Adult Acute Leukemia

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Introduction

Leukemia is a clonal hematopoietic stem cell malignancy, characterized by excessive proliferation, survival, and impaired differentiation of cells. The 2 acute leukemias are acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL). Acute promyelocytic leukemia (APL) is a distinct subtype of AML with very good prognosis and is discussed separately.

Epidemiology

Hematological malignancies account for approximately 7% of new cancers annually. AML is the most common acute leukemia in adults. In 2010, there were an estimated 12,330 new cases and 8950 deaths from AML. It accounts for about 80% of acute leukemias in adults. ALL had an estimated 5330 new cases and 1420 deaths in 2010. The total incidence of all forms of leukemia is 9.6 per 100,000. The annual incidence of AML is 2.7 per 100,000 and ALL is 1.5 per 100,000 population. Both occur slightly more frequently in men and people of European ancestry.[1] ALL has a bimodal distribution with an early peak age of 4-5 years followed by a second peak around age 50. ALL accounts for only about 20% of adult acute leukemias, but accounts for 80% of pediatric acute leukemias.

Acute Leukemia Subtypes

Acute Myeloid Leukemia

AML is a clonal stem cell malignancy that results in the accumulation of immature leukemic blasts in the bone marrow, peripheral blood, and sometimes soft tissues. Patients often present with signs and symptoms consistent with pancytopenia from bone marrow infiltration, including fatigue, weakness, infection, easy bruising, and mucosal bleeding. Once a diagnosis of AML is suspected, a rapid workup is essential to management. Often, it is potentially curable. AML is commonly a disease

Dis Mon 2012;58:219-238
0011-5029/2012 $36.00 + 0
doi:10.1016/j.disamonth.2012.01.011

TABLE 1. 2008 World Health Organization Classification of AML[3]

AML with recurrent genetic abnormalities
1. t(8;21) (q22;q22); *RUNX1-RUNX1T1*
2. inv(16) (p13;1q22) or t(16;16) (p13.1;q22); *CFBF-MYH11*
3. APL with t(15;17) (q22;q12); *PML-RARA*
4. AML with t(9;11) (p22;q23); *MLLT3-MLL*
5. AML with t(6;9) (p23;q34); *DEK-NUP214*
6. AML with inv3(q21q26.2) or t(3;3) (q21;q26.2); *RPN1-EVI1*
7. AML (megakaryoblastic) with t(1;22) (p13;q13); *RBM15-MKL1*
8. Provisional entity: AML with mutated *NPM1*
9. Provisional entity: AML with mutated *CEBPA*
AML with MDS-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified
1. AML with minimal differentiation
2. AML without maturation
3. AML with maturation
4. Acute myelomonocytic leukemia
5. Acute monoblastic/monocytic leukemia
6. Acute erythroid leukemia
a. Pure erythroid leukemia
b. Erythroleukemia, erythroid/myeloid
7. Acute megakaryoblastic leukemia
8. Acute basophilic leukemia
9. Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
1. Transient abnormal myelopoiesis
2. Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm

of elderly people with a median age of diagnosis of approximately 72 years old.[2]

The most widely accepted classification system is the World Health Organization (WHO) system. It was updated in 2001 to encompass etiologic, morphologic, immunophenotypic, clinical, genetic, and molecular features. In 2008, it was updated to incorporate additional scientific and clinical information to refine diagnostic criteria (Table 1).[3] This system has largely replaced the French-American-British (FAB) classification system, which had been used for the prior 3 decades and defined AML into subtypes M0 through M7.[4] The current WHO AML classifications are AML with recurrent genetic abnormalities; AML with myelodysplastic (MDS)-related changes; therapy-related myeloid neoplasms; AML not otherwise specified; myeloid sarcoma; myeloid proliferations related to Down's syndrome; and blastic plasmacytoid dendritic cell neoplasm.

