Acute Leukemias

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This management guide covers the risk factors, screening, diagnosis, staging, and treatment of acute leukemias.

Overview

Hematopoietic malignancies account for 6% to 8% of new cancers diagnosed annually. In 2016, an estimated 60,140 new cases of leukemia will be diagnosed, and 24,400 deaths will be attributable to leukemias of all types. Nearly half of all new cases of leukemias are acute lymphoblastic leukemia (ALL; 6,590) and acute myelogenous leukemia (AML; 19,950). The total age-adjusted incidence of leukemia, including both the acute and chronic forms, is 12.5 per 100,000 population; the incidence of ALL is 1.6 per 100,000 and of AML, 3.6 per 100,000 population.

Epidemiology

Gender

The incidence of both ALL and AML is slightly higher in males than in females.

Age

The age-specific incidence of AML is similar to that of solid tumors in adults, with an exponential rise after age 40. With regard to ALL, 60% of cases are seen in children, with a peak incidence in the first 5 years of life and a subsequent drop in incidence until age 60, when a second peak emerges.

Race and Ethnicity

The incidence of acute leukemia is slightly higher in populations of European descent. Also, a report from the University of Southern California indicates that acute promyelocytic leukemia (APL) is more common in Hispanic populations than in other ethnic groups.

Etiology and Risk Factors

There is wide diversity in the behavior of the various subsets of acute leukemias. Thus, it is unlikely that there is one common cause for these aberrant cellular proliferations. There are, however, some accepted risk factors for leukemogenesis.

Chemical Exposure

The increased incidence of AML and myelodysplasia (pre-leukemia) has been reported in persons with prolonged exposure to benzene and petroleum products. The interval between exposure and the onset of leukemia is long (10 to 30 years). Chromosomal damage is common. Pesticide exposure also has been linked to some forms of AML. The incidence of AML is beginning to rise in developing countries, as industrialization and pollution increase.

Other Environmental Exposures

Exposure to hair dyes, smoking, and nonionic radiation may also increase the risk of leukemia.

Prior Chemotherapy or Irradiation

Use of alkylating agents, such as cyclophosphamide and melphalan, in the treatment of lymphomas, myelomas, and breast and ovarian cancers has been associated with the development of AML, usually within 3 to 5 years of exposure and often preceded by a myelodysplastic phase. Cytogenetic abnormalities, particularly monosomy 5 or 7 as well as mutations of 11q23 (MLL gene...
Acute Leukemias

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rearrangement), and deletion 17p causing a p53 mutation are common. Concurrent radiation exposure slightly increases the risk of leukemogenesis posed by alkylating agents. Topoisomerase II inhibitors (etoposide, teniposide); doxorubicin and its derivatives; mitoxantrone, used to treat ALL, lymphomas, testicular cancer, and sarcomas; and taxanes, used to treat breast cancer, have also been implicated in leukemogenesis. These agents, in contrast to alkylators, are associated with a short latency period without antecedent myelodysplasia and with cytogenetic abnormalities involving chromosome 11q23 or 21q22 in the malignant clone.

Genetic Disorders

An increased incidence of AML is seen in patients with Down syndrome, Bloom syndrome, or Fanconi anemia, as well as in individuals with ataxia-telangiectasia or Wiskott-Aldrich syndrome. In identical twins younger than 10 years, if one twin develops leukemia (usually ALL), there is a 20% chance that the other twin will develop leukemia within a year; subsequently, the risk falls off rapidly and joins that of nonidentical siblings, which is three to five times that of the general population.

Signs and Symptoms

Effects on Hematopoiesis

Leukemia manifests symptomatically by its impact on normal hematopoiesis. Thus, easy fatigability, bruising, bleeding from mucosal surfaces, fever, and persistent infection are all reflections of the anemia, thrombocytopenia, and decrease in functional neutrophils associated with marrow replacement by malignant cells. Bone pain is common in children with ALL (occurring in 40% to 50%) but is less common in adults (5% to 10%). Whereas a marked elevation in white blood cell (WBC) count is the classic hallmark of leukemia, pancytopenia is more common, particularly in patients of all ages with ALL or in older patients with AML, who may have had preexisting marrow dysfunction (myelodysplasia). Only 10% of patients with newly diagnosed AML or ALL present with leukocyte counts greater than 100,000/μL. These patients, however, constitute a poor prognostic group and are at increased risk for central nervous system (CNS) disease, tumor lysis syndrome, and leukostasis caused by impedance of blood flow due to intravascular sludging of blasts, which are “stickier” than mature myeloid or lymphoid cells. Leukostasis may manifest as an alteration in mental status; intermittent or persistent cranial nerve palsies, particularly those involving extraocular muscles; priapism; dyspnea; or pleuritic chest pain caused by small leukemic emboli in the pulmonary vasculature.

Physical Findings

Physical findings in AML are usually minimal. Pallor, increased ecchymoses or petechiae, retinal hemorrhage, gingival hypertrophy, and cutaneous involvement are more common with monocytic (M4 or M5) variants of AML than with other variants of AML. Mild hepatosplenomegaly and lymphadenopathy are seen in many cases, particularly in childhood ALL. Massive hepatosplenomegaly occurs infrequently and should raise the suspicion of a leukemia evolving from a prior hematologic disorder, such as chronic myelogenous leukemia (CML) or myelodysplasia/myeloproliferative disorders. Mediastinal adenopathy is seen in 80% of cases of T-cell ALL, but is less common in pre-B ALLs and is rare in AML. Visceral involvement is also rare, occurring as an initial manifestation of AML in fewer than 5% of cases, but it may be more frequent during subsequent relapses. These focal collections of blasts, called chloromas or granulocytic sarcomas, can present as soft tissue masses, infiltrative lesions of the small bowel and mesentery, or obstructing lesions of the hepatobiliary or genitourinary system. CNS involvement is uncommon at presentation in adult AML (< 1%) and adult ALL (3% to 5%). In most instances, CNS involvement is detected by screening lumbar puncture in high-risk patients who are asymptomatic at the time of the procedure. Symptoms, when they do occur, include headache, diplopia, cranial nerve palsies, radicular pain, and/or weakness in a particular nerve root distribution. CNS involvement usually is restricted to leptomeninges; parenchymal mass lesions are uncommon. Like the CNS, the testes appear to be a “sanctuary” for isolated relapses in pediatric ALL, but rarely in adult ALL. Signs of testicular involvement include painless, asymmetric enlargement.

Metabolic Effects

Metabolic effects of acute leukemia relate primarily to the rate of cell death.

Hyperuricemia
Hyperuricemia with possible interstitial or ureteral obstruction is seen predominantly in AML with moderate leukocytosis and in ALL with bulky adenopathy. This condition may be exacerbated by a rapid response to chemotherapy and the “tumor lysis syndrome” (hyperuricemia with renal insufficiency, acidosis, hyperphosphatemia, and hypocalcemia), which may occur within the first 24 to 48 hours after initiating chemotherapy. To prevent this complication, all patients should receive allopurinol and urine alkalinization before marrow-ablative chemotherapy is initiated. For patients who are intolerant to allopurinol and do not have rapidly rising blast counts, febuxostat is another option. In patients with a high tumor burden, renal insufficiency, or acidosis before initiation of chemotherapy, rasburicase may offer a more rapid treatment for hyperuricemia.

Coagulopathies

Coagulopathies can also complicate the hemostatic defects associated with thrombocytopenia. Disseminated intravascular coagulation (DIC) is most often seen in acute promyelocytic leukemia (APL) because of the release of procoagulants from the abnormal primary granules, which activates the coagulation cascade, leading to decreased levels of factors II, V, VIII, and X, and fibrinogen, as well as rapid platelet consumption. Lysozyme released from monoblasts in M4 and M5 subtypes of AML with monocytic differentiation can also trigger the clotting cascade. Finally, DIC can occur following L-asparaginase chemotherapy for ALL. Fibrinogen and antithrombin III need to be monitored for 10 to 14 days following asparaginase therapy so that adequate replacement of these factors can be provided.

Diagnosis

Abnormalities of the complete blood cell count raise the possibility of leukemia. The diagnosis is substantiated pathologically by a bone marrow examination. All patients should have cytochemistry, immunophenotyping by fluorescent-activated cell sorter using monoclonal antibodies directed at leukemia-specific antigens, and cytogenetic analysis of the marrow or peripheral blood blasts at diagnosis. Samples of marrow should also be collected and preserved for subsequent analysis for molecular mutations. Several of these mutations are used to refine risk stratification in patients with normal karyotype AML. Other tests used to evaluate metabolic abnormalities (electrolytes, creatinine, and liver function tests) and coagulopathies are also needed at diagnosis. A lumbar puncture should be performed at diagnosis in all pediatric patients with ALL and in all patients with neurologic symptoms, regardless of age and pathology.

Pathology and Cytogenetics

Acute leukemias comprise a group of clonal disorders of maturation at an early phase of hematopoietic differentiation. Historically, morphology and cytochemical stains designed to detect intracellular myeloperoxidase or esterases were used in the French–American–British (FAB) system to classify acute leukemias into either myeloid or lymphoid derivations. Coupling these traditional methods with cytogenetic analysis and lineage-specific monoclonal antibodies directed against cell-surface antigens has led to the detection of new prognostic factors and has provided an approach to detect minimal residual disease. In 1997, a panel of hematopathologists under the aegis of the World Health Organization (WHO) met to update the FAB classification of hematologic malignancies, by incorporating immunophenotyping, cytogenetics, and clinical disease features such as prior myelodysplasia and treatment-related AML. The updated 2008 WHO classification (Tables 1 and 2) also has incorporated provisional categories for inclusion of molecular markers, such as mutations of \( NPM1 \) (nucleophosphamin1) and \( CEBPA \) (CCAAT enhancer binding protein alpha), in AML.
Myeloid leukemias

The WHO classification retained the morphologic subgroups of the FAB system in the subgroup of “AML not otherwise specified” but has created new categories that recognize the importance of certain cytogenetic translocations as predictors of response to therapy. In this category are AML with t(8;21)(q22;q22), AML with abnormal eosinophils and inv(16)(p13;q22) or t(16;16)(p13;q11), AML with 11q23 mixed-lineage leukemia abnormalities, and APL with t(15;17)(q22;q11-12) or variants (Table 1). They have also included, for the first time, two molecular genetic mutations that appear to favorably impact outcome. Several studies have now confirmed that a mutation in **NPM1** in the absence of **FLT3** mutation will confer a more favorable outcome for AML patients with normal cytogenetics, while the data on **CEBPA** now suggest that both alleles of the gene need to be mutated to confer a better prognosis.

