalemia

B. Hyperphosphatemia, hyperkalemia, hyperuricemia

C. Hypercalcemia, hyperkalemia, hypomagnesium

D. Hypokalemia, hyperphosphatemia, hypouricemia

12. AB is a 68-year-old female who was diagnosed with AML. Cytogenetic analysis reveals abnormalities not classified as favorable or poor. She has no

actionable mutations per molecular testing. The patient has an ECOG performance status of 2 and a recent echocardiogram reveals a left ventricular ejection fraction of 40%. Which of the following is recommended as induction therapy?

A. Daunorubicin × 3 days, standard dose cytarabine × 7 days

B. High-dose cytarabine

C. Liposomal combination of daunorubicin and cytarabine (CPX-351)

D. Venetoclax + azacitidine

13. RT is a 75-year-old female with significant comorbidities who was diagnosed with AML. Cytogenetic analysis reveals normal cytogenetics and mutational analysis shows wild-type NPM1 without FLT-ITD. What would be the most appropriate induction treatment regimen?

A. Glasdegib 100 mg PO on days 1 through 28 and cytarabine 20 mg SC twice daily on days 1 and 10

B. Cytarabine 3 g/m^2 IV every 12 hours on days 1, 3, and 5

C. Cytarabine 100 mg/m^2/day continuous IV on days 1 through 7 and daunorubicin 45 mg/m^2 IV on days 1 through 3

D. Gilteritinib 300 mg PO daily

14. Which of the following therapies utilized in the treatment of AML would have a drug interaction with concurrent posaconazole (ie, strong CYP3A4 inhibitor)?

A. Azacitidine (oral) and venetoclax

B. Azacitidine (oral) and enasidenib

C. Enasidenib and glasdegib

D. Venetoclax and gilteritinib

15. CP is a 59-year-old female is diagnosed with intermediate risk AML (mutated NPM1 and FLT3-ITD). Following standard induction and consolidation therapies, a bone marrow aspirate and biopsy are performed which reveals a complete remission (CR1). Which of the following treatments is recommended now?

A. Allogeneic transplant if suitable donor identified

B. Maintenance azacitidine

C. Maintenance midostaurin

D. No additional treatment

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** TA is considered high risk due to his WBC (≥50,000/mm^3 (50 × 10^9/L)) at diagnosis. See patient characteristics in the "Acute Lymphoblastic Leukemia" section.

2. **C.** Daunorubicin is used for high-risk ALL induction therapy. CP is considered standard risk until cytogenetics and response to therapy can be assessed. See the "Induction" section for pediatric ALL which discusses that treatment protocols include daunorubicin in induction (four-drug induction) for high-risk or very-high-risk ALL.

3. **A.** Prednisone causes less avascular necrosis in adolescents and young adults. See the "Induction" section for pediatric ALL in which data prednisone and dexamethasone data in standard protocols are discussed.

4. **D.** The patient has *CRLF2* gene rearrangement so she is reassigned to the very-high-risk category which receives the most intensive chemotherapy regimen. See the "Acute Lymphoblastic Leukemia" section for leukemic cell characteristics in which unfavorable or poor prognostic genetic factors such as *CRLF2* rearrangement are discussed.

5. **C.** CPX-351 is indicated to treat newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes in adults and pediatric patients aged one year and older. See the "Treatment—Acute Myeloid Leukemia" section.

6. **A.** CAR-T therapies are associated with significant toxicities that include but are not limited to hypogammaglobulinemia, encephalopathy, seizures, and cytokine release syndrome. See the "Relapsed Acute Lymphoblastic Leukemia" section.

7. **A.** Karyotyping and molecular mutational profiling provide important prognostic information in AML. Patients with t(8;21)(q22;q22) and NPM1 mutation without a FLT3 mutation have a favorable prognosis. See the "Risk Classification" section under "Acute Myeloid Leukemia".

8. **B.** A FLT3 inhibitor such as midostaurin should be integrated into standard induction therapies in patients <60 years old with FLT3/ITD mutations. See the "Treatment—Acute Myeloid Leukemia" section.

9. **C.** Deficiency of TPMT activity or NUDT15 can result in excessive myelosuppression from standard doses of thiopurines. See the "Maintenance Therapy" section.

10. **B.** Adult patients with Ph+ ALL should receive a TKI such as dasatinib incorporated into standard induction therapies such as Hyper-CVAD or CALGB 10701 regimen. The addition of the TKI has improved induction response rates and event-free survival. See the "Acute Lymphoblastic Leukemia in Adults" section.

11. **B.** Electrolyte disturbances commonly seen in TLS include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. See the "Supportive Care" section.

12. **D.** Patients who are not candidates for intensive AML induction chemotherapy with no actionable mutations should receive treatment options such as venetoclax + hypomethylating agents (azacitidine, decitabine), low-intensity HMAs, glasdegib + low dose cytarabine, or best supportive care. See the "Treatment—Acute Myeloid Leukemia" section.

13. **A.** Glasdegib is used in combination with low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are 75 years of age or older or who have comorbidities that may preclude the use of intensive chemotherapy. See discussion of the treatment of elderly patients in the "Induction" section under "Treatment Phases."

14. **D.** Venetoclax has drug interactions with strong or moderate CYP3A4 inhibitors or P-gp inhibitors. Specifically, in the setting of concurrent posaconazole, it is recommended to proceed with initiation and ramp-up dosing starting at 10 mg/day with escalation to 70 mg/day. Concomitant gilteritinib with a combined P-gp and strong CYP3A inducers decreases gilteritinib exposure. It is recommended to consider alternative therapies with strong CYP3A4 inhibitors given the increased risk of adverse drug reactions associated with increased gilteritinib exposure. See Table 4.

15. **A.** The ASTCT recommends allogeneic HSCT for AML patients in CR1 with intermediate- or high-risk disease and CR2 patients. See the "Allogeneic Hematopoietic Stem Cell Transplantation" section.