The etiology for AML is unknown in most cases. However, several known risk factors have been identified. Environmental risk factors, including exposure to ionizing radiation, petroleum, benzene, and benzene-containing compounds, can result in bone marrow damage leading to AML.[5,6] Germ line mutations in *Runx-1* and chromosomal abnormalities in autosomal-recessive disorders, including Bloom syndrome, fanconi anemia, and ataxia telangiectasia, have been associated with AML development.[7,8] Down's syndrome is associated with megakaryoblastic AML.[9] Prior exposure to antineoplastic agents is another major cause of AML. Alkylating agents and DNA-topoisomerase II inhibitors are the 2 classes of drugs most commonly implemented.[5,10] In the case of alkylator exposure, therapy-related AML typically has a latency period of 5-7 years and is associated with antecedent MDS and involves loss or deletions of chromosomes 5 or 7.[11] The latency period for topoisomerase II inhibitors leading to AML is typically 1-1.5 years and is associated with rearrangement of the *MLL* (myeloid/lymphoid or mixed-linage leukemia) gene in chromosome band 11(q23).[12] Antecedent MDS is not usually present.

Most patients present with clinical features secondary to pancytopenia from bone marrow infiltration by leukemic blasts. Patients with anemia commonly complain of fatigue, weakness, pallor, or dyspnea on exertion. In some cases, chest pain may prompt a cardiac workup. Thrombocytopenia may result in easy bruising, petechiae, mucosal bleeds, or epistaxis. Women may complain of heavy menstrual periods. Patients with AML may have elevated, normal, or low white blood cells (WBC) counts. The risk of infection is increased either because of insufficient WBCs (particularly granulocytes) and/or inadequately functioning WBCs (mostly because of immature blasts). Patients presenting with fevers should be managed aggressively with empiric broad spectrum antibiotics because of these abnormalities. In a minority of cases, leukemic infiltration of the skin occurs, resulting in gingival hypertrophy or leukemia cutis—a raised nodular nonpruritic rash.[13] The collection of cells can also form soft tissue masses called chloromas or myeloid sarcomas, or invade the central nervous system (CNS), usually in the context of monocytic or myelomonocytic AML. Hepatosplenomegaly and adenopathy are rare in AML and their presence is likely associated with an antecedent MDS or myeloproliferative neoplasm (MPN), such as chronic myelogenous leukemia.

At presentation, and in the initial course of treatment, there are several clinical scenarios that require rapid identification and treatment. Leukostasis is a complication that results from the leukemic blasts blocking capillary blood flow. This is more common when the blast count exceeds

50,000.[14] Leukostasis is characterized by shortness of breath, cardiac dysfunction, severe muscle aches or cramping, and ocular, neurological, or cognitive dysfunction. This is an oncological emergency and should be treated promptly with leukopheresis. Another complication that can be present at diagnosis, or shortly after initiation of chemotherapy, is tumor lysis syndrome. This is characterized by hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, and renal failure. It is important to keep the patient well hydrated and initiate allopurinol as soon as possible. Finally, there is a risk of disseminated intravascular coagulation (DIC), which can result in life-threatening bleeds. Although more common in APL, it can occur with AML and coagulation studies should be performed on diagnosis.

Diagnosis begins with a complete history and physical. Questions should elicit any history of cardiac, renal, or liver dysfunction as well as any history of prior exposure to chemotherapy and radiation therapy. Diagnosis is made from bone marrow biopsy and aspirate findings correlated with flow cytometry and cytogenetic and molecular genetic studies. A blast count of 20% from bone marrow aspirate or peripheral blood is diagnostic for AML.[15]

Cell surface markers identified by flow cytometry include CD13, CD33, and CD34 found on normal immature myeloid cells.[16] There are multiple other cell markers that are also expressed and are specific to different subsets of AML. A comprehensive metabolic panel to evaluate electrolytes, renal and liver function should be performed. Laboratories evaluating for tumor lysis syndrome and disseminated intravascular coagulation are recommended. A baseline assessment of cardiac function with echocardiogram or multiple uptake gated acquisition scan should be performed as treatment will likely involve administration of potentially cardiotoxic anthracycline chemotherapeutic agents. A baseline chest radiograph and electrocardiogram should be obtained. Central venous access is required. Lumbar puncture is recommended in patients with neurological symptoms, WBC $>$100,000, or monocytic subtype.