The WHO classification also attempts to deal with the evidence that in many older patients, marrow dysfunction antedates the onset of acute leukemia. These myelodysplastic syndromes (MDSs) are characterized by ineffective hematopoietic production and disrupted maturation of one or more cell lines. These abnormalities are often accompanied by loss of chromosomal material, particularly −5 or −5q, −7 or −7q, and −3 or −20. As the bone marrow becomes more dysfunctional, increasing numbers of blasts are seen in the marrow.

In the FAB classification, the demarcation line between myelodysplasia and AML was 30% marrow blasts. However, patients with 20% to 29% blasts (previously classified as refractory anemia with excess blasts in transition [RAEB-t]) have a biologic behavior and poor survival similar to those of patients with AML. The WHO 2008 classification of AML lowered the threshold for the diagnosis of AML to 20% marrow blasts and deleted the FAB category of RAEB-t. In addition, patients with 5% to 20% blasts who have t(15;17), t(18;21), or inv(16) are considered to have AML rather than MDS and should receive AML treatment.

The WHO system further subdivided the AML patients with dysplastic maturation into those with or without antecedent cytopenias (usually 3 months before the AML diagnosis) and those with a history of exposure to chemotherapy agents (alkylating agents, epipodophyllotoxins, or others). The genetic profile of malignant cells has been found to vary widely from normal, with many genes being either overexpressed or suppressed. DNA microarray techniques allow the simultaneous analysis of thousands of genes that are being studied in AML and ALL for their predictive ability to define cohorts of patients with similar outcomes; this process may, in turn, allow the selection of candidate genes that can be used as therapeutic targets in the future. Since 2010, there have been several publications on new molecular markers that may provide additional insights into the disease
pathogenesis. These include mutations of c-Kit, IDH1/IDH2, WT1, RUNX1, TET2, DNMT3A, and MLL. At present, molecular testing on a commercial basis is only available for the most frequently observed mutations (NMP1, FLT3, and CEBPA). Genome-wide expression profiling is ongoing in many research facilities, which may ultimately provide better targets for individualized therapies.

Lymphoblastic leukemias

Lymphoblastic leukemias can arise from either B-cell or T-cell progenitors that arrest at an early stage of maturation and then proliferate. Marrow involvement of more than 25% lymphoblasts is used as the demarcation line between lymphoblastic lymphoma, in which the preponderance of tumor bulk is in nodal structures, and ALL. Approximately 75% of adult ALLs are B cell in derivation and 25% are T cell.

**B-cell ALL.** Most B-cell leukemias are early or “pre-B” cell, expressing CD19 and CD10 (the common acute leukemia antigen) but lacking surface or cytoplasmic immunoglobulin. Chromosomal rearrangements juxtaposing an oncogene with a promoter region are often seen in this disease category (Table 2).

A small fraction (2%) of patients with precursor B-cell ALL lack CD10 expression. Patients with a CD10-negative pro-B phenotype have a high incidence of MLL gene expression (83%), particularly in association with t(4;11)/abn123, and a very poor disease-free survival of 12% at 2 years.

**Mature B-cell ALL.** The more mature B-cell ALL, or Burkitt-cell leukemia, is associated with translocations of the c-MYC gene on chromosome 8 and the immunoglobulin heavy-chain gene on chromosome 14q32 in 80% of cases or with the light-chain genes of chromosome 2p11 or 22q11 in the other 20%. Burkitt-cell leukemia has been removed from the leukemia category by the WHO 2008 classification and is now listed with high-grade B-cell lymphoma.

**T-cell ALL.** T-cell ALL is frequently associated with translocations of T-cell receptor genes on chromosome 14q11 or 7q34 with other gene partners. Prognosis tends to be worse for the type classified as pro-T (CD7+, CD2−, CD5−), pre-T (CD7+, CD2−, CD5−/+), or mature T (CD3+, CD1a−) than for the CD1a+ cortical/thymic type, which makes up the majority of T-cell ALLs. Early T cells often express myeloid markers C13 or CD33. Molecular studies are revealing unique gene expression profiles related to the stage at which the T-cell maturation is arrested leading to aberrant activation of T-cell oncogenes. BCL-2 expression has recently been reported on immature T cells and could serve as a target for drug therapy. Infection with human T-cell leukemia virus 1 (HTLV-1) should be looked for in patients with T-cell ALL presenting with hypercalcemia and lytic bone lesions. HTLV-1 infection is endemic in southern Japan, the southern Pacific basin, the Caribbean basin, and sub-Saharan Africa. High infection rates are also seen in parts of Iran, India, and Hawaii. Recent immigrants from areas where the virus is endemic retain a risk of infection similar to that of their point of origin. However, T-cell leukemia will develop in fewer than 0.1% of persons who carry HTLV-1.

**ALL with myeloid antigen expression vs undifferentiated leukemia**

A subset of patients with leukemia exhibit features of both myeloid and lymphoid differentiation. These patients were originally classified as having mixed-lineage leukemia. Patients with a leukemic clone that expresses two or more ALL antigens and one myeloid antigen account for 20% of adult ALL cases. Although expression of myeloid antigen is considered to be a poor-risk feature in children, it does not constitute a distinct poor-risk feature in adults. Immunophenotyping has also helped to define a group of patients with undifferentiated myeloid leukemia (M0) who previously were likely to be treated as if they had ALL. These leukemias have a primitive morphology and lack myeloperoxidase. On immunophenotyping, they express at least one early myeloid antigen, usually CD13 or CD33, and no T- or B-cell markers. On the basis of immunophenotyping, undifferentiated leukemias are now recommended to be treated in the same manner as myeloid malignancies.

**ALL Prognostic Factors**

Factors known to have an impact on the ability to achieve and maintain remission in ALL include age, lineage derivation, elevated WBC count, and cytogenetic abnormality. In children, rapid early response (< 25% marrow blasts on day 7 from start of therapy) also is strongly associated with better outcome such that patients with slow responses are now treated with intensified regimens postinduction. Detection of minimal residual leukemia cells at the end of induction therapy is perhaps the strongest predictor of poor response reported in the pediatric population, and similar findings are being reported in the adult population. The cure rate for children aged 2 to 12 is over
80%, and recent pediatric studies that included augmented postinduction therapy using additional vincristine, pegasparaginase, and high-dose methotrexate reported a 5-year disease-free survival of 50% to 70% for patients 16 to 21 years of age. Risk factors for relapse were use of nonintensive therapy postinduction in rapid responders, WBC count of 30,000/μL in pre-B-cell ALL and over 100,000/μL in T-cell ALL, and cytogenetics. The 5-year disease-free survival rates have been 40% to 60% in most large adult trials for patients 21 to 40 years of age and less than 30% for those involving patients older than 60 years. Poorer outcomes in adults have been attributed to a higher proportion of patients with poor-risk karyotypes, particularly t(9;22) or the Philadelphia chromosome (Ph+), as well as poorer tolerance to chemotherapy, especially L-asparaginase and high-dose methotrexate.

The 1,500-patient Medical Research Council (MRC) XII/Eastern Cooperative Oncology Group (ECOG) adult ALL trial reconfirmed that age greater than 35 years, elevated WBC count, B-cell lineage, and karyotypic abnormalities are significant independent risk factors for disease-free survival and overall survival in adults. In addition to the previously reported poor-risk karyotypes of t(9;22), t(4;11), and t(8;14), this trial also identified complex (≥ 5) abnormalities and low hypodiploid/near-triploid karyotype as new poor-risk features.

Minimal residual disease detected at 16 to 22 days from the start of induction therapy has proved to be a high predictor of relapse, with a 5-year relapse-free survival of only 15% compared with 71% for patients with no detectable markers for immunoglobulin or T-cell receptor gene rearrangements at that time.

**Cytogenetic and molecular abnormalities**

The most common cytogenetic abnormality in adult ALL is Ph+, which involves translocation of the ABL gene from chromosome 9 to the breakpoint cluster region (BCR) on chromosome 22, forming a new gene product (BCR-ABL) with tyrosine kinase activity. This translocation is found in 95% of cases of CML and in 20% to 30% of newly diagnosed cases of ALL in adults.

The fusion protein produced by the BCR-ABL translocation in Ph+ ALL (p190) differs from the product seen in CML (p210); the p190 product is a smaller protein than the p210 product and has higher tyrosine kinase activity. Use of polymerase chain reaction (PCR) techniques that target only the p210 product will significantly underestimate the incidence of Ph+ ALL. In a recent update of the German ALL trials, 37% of patients were Ph+, with 77% showing the p190 product and 23% showing the p210 product.

Although patients with Ph+ ALL may attain a morphologic remission with conventional chemotherapy (82%), almost all such patients will have persistent molecular evidence of disease on PCR. Patients who do achieve a molecular remission have a longer duration of remission than those who continue to express p190 or p210 activity (30 months vs 12 months, respectively).

The Gruppo Italiano per le Malattie Ematologiche dell’ Adulto (GIMEMA) published outcomes data from a large trial of adult patients with ALL in which both cytogenetic data and molecular probes for specific gene products were combined to define prognostic groups. The molecular abnormalities that were evaluated were t(9;22) BCR-ABL, t(4;11)/MLL-AFA, t(1;19) E2A-PBX1, 9p/p15-p16 deletions, and 6q deletions. Categories based primarily on classic karyotypes were normal, hyperdiploid, and miscellaneous structural abnormalities of uncertain significance.

The use of molecular probes was particularly informative in patients with failed karyotipic analysis or normal cytogenetics. The use of the BCR-ABL probe increased the number of cases with a t(9;22) abnormality from 64 to 104 (26% of patients in the trial); more than 50% of add(9p)/p15-p16 abnormalities were detected only by molecular testing. Patients with t(4;11) and t(1;19) had disease-free intervals of 0.4 to 0.6 years, whereas those with del(6q), hyperdiploid, or pseudodiploid karyotypes had intermediate disease-free survival of 1.3 to 1.6 years; those with a normal karyotype or del(9p)/p15-p16 had better outcomes (2.9 years and 4 years, respectively). Disease-free survival for patients with BCR-ABL was also poor in this study (0.6 years), which antedated the addition of tyrosine kinase inhibitors (TKIs) such as imatinib to chemotherapy. A small subgroup of high-risk ALL patients has been identified as having a gene expression profile similar to BCR-ABL fusion with a deletion or mutation in the lymphoid transcription factor involving the Ikaros family zinc finger (IKZF1) region. The gene profile of these mutations, referred to as “Ph-like,” produce kinase activation leading to cytokine-independent cellular proliferation (mutations in ABL-1, ABL-2, CSF1R, and PGDFRB) or activation of the STAT5 pathway (mutations of JAK-2, CRLF2, EPOR, and IL2RB). The incidence of these mutations increases from approximately 10% in children, to 21% in adolescents, and 27% in adults under 30, and their presence is correlated with a poor outcome.