There are specific cytogenetic and molecular genetic abnormalities routinely tested that provide important prognostic information (Table 2). There are 3 risk groups for AML: favorable, intermediate, and unfavorable. The estimated survival at 5 years is 55%-65%, 38%-40%, and 11%-15%, respectively.[17,18] The disease risk group helps predict response to induction chemotherapy, relapse risk, and overall survival (OS). Balanced translocations resulting in abnormal transcription factor of core-binding factors are associated with a favorable prognosis and include t(8;21), t(16;16), and inv(16).[19] APL, formally classified as M3, is

TABLE 2. Acute myeloid leukemia prognostic factors[11,12,20-24]

Feature	Favorable	Unfavorable	Intermediate
Age	<50	>60	
Karnofsky Performance Status	>60%	<60%	
WBC count at diagnosis	<30,000	>30,000	
MDR1 phenotype	Negative	Positive	
Therapy-related AML or antecedent hematological disorders (MDS, MPN)	Absent	Present (characterized by loss or deletions of chromosomes 5 or 7 or *MLL* gene rearrangements)	
Molecular genetic changes	*CEBPA* mutation; *NPM1* mutation (in the absence of *FLT3* mutation)	*FLT3/ITD* mutation; *KIT* mutation; *MLL* partial tandem duplication; *BAALC* overexpression; *IDH1* and/or *IDH2* mutations; *WT1* mutation	*FLT3/ITD* mutation negative, *NPM1* mutation negative
Cytogenetic abnormalities	t(8;21); t(16;16); inv(16); t(15;17)	Complex karyotype defined as ≥4 unrelated abnormalities, abn(3q) (excluding t(3;5)(q25;q34)), inv(3)(q21q26)/t(3;3)(q21;q26), add(5q)/del(5q), -5, -7, add(7q)/del(7q), t(6;11)(q27;q23), t(10;11) (p11 approximately 13;q23), other t(11q23) (excluding t(9;11) (p21 approximately 22;q23) and t(11;19)(q23;p13)), t(9;22) (q34;q11), -17, and abn(17p)	Normal karyotype

characterized by t(15;17), has a very favorable prognosis, and is discussed separately below. Patients with a normal karyotype fall within the intermediate risk group. About 40% of AML cases have a normal karyotype.[18] A list of unfavorable cytogenetics can be found in Table 2.[20]

In patients with normal cytogenetics, molecular genetics are used to risk stratify patients further into high- or low-risk categories. Two molecular genetic abnormalities associated with a favorable outcome are mutated nucleophosmin member 1 (*NPM1*) and CCAAT/enhancer-binding protein-α (*CEBPA*).[24] *NPM1* mutation occurs in approximately 50%-60% of AML with normal karyotype.[25] Patients with a mutated *CEBPA* or *NPM1* in the absence of fms-like tyrosine kinase 3 (*FLT3*) receptor are significantly more likely to achieve complete remission and have improved overall survival.[26] *NPM1* mutations result in protein to cytoplasm

delocalization. The *CEBPA* gene encodes for a transcription factor needed for normal granulocyte maturation and occurs in about 10% of patients with AML.[27]

FLT3 mutations are associated with a poor prognosis. Mutations in *FLT3* result in internal transmembrane mutation duplications (*FLT3/ITD*) with activation of the *FLT3* receptor tyrosine kinase. This abnormality occurs in about 30% of adults with AML.[23] Other poor risk molecular abnormalities are listed in Table 2.

Other independent poor prognostic features include advanced age (generally defined as >60), poor performance status, WBC >30,000 at presentation, multi-drug-resistant (MDR1)-positive phenotype (P-glycoprotein expression), and antecedent hematological disorders, such as MDS, MPN, and therapy-related myeloid neoplasms.[22,28] Unfavorable cytogenetics are more common in patients >60 with an incidence of 23% compared to 15% in those <60.[20]

Treatment for AML is divided into induction and post-remission therapy. The goal of induction chemotherapy is to reduce the leukemic burden to undetectable levels. Once this is achieved, consolidation is given to maintain the remission. Although individualized in each case, age greater than 60 fare poorly with intensive treatment. Fertility counseling for patients of child-bearing age should be considered before initiation of treatment.

In patients under the age of 60 with good functional status, standard treatment is "7 + 3" with 7 days of continuous infusion cytarabine, 100 or 200 mg m^{-2}, and 3 days of bolus infusion anthracycline (daunorubicin or idarubicin). The goal is to achieve a complete response (CR), which is defined as having less than 5% blasts in the bone marrow, absolute neutrophil count >1000, platelets >100,000, and no extramedullary disease. Studies have shown a CR rate of 55%-80% in patients under the age of 60, based on prognostic group.[29] Conversely, only 35%-55% of patients older than 60 achieve a CR with "7 + 3" induction chemotherapy. Idarubicin was compared to daunorubicin and found to have identical CR, OS, and relapse-free survival rates. However, idarubicin was associated with higher rates of sepsis and death within the first 60 days.[30] Studies evaluating administration of standard-dose vs high-dose cytarabine (HiDAC) over 7 days have been performed as part of induction therapy. Overall, there are no significant differences in CR or OS rates with HiDAC but is associated with increased toxicity.[31,32]

A repeat bone marrow biopsy and aspirate are performed 1 week after the last dose of induction chemotherapy (Day 14) and again after cell count recovery (usually around Day 30). About 50% of patients will have

persistent leukemia indicated by the presence of more than 5% blasts in their bone marrow. In these cases initial therapy has failed and a second cycle of induction chemotherapy is administered. This scenario is associated with worse overall survival and lower CR rates.[33]

Once CR is achieved, the patient receives consolidation therapy. This can include chemotherapy or allogeneic stem cell transplantation. Without consolidation therapy, the vast majority of patients will relapse within 4-8 months of initial treatment.[34] The most commonly used consolidation chemotherapy is HiDAC (3 g/m^2 IV q12h $\times$ 6 doses Days 1, 3, and 5) for 3-4 cycles.

Allogenic HCT (alloHCT) with a human leukocytes antigen (HLA) matched sibling donor or unrelated matched donor should be considered in patients with unfavorable risk disease and select patients with intermediate risk disease as consolidation treatment in first CR. AlloHCT substantially reduces the risk of relapse and provides a potentially curative treatment. Patients with favorable characteristics are not offered alloHCT after first CR, as this has not been shown to improve OS or disease-free survival.[35,36]

Autologous HCT (autoHCT) can be considered in patients without an HLA-matched donor. The advantages of autoHCT include the ability to give high-dose chemotherapy without risk of graft-versus-host disease and lower rates of transplant-related mortality of approximately 6% or less. However, the benefit of graft-vs-leukemia effect is lost. Studies have shown improvement in disease-free survival with autoHCT, but no improvement in OS.[37,38]

The duration of initial CR provides important prognostic information. In patients in whom CR lasted $<$12 months, only 10%-20% will achieve a second CR. If CR lasted $>$12 months, then approximately 40%-50% of patients are able to achieve a second CR.[39,40]

Older patients (age $>$60) with AML are more likely to have higher risk disease with poor-risk cytogenetics, antecedent MDS, multidrug resistance, or other medical comorbidities. Older patients and worse performance status have significantly higher mortality with intensive induction chemotherapy.[21,41] Evaluation of a patient's clinical condition is considered before initiation of treatment. The best treatment option for elderly patients is controversial and should consider anticipated tolerability of chemotherapy. Older patients who are good chemotherapy candidates can be given "7 + 3" with or without an initial dose reduction. This approach is best suited for patients with low- or intermediate-risk disease and can yield a CR rate of up to 70%-80%.[42,43] Patients not considered suitable candidates for intensive chemotherapy can be offered a hypomethylating

TABLE 3. 2008 WHO classification of ALL[3]

Precursor lymphoid neoplasms
B-cell lymphoblastic leukemia/lymphoma, not otherwise specified
B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
1. B-cell lymphoblastic leukemia/lymphoma with t(9;22) (q34;q11.2); *BCR-ABL1*
2. B-cell lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL* rearranged
3. B-cell lymphoblastic leukemia/lymphoma with t(12;21) (p13;q22); *TEL-AML1* (*ETV6-RUNX1*)
4. B-cell lymphoblastic leukemia/lymphoma with hyperploidy
5. B-cell lymphoblastic leukemia/lymphoma with hypoploidy (hypodiploid ALL)
6. B-cell lymphoblastic leukemia/lymphoma with t(5;14) (q31;q32); IL-3;IGH
7. B-cell lymphoblastic leukemia/lymphoma with t(1;19) (q23;p13.3); *E2A-PBX1* (*TCF3-PBX1*)
T-cell lymphoblastic leukemia/lymphoma

agent, such as azacitidine or decitabine, low-dose subcutaneous cytarabine, hydroxyurea, best supportive care with transfusion, and growth factors.[44,45] Given the very poor prognosis in older patients with long-term survival of only 10%, a clinical trial should be considered whenever possible.