Translocations involving the MLL gene at chromosome 11q23 are partnered with several other...
Acute Leukemias
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Chromosomes, including 4q21, 9q22, and 19q13. Translocations involving chromosome 11q23 are frequently seen in secondary leukemias, particularly those arising after chemotherapy with etoposide or teniposide. Although most of these translocations are associated with AML, ALL has also arisen in this setting. All of the 11q23 translocations, as well as the (1;19) translocation, are associated with poorer outcomes when compared with similar immunophenotypes coupled with normal cytogenetics. In patients with T-cell ALL, activating mutations of NOTCH1 in the absence of mutations of NRAS or KRAS or alterations of PTEN confers a favorable outcome. Analysis of genetic abnormalities as well as minimal residual disease (MRD) for the 423 Ph- patients treated on the GRALL 2003 and 2005 trials provides an updated understanding of risk factors for adolescents and for adults under 60 years of age treated using contemporary regimens. Evaluation of patients for MRD was carried out at 6 weeks from initiation of induction graded as undetectable, detectable at < $10^{-4}$, or detectable at > $10^{-4}$. Among the patients with B-cell ALL, 42.7% had detectable disease above $10^{-4}$ as compared to 28.8% of T-cell ALL. The risk of relapse at 5 years was 22.9% for undetectable MRD, 30.8% for MRD < $10^{-4}$, and 60.4% for those with >$10^{-4}$. For patients with the B-cell lineage, roughly 27% had IKZF1 mutations and 11% had MLL gene rearrangements; the incidence of relapse at 5 years was 53.9% for those with IKZF1 mutations vs 28.6% for those without. In the T-cell group, 48% had a high risk genetic profile which carried a 5-year risk of relapse of 55.7%, compared with a risk of 15.4% for those with an isolated NOTCH1 mutation.

**Treatment**

Treatment for patients with ALL and AML can be subdivided into two or three phases. Induction chemotherapy is the initial treatment designed to clear the marrow of overt leukemia. This phase usually involves multiple drugs that cause pancytopenia for 2 to 3 weeks. The purpose of consolidation therapy is to further reduce the residual leukemic burden in patients who are in morphologic remission. Molecular markers of residual disease can often be detected after induction chemotherapy, which indicates the need for further treatment. The intensity of consolidation therapy varies, depending on the risk of relapse (based primarily on cytogenetic or molecular risk groups) and patient age, or comorbid conditions.

Maintenance chemotherapy using low-dose oral chemotherapy for 18 to 24 months has been shown to prolong relapse-free survival in pediatric patients with ALL and in adults with APL. Its value is less clear in adults with ALL as many adults progress before this portion of protocol therapy has been reached; maintenance is used much less frequently in AML treated with intensive chemotherapy.

**Acute Lymphoblastic Leukemia**

**Induction therapy**

The initial goal of therapy is to rapidly reduce the leukemic burden to a level undetectable by conventional methods of light microscopy and flow cytometry, a state that is deemed a complete remission (CR). Two standard induction regimens have been used in adults with ALL—the Hoelzer regimen Table 3, developed by the Berlin-Frankfurt-Munster (BFM) multicenter group, and the Larson regimen Table 4, developed by the Cancer and Leukemia Group B (CALGB). Along with the standard induction schemas, two newer regimens, the hyper-CVAD (high-dose cyclophosphamide, vincristine, Adriamycin [doxorubicin], dexamethasone) regimen from The University of Texas MD Anderson Cancer Center Table 5 and the Linker regimen (2002 version; Table 6), which have an induction drug dosing similar to that of the older regimens but include much higher doses of antimetabolites (cytarabine [Ara-C] and methotrexate) and etoposide for dose-dense consolidations, are outlined in Tables 3–6, along with the standard induction schemas. All of these induction regimens consist of treatment with one cycle each of two regimens with differing mechanisms of cytotoxicity. Overall, CRs are obtained in 80% to 94% of adults younger than 60 years who are treated with any of these regimens. The incidence of death during induction therapy for these trials was low (2% to 9%). Cytokines (such as filgrastim) may be used to shorten the period of cytopenia during ALL therapy.

**TABLE 3: BFM regimen for ALL induction and consolidation**
L-asparaginase has been a major agent in pediatric trials in both induction and consolidation therapies. Although L-asparaginase is used during induction therapy in adults younger than 50 years with ALL (except in the MD Anderson hyper-CVAD regimen), it is rarely used in consolidation therapy. The potential importance of this drug was emphasized by observations on L-asparaginase depletion during induction therapy in a recent CALGB trial, which showed a median survival of 31 months in patients who were depleted vs 13 months for those who were not depleted. They also showed improved depletion using the pegylated form of L-asparaginase (pegaspargase), which has a longer half-life. In most clinical trials, a single dose of pegasparginase (2,000 IU/m²) is now used to replace multiple doses of L-asparaginase. Several pediatric trials have also compared outcomes based on steroid regimens (prednisone vs dexamethasone) and have shown better event-free survival in the dexamethasone arms (81% to 85%) than in the prednisone arms (75% to 79%). The improvement was more prominent in the high-risk patient populations. However, this improvement came at the price of higher risk of infections, myopathy, and avascular necrosis. The bone abnormalities were most obvious in teens and young adults and uncommon in children younger than 10 years. Assessment of outcomes for young adults (< 30 years) treated with either pediatric or adult regimens has shown comparable remission rates but significant differences in long-term disease-free survival. As a rule, the pediatric regimen contains higher and more frequent doses of L-asparaginase as well as stricter adherence to a tight dose schedule. The most recent trial of Total Therapy published by St. Jude’s showed a 5-year event-free survival of 86% in 45 adolescents aged 15 to 18 years vs 87% for the 453 younger patients. The current regimen maximizes vincristine, steroids, and asparaginase and reduces anthracyclines and alkylators in hopes of reducing late second malignancies (Table 7).

A recent Canadian study using a modified pediatric regimen with weekly high-dose L-asparaginase for 30 weeks during intensification in adults aged 18 to 60 years showed an overall survival of 63% and a disease-free survival of 71% at 5 years. Adverse predictors of outcome included age greater than 35 years, MLL gene rearrangement, high WBC count, and less than 80% planned L-asparaginase dose. The regimen was associated with significant morbidity, however, including
infections (47%), avascular necrosis of major joints (32%), thromboembolic events (23%), and peripheral neuropathy (22%). C10403, the US Intergroup trial for adolescents and young adults (16 to 39 years of age) with ALL, used the same regimen administered to patients randomized to the high-risk arm of the contemporaneous Children’s Oncology Group (COG) trial 0232. The results were reported at the 2014 ASH Annual Meeting. Overall event-free survival for the 296 patients was 66% at 2 years, compared with 34% in the prior CALGB trial using the Larson regimen. The relapse rate was 25%. Risk factors identified included the presence of the Ph-like gene signature, which was associated with a 2-year event free survival rate of 57%, compared with a rate of 81% for non-Ph-like signatures. MRD was measured at the end of induction using quantitative real-time PCR; patients who were MRD-negative had a disease-free survival rate of 90% at 2 years compared with 60% for those with measurable disease. Despite the intensified regimen with liberal use of asparaginase, the mortality rate during induction was only 2%. While hyperbilirubinemia and transaminitis occurred in over 25% of patients, grade 3 neuropathy occurred in 15.7% and pancreatitis in only 4% of patients, adverse event rates similar to those seen in the pediatric trial that included patients up to 29 years of age. Therefore, the COG 0232 regimen should become the new standard approach for adolescents and young adults with newly diagnosed Ph− ALL. The 2003 and 2005 trials by the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) used similar regimens in patients up to age 60; however, the risks of death during induction and of death in patients with CR were substantially higher (13% and 15%, respectively) for patients older than 45 years of age compared with patients aged 45 and younger (for whom the risks were 4% and 2%, respectively).

**T-cell ALL.** There is evidence that patients with T-cell ALL may benefit from early treatment with Ara-C and cyclophosphamide. Pharmacologic studies show high levels of Ara-C triphosphate accumulation in T lymphoblasts and synergy between cyclophosphamide and Ara-C in cell lines of T-cell malignancies. T lymphocytes also have a lower expression of polyglutamate synthetase than pre-B blasts. Randomized trials in children with T-cell ALL showed that the use of high-dose methotrexate (up to 5 g/m²) also improved outcome. Adults with T-cell ALL treated in the MRC UKALL XII/ECOG 2993 trial had a 94% CR rate and a 48% 5-year survival. Patients with complex cytogenetics, however, had a very poor outcome, with a survival of 19% at 5 years. Adult patients with T-cell ALL with mutations of NOTCH1/ FBXW7, who accounted for 69% of the patients treated on the French pediatric-type GRAALL trials, showed a significant event-free survival (65%) compared with patients who lacked the mutation (30%); overall survival was also significantly better at 3 years (74% vs 51%) for the group with mutations. Further studies of this population have refined the risk-group base by also looking at RAS and PTEN mutations. For those with mutated NOTCH1/ FBXW7 and unmutated RAS or PTEN, the 5-year relapse-free survival was 85% vs 42% for those with any of the other combinations. In the US Intergroup trial, no difference in disease-free survival was found between B-cell and T-cell ALL.

**Mature B-cell ALL.** Patients with the mature B-cell ALL (Burkitt leukemia) experienced an improvement in survival when high doses of cyclophosphamide, methotrexate, and Ara-C were incorporated early in the treatment course (Hyper-CVAD regimen; Table 5). The probability of leukemia-free survival improved from 35% with standard ALL induction therapy to 60% to 70% with these newer regimens. Rituximab is also being added in patients whose blasts express CD20.