After induction chemotherapy, most elderly patients relapse within 4 months without consolidation therapy. Unfortunately, even with consolidation treatment, only approximately 10% of elderly patients maintain a durable remission and long-term survival. Many elderly patients are not considered eligible for alloHCT because of age and comorbidities. Use of HiDAC consolidation is not routinely used in older patients and results in unacceptably high CNS toxicity and mortality and does not improve the overall clinical outcome.[46,47] Treatment with 2 cycles "5 + 2" using an anthracycline for 2 days and cytarabine, 100 mg m^{-2} for 5 days, is 1 option. The role of reduced intensity conditioning alloHCT in patients up to age 75 is being evaluated as a possible option for "fit" elderly patients eligible for transplants with encouraging results.[48,49]

Acute Lymphoblastic Leukemia

ALL is a clonal stem cell malignancy of excessive lymphoblast proliferation. As with AML, the revised 2008 WHO classification has replaced the former FAB system. It is now understood that ALL and lymphoblastic lymphoma are the same disease entities at the morphologic and immunophenotypic levels and classified as either B- and T-cell lymphoblastic leukemia/lymphoma (B-ALL and T-ALL). B-ALL is further divided based on recurrent molecular and cytogenetic abnormalities (Table 3). The terms precursor B- and T-cell lymphoblastic leuke-

mia/lymphoma are no longer used.[3] Although classified as the same, the lymphomatous form often presents with bulky adenopathy, such as a mediastinal mass. The leukemic type has predominately bone marrow, defined as ≥25% bone marrow infiltration. However, there can be significant overlap between these.

In most patients the etiology for ALL is unknown. Studies have shown higher rates among monozygotic and dizygotic twins. Diseases with chromosomal instability, such as Bloom's syndrome, fanconi anemia, and ataxia-telangiectasia, are associated with increased risk of ALL. Patients with diseases of inherited chromosomal abnormalities, including Down's syndrome and Klienfelter's syndrome, are at higher risk for ALL.[50-53] Human T-cell lymphotrophic virus Type 1 is associated with adult T-cell ALL. Human immunodeficiency virus and Epstein–Barr virus are also risk factors for the development of ALL.[54,55]

Patients usually present with clinical sequelae from cytopenias secondary to bone marrow suppression from leukemic cell infiltration. This includes fatigue, infection, and easy bruising. B-symptoms, including unintentional weight loss, fevers, and night sweats, may be present. Bone and joint pain occur more frequently in children. Physical examination findings may include petechiae, ecchymoses, or pallor. Splenomegaly, hepatomegaly, and lymphadenopathy occur in about 50%. CNS involvement occurs in 5%-8% and may manifest with cranial nerve abnormalities or meningeal symptoms. Other sites of involvement may include skin lesions called leukemia cutis, and osteolytic bone lesions, or testicular or mediastinal masses. Mediastinal masses are more common in T-cell ALL and rare in B-cell ALL.

ALL is diagnosed and characterized by a combination of morphology, immunophenotyping, cell surface markers, cytogenetics, and molecular characteristics. After appropriate history and physical examination, the next diagnostic step is bone marrow biopsy and aspiration. Specific flow cytometry and cytogenetics tests should be performed. Sometimes a tissue diagnosis is made from mediastinal masses or other similar lesions. Testicular examination in men and lumbar puncture should be performed and sent for cytology and flow cytometry because the testes and CNS are sanctuary sites for ALL. Peripheral blood containing circulating blasts can also be sent for analysis; however, as many as 10% of patients lack circulating blasts at time of diagnosis. Blasts appear smaller than AML blasts and are agranular. Auer rods are never present.

By histochemistry, ALL blasts are variably positive for periodic acid Schiff and negative for myeloperoxidase staining. Determination of immunophenotype by flow cytometry is essential. Cells are typically

TABLE 4. Adult acute lymphoblastic leukemia prognostic factors[59,61-66]

Feature	Favorable	Unfavorable
Age	<35	>60
WBC count	<30,000 (B-cell ALL)	>100,000 (T-cell ALL)
Immunophenotype	T-cell ALL	B-cell ALL or immature T-cell ALL
CNS involvement	Absent	Present
Molecular genetic changes	*NOTCH1* mutation	*BAALC* expression
Cytogenetic abnormalities	t(12;21) *ETV6/RUNX1*; high hyperdiploidy; del 9p	t(9;22) *BCL/ABL*; *MLL* gene rearrangements; t(8;14); complex karyotype; low hypodiploidy; near haploidy
Time to complete remission	≤4 wks	
Detection of MRD after induction therapy	Absent	Present

positive for terminal deoxytransferase. Other cell surface markers are used to distinguish between B- and T-cell ALL. Overall, B-cell ALL is diagnosed approximately 85% of the time and T-cell ALL in about 15%. Recognition of different antigens determines the degree of differentiation. Early B-cell antigens occur in 5%-10% of ALL cases, also known as pro-B-cell ALL. These are CD19-, CD79a-, and CD22-positive. Common ALL antigen is positive CD10 and present in 40%-50% of cases. Cytoplasmic immunoglobulin occurs with pre-B-cell ALL and surface immunoglobulin (usually IgM; express a clonal light chain and terminal deoxytransferase negative) with mature B-cell ALL (Burkitt leukemia) occurring in 2%-5% of cases.[56] T-cell markers are absent in B-cell ALL. In T-cell ALL, typical antigens include CD2, CD7, CD38, CD1a, CD4, and CD8. As with B-cell ALL, variations in antigen expression are used to determine stages of cell differentiation and maturity. Mature T-cell ALL have surface CD3 and express CD4 or CD8 but not both.[57]

As in AML, cytogenetic abnormalities aid in diagnosis and can provide important prognostic information (Table 4). Methods to detect cytogenetic changes are karyotype, fluorescence in situ hybridization, and real-time polymerase chain reaction (RT-PCR) for specific recurrent abnormalities. In up to 25% of cases, no cytogenetic abnormalities are identified.[58] Alteration in chromosome number alone occurs in about 10% of cases. Hyperdiploidy of >50 chromosomes is associated with improved prognosis.[59] Hypodiploidy (<45 chromosomes) occurs more commonly in children and adolescence and is considered a poor prognostic indicator. Those with low hypodiploidy (33-39 chromosomes) and near-haploidy (22-29 chromosomes) have particularly poor prognosis.[60] A complex karyotype, defined as 5 or more chromosomal abnormalities,

carries a poor prognosis. Adult patients with Deletion 9(p) have a more favorable outcome.[59]

Multiple known recurring cytogenetic translocations have been recognized (Table 4). B-cell ALL translocations include t(9;22) *BCR/ABL*, t(12;21), t(4;11), t(1;19), and t(v;11q23) *MLL* (myeloid/lymphoid or mixed-linage leukemia) rearrangement. Philadelphia (Ph) chromosome-positive ALL is the result of t(9;22) and is more common in adults. This results in a juxtaposition of the *ABL* gene from chromosome 9 to fuse with the *BCR* gene on chromosome 22. The most common molecular weight of the fusion protein in ALL is 190 kDa (p190). The fusion yields *BCR/ABL1*, which results in uncontrolled cell proliferation via the tyrosine kinase pathway. It occurs is approximately 25%-30% of adult ALL cases and is an adverse prognostic feature. The incidence increases with age. Tyrosine kinase inhibitors (TKI), such as imatinib and dasatinib, are used in conjunction with chemotherapy in patients with Ph chromosome-positive ALL.[67,68] The administration of TKI has improved outcomes.[69]