**Ph+ ALL.** The development of imatinib, a selective BCR-ABL tyrosine kinase inhibitor (TKI), provided a potent new agent in the treatment of Ph+ ALL. As a single agent, it produced CRs in 30% of patients with relapsed Ph+ disease. Several centers have reported improved remission rates of 90% to 95% when imatinib (600 mg/d) was added to initial induction therapy (usually in regimens lacking L-asparaginase), without additional toxicity. With continuation of imatinib through consolidation therapy, 50% to 60% of patients will achieve a molecular remission by 60 days post induction. Patients who achieve a molecular remission and continue on imatinib therapy have an improved disease-free survival of 62% at 3 years, compared with 14% at 1 year in the pre-imatinib era. Clinical trials are being designed to incorporate more potent TKIs such as dasatinib or nilotinib, which have shown activity in relapse settings. The Italian GIMEMA Ph+ ALL trial has used dasatinib along with corticosteroids as initial therapy for older adults with Ph+ ALL. Forty-nine of 53 patients achieved a hematologic remission by day 22, with 10 patients showing a greater than three-log reduction in BCR-ABL by PCR. BCR-ABL levels of less than $10^{-3}$ by day 85 correlated with disease-free survival; however, fewer than 25% of patients achieved a molecular remission with this regimen. The US cooperative groups have completed a trial of dasatinib combined with hyper-CVAD with or without allogeneic transplant for patients younger than 50 years. The similarities in activation pathways in the Ph-like ALLs suggest that the use of TKIs such as dasatinib might be useful in patients who show...
activation of ABL1, ABL2, CSF1R, and platelet-derived growth factor receptor (PDGFR), while ruxolitinib may benefit patients showing activation of the STAT5 pathway (JAK2, CRLF2, EPOR, and IL2RB).

Consolidation therapy
The BFM, CALGB, Linker (2002), and hyper-CVAD COG regimens for ALL are outlined in Tables 3–6. The CALGB Intergroup Study regimen for adults aged 40 or younger uses a more dose-intensive consolidation with asparaginase as well as late dose intensification. Based on preliminary results presented at the 2014 American Hematological Society (ASH) Annual Meeting, the CALGB regimen is likely to become the new standard for younger adults. As yet, no randomized trials have compared these regimens. However, in sequential studies from Memorial Sloan-Kettering Cancer Center, the BFM group, and the Linker study, use of multiple cycles of non–cross-resistant drugs for three to eight cycles after remission followed by maintenance with methotrexate and mercaptopurine resulted in overall long-term disease-free survival rates of 38% to 52%

Long-term outcome data from 282 patients treated with hyper-CVAD showed an 81% CR rate after cycle 1A and a 92% rate after receiving both cycles 1A and 1B (Table 5); a 5% overall death rate during induction was noted, although treatment-related mortality reached 15% in patients older than 60 years despite the use of granulocyte colony-stimulating factor (G-CSF). At a median follow-up of 63 months, the 5-year disease-free survival was 38%, similar to that reported in the BFM and CALGB trials. In this series, adverse prognostic factors for disease-free survival were age 45 years and older, poor performance status, WBC count greater than 50,000/μL, Ph+ cytogenetics, more than one cycle to achieve a CR, or more than 5% residual blasts at day 14. Patients with none or one of these factors had a 52% 5-year disease-free survival rate, vs 37% for patients with two or three factors and only 10% for patients with at least four risk factors.

In the 2002 Linker trial, which intensifies the consolidation with alternating cycles of higher-dose Ara-C and etoposide alternating with cycles of high-dose methotrexate, the 5-year relapse-free survival rate was 52% overall and 60% for patients with standard-risk features. Prognostic features that were associated with a poor outcome in this study included pre-B ALL with a WBC count greater than 100,000/μL at diagnosis, cytogenetic abnormalities involving chromosome 11q23 or t(9;22), and time to remission more than 30 days. Without either allogeneic or autologous transplant, all high-risk patients relapsed within a short time (1 month to 9 months). A recent update of the Ph− pre-B ALL subgroup showed a 3-year disease-free survival rate of 60% and an overall survival rate of 50%

The French Leucémie Aiguë Lymphoblastique de l’Adulte (LALA)-94 trial of 922 patients was designed to look at post-remission therapy that was stratified by risk of relapse. The standard-risk patients who achieved CR with one cycle of induction therapy were randomized to receive either conventional cyclophosphamide, Ara-C, and mercaptopurine or early intensification with intermediate-dose Ara-C (1 g/m² × 8 doses) and mitoxantrone.

In this study, there was no difference in 5-year disease-free survival (33% conventional vs 37% early intensification, with an overall survival at 5 years of 44%). High-risk patients included those with defined cytogenetic risks (excluding Ph+), WBC count greater than 30,000/μL, and CNS disease at diagnosis or who required more than 35 days to achieve CR. Patients with a sibling donor received allogeneic transplant in CR, with the remainder randomized to receive either the early intensification chemotherapy or autologous transplant. The 5-year disease-free survival was 45% for those who received allogeneic transplant and 23% for those without a donor. There was no significant difference in overall survival with chemotherapy vs autologous transplant, but there was a different pattern of relapse, with fewer late relapses in the autologous patients.

High-risk patients. High-risk patients are being selected for dose-intensive therapies, including high-dose cytarabine (HDAC) and methotrexate or etoposide, high-dose methotrexate, L-asparaginase, or TKIs such as imatinib or dasatinib in the case of Ph+ ALL. Patients with high-risk features, including Ph+, have disease-free survival of 50% to 60% when allogeneic stem cell transplant is performed in first CR for adults.

The presence of minimal residual disease using PCR-based probes or multicolor flow cytometry at end of induction in pediatric series or 6 weeks from the start of therapy in adults has been the strongest predictor of relapse and should inform choices regarding intensified therapy or allogeneic transplant.

Allogeneic hematopoietic cell transplant
Myeloablative allogeneic hematopoietic cell transplant (HCT) combines dose-intensive chemotherapy
and radiation therapy with the immunotherapeutic aspects of graft-vs-leukemia effect from donor antitumor surveillance. Relapse rates following allogeneic HCT for high-risk patients are significantly lower (15% to 20%) than relapse rates for patients who do not receive transplants (50% to 65%), but transplant-related mortality is high (20% to 30%) and increases with age. Several studies have shown improved survival for high-risk patients who receive allogeneic transplants in first CR. Results from the ECOG/MRC trial also showed improved disease-free survival (62% vs 52%) at 5 years for standard-risk patients who received a transplant from a sibling donor. Three sequential French ALL trials as well as the ECOG/MRC trial failed to show any survival advantage for autologous HCT compared with 2.5 to 3 years of consolidation and maintenance chemotherapy.

For patients with Ph+ ALL, imatinib has provided a means to achieve molecular remission in approximately half of these very high-risk patients; this has allowed physicians more time to identify an unrelated donor. Studies that will assess the impact of molecular remission pre-HCT on the risk of relapse are in progress. Imatinib (400 mg/d orally) is also studied in the post-HCT phase. Patients who remain molecularly positive or revert to a positive state are at high risk for relapse and should be considered for treatment with a second-generation TKI such as dasatinib or nilotinib. (See the chapter on Chronic Myeloid Leukemia for further details.)

CNS prophylaxis

CNS relapse occurs at a much higher frequency in patients with ALL than in those with AML. The rate of CNS relapse was 20% in the first year in a pediatric ALL trial in which the CNS therapy was attenuated to a subtherapeutic level. Patients with ALL require preemptive therapy for occult CNS disease with intrathecal methotrexate and/or Ara-C preferably combined with regimens employing high-dose systemic Ara-C or methotrexate. Pediatric trials showed that regimens which used dexamethasone at a daily dose of at least 6 mg/m² had lower rates of CNS relapse (3.7%) than regimens which used prednisone 40 mg/m² (7.1%) because of higher CNS penetration and longer retention. This has changed the pediatric practice to omit cranial radiation as a component of CNS prophylaxis, thus minimizing risks for late neurocognitive problems in children. Specific use of intrathecal liposomal Ara-C should not be used concomitantly with high-dose systemic chemotherapy, such as Ara-C, methotrexate, or etoposide, which crosses the blood-brain barrier, resulting in a high risk (15% to 20%) of serious neurotoxicity (seizures, cauda equina syndrome, and encephalitis).

Maintenance therapy

Maintenance therapy with daily mercaptopurine and weekly methotrexate for 18 to 24 months beyond consolidation remains the standard of care for children with ALL. In the Intergroup trial for adolescents and young adults with ALL, maintenance with these agents plus intermittent vincristine was maintained for 2 years in females and 3 years in males. (see Tables 3–6 for maintenance regimens). In individuals who have mature B-cell ALL, it is unlikely that maintenance therapy has any effect. In other high-risk adult populations, more than half of patients relapse while receiving maintenance therapy, indicating the need for other strategies to eradicate minimal residual disease. For patients with Ph+ ALL, maintenance TKI therapy is more important than mercaptopurine or methotrexate in preventing relapse. Patients should be monitored with quantitative PCRs for BCR-ABL transcripts. Rising BCR-ABL levels should provoke a search for mutations in the gene product and lead to a change in either the dose of TKI or the type of TKI administered. Rising levels may also be a harbinger of relapse.

Treatment of relapse

Treatment of relapsed adult ALL is a major challenge. Because most protocols for initial treatment incorporate 6 to 11 agents with different cytotoxic mechanisms, a selection process for drug resistance has occurred. The overall remission rate for relapse therapy is 30% to 40%, with a median duration of remission of 6 months. In the MRC/ECOG trial, the 5-year overall survival for adults who relapsed was 7% in the absence of allogeneic transplant. Thus, the main thrust of many of the salvage regimens is to achieve sufficient cytoreduction to allow a patient to proceed to an allogeneic transplant, which is the mainstay of therapy for relapsed disease.

Salvage strategies. Salavge strategies include reinduction with the initial regimen in patients with late relapse, or high-dose antimetabolites (Ara-C or methotrexate [see hyper-CVAD regimen, Table 5]) in those who relapse early. Novel therapeutic approaches include monoclonal antibodies and chemotherapeutic agents with either novel delivery systems to improve intracellular delivery or novel mechanisms of action, such as proteasome inhibitors, for Ph− ALL, as well as some refined standard purine analogs, such as clofarabine, and newer-generation TKIs for Ph+ ALL. A recent
Dasatinib, a kinase inhibitor of multiple targets including BCR-ABL, c-Kit, Src, and PDGFR, has been shown to overcome imatinib resistance in approximately 30% of Ph+ ALL patients. Transplant in second remission. Nilotinib, an imatinib analog with high binding affinity to BCR-ABL, induce remissions in up to 30% of patients. These remissions are short-lived but may control the leukemia long enough for a donor to be identified, thus providing an option for an allogeneic transplant if a suitable donor is found. In individuals with Ph+ ALL or CML in lymphoid blast crisis, imatinib (400 to 800 mg/d orally) can induce remissions in up to 30% of patients after two cycles; the majority of those patients (82%) also were in molecular remission at that time. Despite the high rate of molecular remission, remission durations were short, with a median relapse-free survival time of 5.8 months. Grade 3 toxicities included infections, confusion, seizures, hypertension, and thrombocytopenia. Neurologic toxicity grade 3 occurred in 11% but was reversible; 2% of patients had grade 3 cytokine release syndrome. The treatment dose for the large phase II trial was 9 µg/d continuous infusion for week 1 and 24 µg/d continuous infusion for weeks 2 to 4. Patients with high tumor burden received prephase treatment with dexamethasone to minimize cytokine release syndrome.