The t(12;21) yielding *ETV6/RUNX1* is associated with hyperdiploidy and improved prognosis. This translocation only occurs in about 3% of adults compared to 15%-25% of children. It is the most common translocation in children.[62] The t(1;19) is also associated with better outcomes. This occurs in about 30% of childhood pre-B-cell ALL.[70] In contrast, the t(4;11) and t(v;11q23) abnormalities result in poor prognosis. Both involve *MLL* translocations. The t(4;11) is rarely found in adults but can occur in up to 60% of those less than 12 months old. This translocation involves 11q23 and results in a *MLL/AF4* fusion gene leading to tyrosine kinase pathway activation. Patients with *MLL* abnormalities have worse survival and more treatment failures.[63,71] The t(8;14) involves immunoglobulin heavy chain and *c-MYC* translocations and occurs in Burkitt's leukemia. Molecular genetics to detect specific genetic expression abnormalities are used to aid in prognosis. One example specific to T-cell ALL is the gain-of-function *NOTCH1* mutation. This occurs in about 50% of patients and is a good prognostic indicator.[61] *BAALC* gene expression is also a poor prognostic feature for both T- and B-cell ALL.[64]

In patients less than 60, cure is achieved in 30%-40%. However, only 10%-15% of those between 60 and 70 and $<5\%$ of those >70 years old achieve long-term survival. Cure rates are higher in children because of better cytogenetics, including infrequent Ph chromosome-positive ALL and potential differences in treatment practices among pediatric hematologists and adult hematologists.

Prognostic factors at time of diagnosis include age, WBC count, immunophenotype, CNS disease, cytogenetics, and molecular abnormalities. Prognostic factors based on response to treatment include time to complete remission and detection of minimal residual disease (MRD). Based on age, children ages 1-9 have the best outcomes. Patients <35 have a favorable prognosis, whereas those >60 have an adverse prognosis. A WBC of $<30 \times 10^9$/L for B-cell ALL is favorable and $>100 \times 10^9$/L for T-cell ALL is unfavorable. T-cell lineage ALL has a more favorable prognosis compared to B-cell ALL and immature T-cell ALL.[65,72] CNS disease at diagnosis is a poor prognostic feature.[73] Achievement of CR within 4 weeks is considered favorable, whereas late CR conveys poor prognosis. Patients with no MRD ($<0.01\%$ by flow cytometry or PCR) after induction therapy are at lowest risk for relapse. Most patients with MRD ($>0.01\%$) will eventually relapse.[66,74]

Treatment for adult B- and T-cell ALL is categorized broadly into induction phase, consolidation therapy, maintenance therapy, CNS prophylaxis, and allogeneic stem cell transplant. The goal of induction therapy is to achieve complete remission. Standard therapy will achieve CR in 80%-90% of patients. However, remission is short-lived without consolidation therapy. Before induction therapy, baseline cardiac function should be assessed; central venous access should be obtained, and complete laboratory evaluation and infectious workup should be performed. In patients of child-bearing age, fertility-preserving counseling is advised. Diagnostic studies as described above should be obtained, including CNS analysis. Whenever possible, patients should be offered a clinical trial.

There are many ALL induction regimens, including chemotherapies, such as cyclophosphamide, anthracycline, vincristine, asparaginase, and glucocorticoids. The major toxicities of this regimen include tumor lysis syndrome, infections, and asparaginase-related toxicities, such as pancreatitis, coagulopathy, and hepatotoxicity.[75,76] The addition of rituximab to CD20-positive ALL improves survival in patients <60 years.[77] In patients with *BCR/ABL* translocation, the addition of a TKI (imatinib, dasatinib, nilotinib) improves CR and OS rates.[78,79] Other novel TKIs are being studied. Bone marrow biopsy and aspirate are performed at Day 14 and after marrow recovery (around Day 28) to assess for persistent and MRD. Persistent disease at Day 14 and detection of MRD after marrow recovery are considered treatment failures and require reinduction chemotherapy.

CNS prophylaxis should be administered because CNS relapse can occur in up to 75% of patients at 1 year if not administered. One option

employed more commonly for children is intrathecal methotrexate and 24 Gy of cranial irradiation. In adults, administration of intrathecal methotrexate, cytarabine, and corticosteroids can be used in lieu of cranial irradiation.[80,81] Alternatively, high-dose systemic methotrexate or cytarabine will cross the blood–brain barrier and provide treatment to the CNS.