An area of burgeoning interest is the production of autologous T cells that have been genetically engineered to express a chimeric antigen receptor (CAR) targeted to the anti-CD19 antigen. A viral vector has been inserted into the T cells to promote in vivo replication of these T cells post infusion. These CAR T cells are being used to target a spectrum of CD19 expressing B-cell malignancies, including ALL, to create the equivalent of an autologous “graft vs leukemia” effect. Complete remissions were obtained in 27 of 30 relapsed, highly refractory patients at 1 month post CAR T-cell infusion, with an MRD-negative state achieved in 22 of 27 patients. At a median follow-up of 7 months (1 to 24 months), 19 patients still had CR, and 15 of these patients required no further treatment. These stem cell infusions have been followed by significant cytokine-mediated toxicities that required either high-dose corticosteroids or cytokine blockade with the anti–interleukin (IL)-6 inhibitor, tocilizumab.

Clofarabine has been approved for treatment of relapsed/refractory ALL in children. Of 61 patients, 12 achieved CR, including children who had relapsed following allogeneic transplant. The maximum tolerated dose was 52 mg/m² infused over 2 hours daily for 5 days. Significant toxic effects include febrile neutropenia, anorexia and nausea, capillary leak syndrome, hepatotoxicity, and rash. A small, phase I trial combined clofarabine, etoposide, and cyclophosphamide in patients with relapsed ALL (n = 20) or AML (n = 5). Nine of 13 pre-B-cell ALL patients achieved CR, compared with 1 of 5 of those with T-cell ALL. Four patients developed severe liver toxicity, including veno-occlusive disease of the liver in patients with prior stem cell transplant or hepatitis. Clofarabine is now also being integrated into preparative regimens for allogeneic transplant in combination with either busulfan or melphalan for reduced intensity conditioning. Liposomal vincristine also has been explored in combination with dexamethasone for relapsed ALL. In 2013, the US Food and Drug Administration (FDA) approved intravenous liposomal vincristine (2.25 µg/mL² given on a weekly schedule) for the treatment of relapsed Ph− ALL. The CR rate was 20%, with a median duration of remission of 23 weeks. The major non-hematologic toxicities were peripheral neuropathy and constipation.

Another agent that is being evaluated in combination for relapsed ALL is bortezomib. While this agent has had low activity when used alone in the relapse setting, it does seem to sensitize lymphoblasts to standard agents. In a phase I/II trial by Messinger et al, bortezomib combined with vincristine, dexamethasone, pegylated L-asparaginase, and doxorubicin produced marrow CRs in 16 of 20 patients (aged 1 to 22 years) with pre-B-cell ALL in either first or second relapse; the two T-cell ALL patients did not respond. Overall survival at 24 months was estimated to be 41%, with nine of the responders proceeding to stem cell transplant.

In individuals with Ph+ ALL or CML in lymphoid blast crisis, imatinib (400 to 800 mg/d orally) can induce remissions in up to 30% of patients. These remissions are short-lived but may control the leukemia long enough for a donor to be identified, thus providing an option for an allogeneic transplant in second remission. Nilotinib, an imatinib analog with high binding affinity to BCR-ABL, has been shown to overcome imatinib resistance in approximately 30% of Ph+ ALL patients. Dasatinib, a kinase inhibitor of multiple targets including BCR-ABL, c-Kit, Src, and PDGFR, has a 325-fold greater potency than imatinib and can provide short-term salvage therapy for patients.
whose disease progresses while they are receiving combinations of imatinib and chemotherapy. Dasatinib has a higher propensity for complications related to serositis, with significant pleural and peritoneal effusion. There is some evidence of CNS penetration for dasatinib compared with imatinib. Patients with Ph+ ALL who develop active CNS disease should be switched to dasatinib in conjunction with intrathecal chemotherapy. Ponatinib is a third-generation inhibitor of BCR-ABL and has activity against the T315I mutation (which neither dasatinib nor nilotinib possesses). Preliminary data showed a 28% complete cytogenetic remission and a 37% hematologic remission among 89 CML/blast crisis or Ph+ ALL patients, including one-third of those with T315I mutations. However, recently ponatinib was reported to be associated with significant risk of thrombotic events; this has led to restriction of the agent to patients with the T315I mutation using a risk evaluation and mitigation strategy (REMS) program, established by the FDA in 2014. For patients with T-cell ALL, nelarabine remains the best single agent, with remission rates of 30% to 50%. Clinical trials are being designed to combine this agent earlier in treatment in hopes of decreasing the relapse rate.

**Acute Myeloid Leukemia**

Although the chemotherapeutic agents used in the initial therapy for younger patients with AML have not changed much in the past 30 years, our knowledge of the biology of leukemia has increased. The identification of prognostic factors can provide more realistic expectations of response to standard treatment and can define the population for whom investigational therapy is appropriate early in the course of disease. The majority of patients with AML tend to be older than 65 years of age, and the challenge of devising effective treatment options that can be tolerated in this age group has become a major focus of myeloid leukemia research.

**Prognostic factors**

Cytogenetic abnormalities are the major predictors of remission and risk of relapse for patients with AML. Patients with translocation of genetic material involving core binding factor (CBF) regions [(t(15;17), t(8;21) inv(16), or t(16;16)] have a good prognosis, with remission rates of 88% and 5-year disease-free survival rates of 55% to 80%, whereas patients with loss of genetic material from chromosome 5 or 7 (−5 or −5q, −7 or −7q) and complex karyotypic abnormalities (defined as more than five abnormalities) have lower rates of CR (30% to 40%) and disease-free survival (5%) at 5 years. Another poor-risk karyotype is t(3;3)(q21;q23), which is correlated with ecotropic viral integration site 1 (EVI1) expression. EVI1 expression also occurs in about 4% of patients with a normal karyotype and about half of those with the **MLL** gene rearrangement. In patients with the **EVI1** gene rearrangement, the median survival is 10.3 months with 0% 5-year relapse-free survival. With more detailed genetic mapping of leukemia cells, new molecular markers are being identified, which may explain some of the initiation events in transforming cells from normal to leukemic. Internal duplication of **FLT3** can be found in one-third of patients with normal cytogenetics or in patients with t(15;17) (APL) but is uncommon in either poor-risk karyotypes or non-APL translocations. This abnormality does not appear to have an impact on remission, but it is a predictor for relapse (74% relapse rate in patients with a normal karyotype with an isolated biallelic **FLT3** mutation vs 46% for patients with wild-type **FLT3**). In patients with otherwise favorable cytogenetic abnormalities [t(8;21) or inv(16)], the presence of c-**KIT** mutation increases the risk of relapse. Mutations of nucleophosmin (nucleolar phosphoprotein B23, numatrin; **NPM1**), which shuttles nucleic acids and proteins from the nucleus to the cytoplasm as well as binding **TP53**, are also a commonly reported abnormality, present in 47% of patients with a normal karyotype. Although there is frequent overlap with **FLT3** mutations, patients with an isolated **NPM1** mutation and a normal karyotype have a 60% disease-free survival vs 40% for those with either wild-type or mutations of both **FLT3** and **NPM1** and 20% for those with an isolated **FLT3** mutation. Other molecular mutations in patients with normal cytogenetics that have been reported to favorably impact relapse-free survival are biallelic **CEBPA** and neuroblastoma RAS viral (v-ras) oncogene homolog (**NRAS**), while **MLL** partial tandem duplication and **RUNX1** mutations carry unfavorable implications. Recently, an updated genetic risk classification has been reported by the European LeukemiaNet using data from a large German cooperative group trial that included 847 patients aged 18 to 60 years and 710 patients over age 60 years. The favorable group now includes patients with normal karyotype (NK) with a mutation of **NPM1** but no mutation of **FLT3** and NK with **CEBPA** mutation as well as inv(16) or t(8;21). The intermediate group was subdivided into intermediate I and intermediate II. Intermediate I included NK AML with wild-type **NPM1** (**NPM1**-negative) and either mutated (**FLT3**-positive) or wild (**FLT3**-negative) or with mutations of both. The ratio of **FLT3-ITD** mutation to the normal allele was also an important factor.
with significantly shorter survivals in patients with a ratio greater than 0.8. Intermediate II included t(9;11) (p22;q23) and other cytogenetic abnormalities not listed in either favorable or unfavorable. The unfavorable group included inv(3) (q21;26A) or t(3;3), t(6;9) (p23;q34), t(v;11)(v;q23) MLL rearrangements −5, del5q, −7, abn(17p) and complex karyotypes. Among patients younger than 61 years, those in the intermediate I group had a higher rate of relapse and a lower relapse-free survival but similar overall survival compared with the intermediate II group. Among older patients, there was no difference between the intermediate I and II groups. Other molecular mutations with prognostic significance in NK AML include those of IDH1, IDH2, TET2, and DMT3A. Next-generation sequencing will also allow us to identify combinations of gene activation in a signaling pathway that may provide targets for future therapy. Other potential targets include proteosomes and ribosomal RNA.

Poor-risk cytogenetics; antecedent MDS; and a high incidence of ATP-binding cassette, sub-family B (MDR/TAP), member 1 (ABCB1) protein, commonly referred to as “multidrug-resistance protein,” are found more commonly in patients older than 60 years, which has been used to explain the lower CR rates (30% to 55%) seen in older individuals compared with their younger counterparts (60% to 80%). Many older patients with preexisting MDS may clear marrow blasts with antileukemic treatment but may still have impaired hematopoiesis and persistent cytopenias, since they may have no residual normal stem cells to repopulate the marrow.

Induction therapy

Ara-C and an anthracycline such as daunorubicin or idarubicin have been the standard drugs used for AML induction chemotherapy for more than 30 years (Table 8). Depending on the prognostic groups, remission rates of 60% to 80% are seen in younger patients (< age 60 years) and rates of 35% to 55% are seen in older patients (> age 60 years). Recent studies have focused on optimizing anthracycline dosing. In 2009, the ECOG published results of a phase III trial comparing the prior standard dose of daunorubicin (45 mg/m²) with 90 mg/m², both given on days 1 to 3 along with 7 days of infused Ara-C (100 mg/m²/day). CR rates were higher for the group using high-dose daunorubicin than for those using the standard dose (71% vs 53%, respectively), and median survival was also improved (23.7 months vs 15.7 months) in patients up to 60 years of age. A large European consortium study by Lowenberg et al compared the same doses in patients older than 60 years; an improved CR rate was seen in the high-dose daunorubicin group (52%) when compared with the lower-dose group (35%). The 30-day mortality was 11% and 12%, respectively. Patients 60 to 65 years of age benefited most and exhibited a higher event-free survival (29% vs 14%) and overall survival (38% vs 23%).

The Acute Leukemia French Association (ALFA) 9801 study compared 80 mg/m² of daunorubicin for 3 days with 12 mg/m² of idarubicin given for 3 or 4 days along with standard infusion of cytarabine in 468 AML patients between the ages of 50 and 70 years. After two consolidation courses based on intermediate cytarabine doses, patients in continuous remission were randomly assigned to receive or not receive maintenance therapy with recombinant IL-2 for 12 months. CR rates were 70% for those who used daunorubicin, 83% for those who used idarubicin for 3 days, and 78% for those who used idarubicin for 4 days. There was no difference in relapse incidence, event-free survival, or overall survival. At 2 years, event-free survival was 23.5%, and overall survival was 38%. Neither intensification of anthracycline doses nor maintenance with recombinant IL-2 impacted the course of AML significantly. This implies that idarubicin at 12 mg/m² for 3 days should produce response equivalent to 90 mg/m² of daunorubicin for 3 days, and that for patients up to age 65, anthracycline dose intensification provides higher remission rates. The most recent MRC AML trial for patients up to age 65 compared daunorubicin at a dosage of 60 mg/m² vs 90 mg/m² and found no significant difference in remission rates or rates of relapse. This now defines the minimum dose of daunorubicin that should be employed in initial treatment of AML.

**TABLE 8: AML induction and consolidation therapies**
Acute Leukemias
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Previous attempts to improve outcomes in patients younger than 60 years focused on dose escalation of Ara-C in induction and/or consolidation. Both the Australian Leukemia Study Group (ALSG) and the Southwest Oncology Group (SWOG) compared standard-dose Ara-C and daunorubicin (and etoposide in the ALSG trial) with HDAC in patients younger than 50 years (Table 8). The CR rates were 71% and 74%, respectively, for standard-dose vs high-dose therapy in the ALSG study and 55% and 58%, respectively, in the SWOG trial. In both studies, there was a significantly higher disease-free survival for the high-dose arm at 5 years (48% vs 25% for ALSG and 33% vs 22% for SWOG) but no difference in overall survival because of increased early toxicity in the HDAC arm. A more recent analysis of HDAC vs standard Ara-C induction comes from the EORTC/GIMEMA trial in 1,900 patients 15 to 60 years old; the results showed statistically better CR rates of 78% for HDAC vs 72% for the standard arm. The overall survival was superior in patients < 46 years old (51.9% vs 48%, P = .001) but not in patients 46 to 60 years of age (33% vs 34%). Subgroup analysis showed HDAC benefited patients with secondary AML, FLT3/ITD mutations, and very-poor-risk cytogenetics. However, a 1,700-patient German trial showed no difference in disease-free survival when two cycles of HDAC and mitoxantrone (HAM) were compared with one cycle of the standard-dose Ara-C-containing regimen followed by HAM. The overall disease-free survival was 40% for both arms in patients younger than 60 years and 29% for those older than 60 years; 80% of young patients received both cycles, whereas only one-third of patients over 60 received cycle 2, irrespective of dose intensity of the initial cycle. Other agents such as mitoxantrone and etoposide also have antileukemic activity, but no significant increase in remission rates or relapse-free survival has been seen when mitoxantrone was substituted for an anthracycline or etoposide was added to infusional Ara-C and daunorubicin. Currently, there is a US intergroup trial in younger patients (< 60 years) comparing infusional Ara-C and daunomycin 90 mg/m² vs higher-dose Ara-C 1,500 mg/m² for 4 days and idarubicin 10 mg/m² on days 1, 2, and 3 vs the same Ara-C and idarubicin schedule combined with pretreatment with the histone deacetylase inhibitor vorinostat. This combination was chosen on the basis of MD Anderson data, which showed a CR rate of 85% with the triple combination. The role of monoclonal antibodies in the treatment of AML was begun using gemtuzumab ozogamicin (Mylotarg), an anti-CD33 antibody conjugated to calicheamicin. This agent was originally given accelerated approval by the FDA in 2000 for the treatment of relapsed AML in older patients after showing a 16% to 23% remission rate when used as a single agent. In the British MRC AML15 trial, a survival benefit was seen in patients younger than 60 years with the use of a single dose of 3 mg/m² during induction and consolidation; the benefit was seen primarily in those with favorable cytogenetics. In contrast, the SWOG randomized phase II study conducted in the United States failed to show any improvement in remission rate when combined with cytarabine and daunorubicin in initial induction for patients younger than 60 years. In addition, early mortality during induction was higher in the gemtuzumab arm (5.7%) than in the standard-therapy arm (1.4%). On the basis of these data, the drug was withdrawn from the commercial market in the United States in October 2010. In the interim, two European trials in older adults (> 50 years) reported improved survival. The French ALFA trial enrolled 280 de novo AML patients between 50 and 70 years of age who were randomized to receive either standard infusional cytarabine with daunorubicin 60 mg/m² for 3 days or the same regimen with gemtuzumab 3 mg/m² on days 1, 4, and 7. The CR rates were similar, at 75% and 81%, respectively. Updated trial results, after a median follow-up of 4 years, were presented at the 2014 ASH Annual Meeting. The event-free survival rate remained superior for gemtuzumab, at 31% vs 19% for the control group and a median event-free survival time of 18.6 months vs 9.7 months (P = .006). Relapse-free survival also remained superior at 38% vs 25%, but overall survival was no longer better at 44% vs 36%, with a median overall survival time of 25.4 months. The advantage was seen in patients with favorable or intermediate risk or FLT3 mutation; no difference was seen in the unfavorable cytogenetic risk group. Toxicity was higher in the gemtuzumab arm, with prolonged thrombocytopenia being the predominant issue; deaths during induction were 4% and 6%, respectively. Grade 3/4 liver toxicity occurred in 13% of patients in the gemtuzumab arm vs 6% in the standard-therapy group and included two deaths from veno-occlusive disease. Neutropenia was also more prolonged in the consolidation courses, which included the investigational agent. In contrast, the US intergroup trial in younger patients (< 60 years) randomized patients to infusional Ara-C and daunorubicin 60 mg/m² with or without gemtuzumab 6 mg/m² on day 4. The patients who achieved remission then received three cycles of HDAC consolidation followed by randomization to observation or three monthly doses of gemtuzumab at 5 mg/m². The CR rates were 69% and 70%, and the 5-year relapse-free survivals were 42% and 43%. Currently, newer monoclonal antibody constructs targeting CD33 and CD45 are in progress. Another
theme that has been explored is the use of either double purine analogs either alone or in combination with anthracyclines. The Polish Leukemia Group reported a favorable outcome in a large phase III trial that added either intravenous cladribine 5 mg/m² on days 1 to 5 or fludarabine 25 mg/m² on days 1 to 5 to the backbone of 7 days of infusional cytarabine and daunorubicin 60 mg/m² on days 1 to 3. The remission rate was 67.5% for daunorubicin, cytarabine, and cladribine (DAC) vs 56% for daunorubicin and cytarabine (DA) and 59% for daunorubicin, cytarabine, and fludarabine (DAF). Overall survival was 45% at 3 years for DAC and 33% and 35% for DA and DAF, respectively \((P = .02)\). Others have reported good outcomes combining higher-dose cytarabine and clofarabine without anthracycline.

More recently, interest has focused on incorporating molecular targets into AML therapy. Among normal karyotype AML, FLT3 is the most prevalent abnormality with a negative impact. There have been several trials in the past few years trying to combine FLT3 tyrosine kinase inhibitors with conventional chemotherapy in younger patients during induction and consolidation or as maintenance post therapy/allogeneic transplant. The trials have included midostaurin, sorafenib, lestaurtinib, and quizartinib. In a single-agent trial of sorafenib for relapsed AML, 6 of 13 patients had CR with incomplete blood count recovery and another 6 had significant reduction in marrow blasts. The responses were short (median, 72 days) with the emergence of point mutations at D835. Quizartinib, which is a more potent FLT3 inhibitor, has shown activity as a single agent in patients with relapsed AML; in the phase I study, 30% of patients had significant marrow reduction of blasts, with 10% attaining CR. The maximum tolerated dose was 200 mg/d PO. Sorafenib is the agent which has been most frequently combined with standard chemotherapy. Investigators from MD Anderson reported a phase II trial of sorafenib combined with standard dose Ara-C and idarubicin. The CR was 88%. With a median follow-up of 52 months, 65% of patients had relapsed with a median disease-free survival time of 13.8 months and an overall survival time of 29 months. The median overall survival time was 42 months for FLT3− patients and 15.5 months for FLT3+ patients. At the 2014 ASH Annual Meeting, Rollig et al reported on the outcomes of a randomized of Ara-C/daunorubicin with or without sorafenib in patients under 60 years of age. The study did find a positive survival advantage in the sorafenib arm irrespective of FLT3 mutational status. However, the control arm also had a lower plateau than expected. While CBF AMLs carry a relatively favorable outcome (5-year disease-free survival of 55% to 60%), approximately 25% of these patients harbor a cKIT mutation, which confers a much worse prognosis. At the 2014 ASH Annual Meeting, Marcucci et al reported on a phase II trial combining the broad-spectrum TKI dasatinib added to standard Ara-C/daunorubicin induction and HDAC consolidation as well as 12 months of maintenance dasatinib. With a median follow-up of 24 months, the disease-free survival rate was 71% and overall survival was 85%. For patients < 60 years, the disease-free survival was 77% vs 50% for patients ≥ 60 years; relapse rates were 13% and 36%, respectively. There was no difference in outcomes based on c-KIT mutation.

Initial treatment of AML in older patients

The majority of AML patients are older than 60 years and constitute a group whose disease has a higher prevalence of unfavorable cytogenetics. Many also have poor marrow regenerative characteristics because of prior myelodysplasia. These patients are frequently burdened with comorbid conditions, which make them poor candidates for conventional Ara-C/anthracycline-based chemotherapy. Cytogenetics and performance status were the two most important predictive factors in this age group, followed by age in 5-year increments and secondary AML. Mitoxantrone and etoposide were compared with Ara-C and daunorubicin as induction chemotherapy for patients older than 55 years in SWOG trials. CR rates were 44% for Ara-C and daunorubicin and 33% for mitoxantrone and etoposide, and median survival was 8 and 6 months, respectively. Older patients (> 65 years) with poor-risk cytogenetics have a CR rate of less than 30% with standard induction chemotherapy, whereas those with a normal or favorable karyotype have a CR rate of 45% to 50%. Mortality rates for induction tend to increase significantly in patients over 70 years of age who are treated with conventional chemotherapy (and mortality rates are sometimes equivalent to the expected possible rates of remission). This problem has generated much interest in developing treatment approaches for older patients deemed to be “unfit for chemotherapy.” The European Leukemia Net has developed a web-based scoring tool which evaluates the probability of CR and death during induction with conventional chemotherapy (http://www.aml-score.org). Since cytogenetic and molecular risk are important factors in our expectation of achieving remission, it may be helpful to await the results of cytogenetic and molecular mutational profiles before choosing conventional chemotherapy in patients who are “fit” for such therapy. Recent trials from the German
Leukemia Study Group (GLSG) showed a benefit to chemotherapy in patients older than 60 years using Ara-C, idarubicin, and etoposide in those with either favorable cytogenetics or normal karyotypes with NPM1-positive/FLT3-negative mutational status, with a CR rate of more than 60% and a remission duration of 1,125 days. In other subgroups, the remission rates were 42%, with a remission duration of 440 days, and only 210 days for those who were FLT3-positive. Given these underwhelming outcomes combined with 30-day mortality in excess of 15% in many trials of Ara-C-based chemotherapy, new agents are being assessed as initial therapy for patients with abnormal karyotypes.

Clofarabine has also been evaluated as a single agent for older patients with AML. In phase II trials using a dose of 30 mg/m² IV for 5 days for induction therapy, CR was achieved in 38% of patients older than 60 years (median, 71 years). Patients who achieved remission received a maximum of six cycles of consolidation therapy (20 mg/m² for 5 days). The median disease-free survival was 37 weeks, with a median survival of 59 weeks for those who achieved CR or complete pathologic response. The 30-day mortality was 10% for those older than 70 years. A British trial in a similar population also had a CR of 32%, and an additional 16% had a CR with incomplete blood count recovery. Mortality at 30 days was higher (18%). The median overall survival time was 19 weeks for patients with CR and 5 weeks for those who did not achieve CR. The US Intergroup trial, which compared single-agent clofarabine vs standard Ara-C/daunorubicin in patients over 60 years old, was recently suspended due to excess toxicity in the clofarabine arm. Given that more than 25% of older patients have some antecedent history of cytopenias, trials of hypomethylating agents have been assessed for patients designated as “unfit” for conventional chemotherapy; these have included either decitabine or 5-azacitidine, administered either alone or in various combinations. Because these agents are less cytotoxic, the time to achieve response tends to be longer and is often not assessed until after a minimum of two cycles. The original phase III trial of azacitidine for treatment of high-risk MDS included more than 100 patients who would now be classified as having AML (20% to 30% marrow blasts). The 2-year overall survival for this group was 50% for those treated with azacitidine vs 16% for patients treated with supportive care. A more recent example of the outcomes achieved with this approach was presented at the 2014 ASH Annual Meeting, comparing azacitidine vs conventional care (which could include chemotherapy, low-dose ara-C, or supportive care in patients with > 30% marrow involvement and WBC < 15,000). Median age was 76 years. The CR rate was 22% for azacitidine and 16% for conventional care. Median survival time was 12.7 months for patients treated with azacitidine and 6.3 months for conventional care. Results of treatment with decitabine at 20 mg/m² for 10 days showed a CR rate over 30% and 2-year overall survival of over 20%.

Sidebar: A phase I/II study of vosaroxin and decitabine in newly diagnosed older patients with AML and high-risk MDS was reported at the 2014 ASH Annual Meeting. Vosaroxin is a quinolone-derived topoisomerase II inhibitor that causes site-selective DNA damage. It was combined with the 5-day decitabine schedule in escalating doses in 35 patients with a median age of 71 years. The CR rate was 50% with an additional pathologic CR rate of 27%; at the time this study was presented however, the follow-up period had been less than 6 months. Another new agent now being explored is CPX-351, which is a liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio (which has been demonstrated in vitro to be the optimally synergistic proportion of drugs). In a phase I/II trial, CPX-351 was compared against standard-dose ara-C and daunorubicin in 126 older patients (60 to 75 years old) with untreated AML. CR and CR with incomplete hematologic recovery (CRI) were seen in 66.7% of patients treated with CPX-351 vs 51.2% of those who received standard therapy; for patients with secondary AML, the CR rates for the two groups were 57.6% vs 31.6%. While recovery of WBC and platelets was slower, the rate of infection-related deaths was lower (3.5% vs 7.3%) as was the 60-day mortality (4.7% vs 14.5%) for CPX-351 as compared to standard therapy (Mayer LD et al: 56th ASH, 2014: abstract 2305).

Consolidation therapy

Once remission of AML is attained, consolidation chemotherapy is required to achieve a durable remission or cure. Standard consolidation regimens are listed in Table 8.

In the landmark CALGB study, 596 patients in CR were assigned to receive four courses of post-remission Ara-C in one of three dosages: 100 mg/m² as a continuous infusion for 5 days, 400 mg/m² as a continuous infusion for 5 days, or 3 g/m² as a 3-hour infusion every 12 hours on days 1, 3, and 5. For patients 60 years or younger, the percentage of those in CR at 4 years was significantly higher in the HDAC group (44%) than in either the 400 mg/m² or 100 mg/m² group (29% and 24%, respectively). For patients older than 60 years, consolidation dose intensity had no impact on
disease-free survival, with all groups plateauing at a rate of 16% by 2 years. However, more recent information suggests that for the small subset of patients with favorable cytogenetic or molecular markers, modified HDAC (1.5 to 2 g/m²) may improve outcomes in patients 60 to 70 years of age. Other approaches to consolidation therapy include one to three cycles of consolidation followed by autologous or allogeneic HCT. In recent years, autologous HCT has fallen out of favor in the US as alternative donor sources (unrelated donor, umbilical cord blood, or haploidentical family donor) now provide options for allogeneic HCT. Historically, these approaches tend to be limited to patients younger than 60 years and have produced long-term disease-free survival rates of 45% to 60% in several studies. Long-term disease-free survival is strongly influenced by cytogenetic and molecular abnormalities present at diagnosis. Transplant options should be considered for patients with high-risk features while in first remission, because of poor outcomes with conventional chemotherapy. However, patients with t(8;21), inv(16), or isolated NPM1 mutations can expect a 60% relapse-free survival following three or four cycles of HDAC. For these patients, HCT should be reserved for relapse or second remission. Molecular mutations are being used to identify patients with normal karyotypes with a high risk (≥ 50%) of relapse for whom multiple cycles of HDAC consolidation therapy will not be sufficient to prevent relapse. For older patients, the data on the benefits of consolidation therapy are less clear. HDAC with some dose modifications is a reasonable option for patients aged 60 to 65 years with favorable cytogenetic/molecular profiles, but for the majority of older patients, there is little evidence that more than one cycle of standard-dose consolidation therapy is better than the more intensive regimens. In patients who recover with dysplastic marrows without frank leukemia, many practitioners will institute therapy using hypomethylating agents to forestall the subsequent evolution to AML. Trials assessing this strategy are in progress.

Reduced-intensity conditioning regimens are being employed as treatment options in older patients and in those with comorbidities that would otherwise preclude full-dose allogeneic transplant. Preliminary results from several centers have shown 1- and 2-year disease-free survival rates of 50% for patients aged 55 to 70 years who received reduced-intensity allogeneic transplant for consolidation of first remission.

**CNS prophylaxis**

CNS prophylaxis is not routinely recommended for adult patients with AML. Exceptions for which a screening lumbar puncture should be considered following remission induction therapy include those at high risk for CNS recurrence, ie, patients with a WBC count greater than 50,000/μL at presentation or those with myelomonocytic or monocytic AML (FAB M4 or M5). Patients who receive HDAC (≥ 2 g/m²) for induction or consolidation therapy achieve therapeutic drug levels in the cerebrospinal fluid, obviating the need for intrathecal therapy. Patients given conventional Ara-C doses may be treated with intrathecal methotrexate (12 mg) or intrathecal Ara-C (30 mg). Both agents can be combined with intrathecal hydrocortisone (30 mg) for patients with active CNS disease.

**Treatment of refractory or relapsed AML**

Patients who do not respond to initial therapy or who relapse within 6 months of attaining CR, as well as those with antecedent myelodysplasia or therapy-related AML, are considered to have relatively resistant disease. Efforts to overcome drug resistance have focused on (1) HDAC-containing regimens, (2) new agents, and (3) targeted therapy using leukemia-specific monoclonal antibodies conjugated with radionuclides or toxins.

**HDAC.** High doses of Ara-C (2 to 3 g/m² for 8 to 12 doses) paired with mitoxantrone, etoposide, methotrexate, or fludarabine have produced short-lived CRs in 40% to 60% of relapsed patients with AML (see Table 9 for dosage regimens). Response rates were higher in patients who had received...
standard-dose Ara-C for induction therapy and who had subsequently relapsed than in those in whom induction therapy had failed. The median duration of remission was 4 to 6 months. Combinations of mitoxantrone and etoposide have been reported to produce a 40% to 50% CR rate in patients who had relapsed or for whom standard-dose Ara-C and anthracycline had failed, again with a median duration of remission of 4 to 6 months. Combinations of intermediate-dose Ara-C (1 g/m²/d for 6 days) with mitoxantrone and etoposide produced CR rates of 79% in relapsed patients and 46% in those who did not respond to induction therapy or had AML evolving from MDS, with a median CR duration of 8 months.

**New agents.** Nucleoside analogs, such as cladribine and fludarabine, showed activity in pediatric patients with AML. A British trial reported a 61% CR rate for a combination of fludarabine, Ara-C, G-CSF, and idarubicin, with a median CR duration of 7 months. Treatment with clofarabine yielded a 16% remission rate in a phase I/II trial in patients with relapsed AML as a single agent and a 46% CR and a 61% CR with incomplete platelet recovery when combined with Ara-C (2 g/m²). The recently released results from the phase III CLASSIC I trial, which compared clofarabine at 40 mg/m² plus Ara-C 1 g/m² each for 5 days with Ara-C at 1 g/m² daily for 5 days and placebo for patients older than 55 years with relapsed AML, showed a CR rate of 35% for the combination vs 18% Ara-C alone. However, the overall survival was identical for both groups, at 6.6 vs 6.3 months, respectively. Thirty-day mortality was 16% in the clofarabine-containing arm vs 5% in the Ara-C-alone arm (P = .02).

**Targeted therapy.** Sorafenib, a small molecule kinase inhibitor, has shown activity in FLT3-positive AML. Sorafenib was combined with 1.5 g/m² of cytarabine plus idarubicin in a phase I/II trial of relapsed/refractory AML. CRs were achieved in 14 of 15 FLT3-positive patients and in 24 of 36 unmutilated patients, who had a 1-year overall survival of 74%, but 10 of 14 of the FLT3-positive had relapsed. Investigators from MD Anderson reported a 40% CR rate among FLT3-positive relapsed AML patients who received a combination of azacytidine and sorafenib. Tosedostat, an oral aminopeptidase inhibitor, was tested in a phase I/II trial in older patients with relapsed AML or in those who were “unfit” for standard induction therapy at a maximum total dose of 130 mg daily. Seven of 51 patients achieved clearing of marrow blasts and another seven had greater than 50% reduction in marrow blasts, to between 5% and 15%. The majority of responders had marrow blasts less than 40% at the start of therapy, with responses lasting 1 to 6 months. Synergy has been shown in vitro between this drug and agents such as tretinoin (all trans retinoic acid, ATRA), cytarabine, and bortezomib.

**Transplant for relapsed disease.** Although none of the previous options currently offers more than a 10% to 15% chance of long-term disease-free survival, they do provide temporary cytotransformation sufficient to permit further allogeneic HCT from sibling or unrelated donors. Allogeneic HCT achieves a 30% to 40% disease-free survival rate at 5 years in patients transplanted during first relapse or second remission. Autologous bone marrow transplant also has curative potential for patients beyond first CR, with most large series reporting disease-free survival rates of 30% to 35% in select patients (usually those with good-risk cytogenetics or initial CR duration longer than 1 year). New methods of hematopoietic cell purging and post-transplant immune stimulation also are being explored to decrease relapse-related mortality.

**Acute Promyelocytic Leukemia**

APL represents a uniquely homogeneous subset of AML defined by its cytogenetic abnormality, t(15;17), which results in fusion of the retinoic acid receptor (RARA) gene on chromosome 17 with the promyelocytic leukemia (PML) gene on chromosome 15. This abnormality yields the PML/RARA fusion protein, detectable by PCR techniques, which is useful for both diagnosis and evaluation of minimal residual disease. Most patients (80%) with APL have characteristic hypergranular blasts; laboratory evidence of DIC is present in 70% to 90% of patients at diagnosis or shortly after. Hemorrhagic events contribute 10% to 15% excess mortality during induction chemotherapy for APL compared with other AML subtypes. Prompt initiation of ATRA in suspected cases of APL will minimize the coagulopathy and decrease mortality.

Because of the unique biology and specific clinical features of APL, induction and consolidation regimens for APL differ from strategies used for other pathologic subgroups.

Involvement of the RARA gene in the pathogenesis of APL suggested the use of retinoids as therapy. A study from Shanghai showed CR rates of 85% with single-agent ATRA and offered the advantages of a shorter neutropenic period (2 weeks) and slightly faster resolution of DIC (4 days vs 7 days) compared with standard chemotherapy with Ara-C and daunorubicin. Normalization of marrow morphology and cytogenetics requires 30 to 60 days of ATRA.
Initial treatment options

The backbone of APL induction therapy includes an anthracycline and ATRA (Table 10). The French and North American APL trials have also included standard-dose Ara-C as an integral part of induction and consolidation therapies. All three groups report CR rates in excess of 90% in patients with an initial WBC count of less than 10,000/µL. On the basis of data from the Programa para el Estudio de la Terapéutica en Hemopatía Maligna (PETHEMA) trials, a stratification schema of risk of relapse was constructed using WBC and platelet counts at presentation. Patients with a WBC count of less than 10,000/µL and a platelet count of more than 40,000/µL have a disease-free survival of 97%; those with a WBC count of less than 10,000/µL and a platelet count of less than 40,000/µL have a disease-free survival of 86%; and those with a WBC count of more than 10,000/µL have a disease-free survival of 78%.

In a comparison of the outcomes from the Spanish LAP 99 trial and the French APL 2000 trial, the CR rates and 3-year survival rates were similar for the low- and intermediate-risk groups, with a lower rate of relapse (4% vs 14%) and fewer days in the hospital (50 days vs 72 days) for the group that did not receive Ara-C. In patients with elevated WBC counts (10,000/µL or higher), Ara-C during induction significantly increased CR rates (95% vs 83%). Survival at 3 years was also higher for the group receiving Ara-C (92% vs 81%), and relapse was lower (9.9% vs 18.8%). In the LAP 99 trial, the use of ATRA along with anthracycline in consolidation significantly decreased the relapse rate among the low- and intermediate-risk groups. All three European cooperative groups currently use Ara-C in the consolidation regimens for high-risk patients.

The most recent North American Intergroup trial showed improved relapse-free survival when two cycles of arsenic trioxide were used as the initial component of consolidation. All three groups were monitored for molecular remission at the end of consolidation and at frequent intervals during 2 years of maintenance chemotherapy. In the most recent PETHEMA/HOVON (Dutch-Belgian Hemato-Oncology Cooperative Group) and GIMEMA trials, the incidence of molecular positivity at the end of consolidation was between 0.4% and 1.1%. Relapse rates are lower than 5% for low-risk patients, and new trials will evaluate the need for maintenance therapy for this group. The most recent GIMEMA trial did not show a benefit of maintenance ATRA with or without mercaptopurine-methotrexate.

Small, single-institution series have reported favorable remission and disease-free survival rates in patients induced with arsenic trioxide alone (CR of 86%) or combined with ATRA (95% for low- and intermediate-risk patients). High-risk patients had poorer response rates (CR of 75%) despite the addition of gemtuzumab ozogamicin (9 mg/m²) on day 1 of induction therapy. In 2013, the results of a large international trial directly comparing ATRA plus chemotherapy with ATRA plus arsenic trioxide (ATO) in patients with low- or intermediate-risk disease was published in the New England Journal of Medicine. The arsenic-based therapy achieved a CR rate of 100% in the evaluable patients, with a 2-year event-free survival of 95% compared with a CR rate of 95% and a 2-year event-free survival of 86% for the chemotherapy arm (P = .02). The incidence of relapse was 1% in the arsenic group and 6% in the chemotherapy group. The ability to provide a non-chemotherapy-based regimen with less risk of cardiotoxicity and lower risk of secondary myelodysplasia will dramatically change the treatment of APL. While arsenic trioxide does carry fewer risks of cardiotoxicity and secondary MDS/AML, it is cumbersome and time-consuming to administer and requires careful
monitoring of electrolytes (Ca++, Mg++, and K+), with maintenance of these minerals at the upper levels of the normal range to minimize the risks of QTc prolongation and ventricular arrhythmias. There was a 16% incidence of QTc prolongation in the ATRA plus arsenic regimen, and the incidence of hepatic dysfunction was high (63%), although these abnormalities resolved with discontinuation of medication. There has also been an Australian trial of ATRA, arsenic, and idarubicin as induction therapy for APL that included high-risk patients (20%). The CR rate was 95% with a 2-year overall survival of 93% and a failure-free survival rate of 88%. The use of prophylactic corticosteroids during the first 10 days of induction therapy prevented deaths due to differentiation syndrome. 

**Sidebar:** Investigators in China have conducted a trial comparing an oral formulation of arsenic (tetra arsenic tetra sulfide [As4S4] with arsenic trioxide, both combined with ATRA. Results appear equivalent as first-line therapy for APL. This would provide a much more patient-friendly, convenient therapeutic option (Zhu HH et al: J Clin Oncol 31:4215-4221, 2013).

**Differentiation syndrome**

“Differentiation syndrome” (formerly known as ATRA syndrome) develops in approximately 25% of patients with APL. Symptoms of this syndrome are fever, respiratory distress with pulmonary infiltrates or pleural effusions, and cardiovascular collapse. Temporary pseudotumor cerebri is a fairly common (10%) adverse effect of ATRA. Although these symptoms most often correlate with leukocytosis (WBC count > 10,000/μL), many patients develop symptoms with WBC counts between 5,000/μL and 10,000/μL. The syndrome is seen in patients treated with arsenic trioxide as well as in those treated with ATRA. Because the combination of ATRA and arsenic was thought to be associated with a higher risk of differentiation syndrome, all the patients in the Lo-Coco trial received prophylaxis with prednisone 0.5 mg/kg from day 1 until completion of induction therapy. Despite the prophylaxis, 19% of patients in the arsenic arm and 16% in the chemotherapy arm required treatment with higher doses of dexamethasone.

Treatment of this syndrome involves prompt use of high-dose corticosteroids (recommended dosage is dexamethasone 10 mg q12h until disappearance of symptoms and for a minimum of 3 days); initiation of conventional Ara-C/daunorubicin chemotherapy in high-risk patients or hydroxyurea in low-risk patients to control leukocytosis; and temporary discontinuation of ATRA or arsenic trioxide.

**Relapse therapy**

Arsenic trioxide is now the standard reinduction therapy for patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy. As a single agent, arsenic trioxide has produced CR in 34 of 40 patients (85%) with relapsed APL, with 86% of patients achieving molecular remission. Relapsed patients who achieved a molecular remission with arsenic trioxide alone had a median relapse-free survival of 18 months; those who received arsenic trioxide followed by autologous transplant have had relapse-free survivals in excess of 70% at 2 years. Allogeneic transplant should be reserved for those who do not achieve a molecular remission. Gemtuzumab ozogamicin is also an effective agent for patients with relapsed APL. In a small series, 91% of patients with a molecular relapse of APL achieved a molecular remission following two doses of gemtuzumab ozogamicin (6 mg/m²). Although this drug is no longer commercially available, efforts are in progress to maintain access to the drug for patients with relapsed APL.

**Monitoring response to therapy.** Reverse-transcriptase PCR for the PML/RARA fusion protein can be used to follow response to therapy. The marker clears slowly, with many patients still testing positive following induction therapy. However, patients with persistence of PML/RARA fusion protein at the end of consolidation therapy are at high risk for relapse, as are those with reemergence of the marker following a period without detectable protein. Salvage chemotherapy should be considered for patients with persistent or recurrent confirmed molecular relapse.

**Suggested Reading**

**On ALL**


Grupp SA, Kalos M, Barrett D, et al: Chimeric antigen receptor-modified T cells for acute


**On AML**


Marcucci G, Geyer S, Zhao W, et al: Adding KIT inhibitor dasatinib (DAS) to chemotherapy overcomes the negative impact of KIT mutation/over-expression in core binding factor (CBF) acute
Acute Leukemias

On AML


On APL


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