Once CR is achieved with induction therapy, consolidation therapy is administered to improve OS and eradicate any possible MRD. Regimens consist of combinations of cytarabine, anthracycline, cyclophosphamide, methotrexate, and 6-mercaptopurine. Repeat administration of the consolidation regimen is continued over about 6 months. Once consolidation therapy is complete, maintenance therapy of daily low-dose oral mercaptopurine and oral weekly methotrexate with intermittent intravenous infusions of chemotherapy, such as vincristine, is continued over the next 18 months to 3 years.

Allogeneic stem cell (allo-HCT) transplant is used in select patients to improve long-term survival and cure rates in patients with ALL. Ideally, the donor should be an HLA-matched sibling donor; however, a matched unrelated donor can also be considered. Although the specific criterion for transplant referral remains controversial, the decision to transplant after first CR in patients with high-risk features, such those with *MLL* abnormalities or Ph-positive ALL, should be considered. The 10-year survival in high-risk patients is 44% compared to 11% in those not transplanted.[82] In addition, patients who achieve CR2 after relapse should also be referred for allo-HCT. The use of reduced-intensity condition regimens is being studied in select populations as an option to reduce the risk of transplant-related mortality. The role of autologous stem cell transplant remains controversial with some trials showing no significant benefit over standard chemotherapy.[83]

Acute Promyelocytic Leukemia

APL is a clinically, and by nature, unique form of AML. It results from maturation arrest at the promyelocytic stage of granulocyte maturation. APL has a cure rate of about 70%-80% but is associated with higher early mortality from DIC complications. It is classified as APL with t(15;17)(q22;q12) according to WHO classification.[3] This balanced translocation results in fusion between retinoic acid receptor α (*RARA*) on chromosome 15 and promyelocytic leukemia (*PML*) on chromosome 17, impairing cell differentiation. It is classified as AML-M3 by the antiquated FAB classification system and accounts for 5%-15% of AML cases annually. It is more common in Hispanics and younger people with a median age

of 30-40 years.[84] There is no difference in gender incidence. Diagnosis is made when the t(15;17) is demonstrated by fluorescence in situ hybridization for the *PML/RARA* fusion. In most cases, this test can be performed within 24 hours. To confirm diagnosis, reverse transcriptase PCR can be performed. In addition, promyelocytes will be found in the bone marrow and peripheral blood.

For APL, promyelocytes are characterized by cells with a large nucleus, which is bilobed or creased. About 75% have a hypergranular cytoplasm with dark purple to bright pink granules. In one-quarter of patients, the cytoplasm is microgranular with no obvious granules present by light microscopy.

Clinically patients present with features similar to AML because of pancytopenia; however, there is a very high propensity for DIC. Approximately 65%-90% of patients have DIC around the time of diagnosis.[85] This is due to APL blast release of proteolytic enzyme granules resulting in severe thrombosis, hyperfibrinolysis, and coagulopathy. The major cause of early mortality is from hemorrhage, often intracranial or pulmonary.[85] Therefore, immediate treatment with all-trans retinoic acid (ATRA) should be initiated if APL is suspected, even before definitive diagnosis can be made. Coagulopathy typically improves after 5-7 days of treatment.

The unique biology of APL uses different treatment strategies compared to other forms of acute leukemia. APL results from the translocation of chromosomes 15 and 17, which causes a maturational arrest of granulocytes. There are 2 treatments which target this: ATRA and arsenic trioxide (ATO). Once APL cells are exposed to those agents, they undergo rapid differentiation to mature neutrophils. As a single agent, ATRA results in a CR in about 80% of patients. While receiving ATRA or ATO, patients should be closely monitored for development of differentiation syndrome characterized by dyspnea, fever, weight gain, hypotension, and pulmonary infiltrates. Treatment of differentiation syndrome with dexamethasone is highly effective.[86]

The treatment paradigms for APL have evolved over the past decade. Initially, ATRA was combined with the traditional "7 + 3." Use of daunorubicin, cytarabine, and ATRA achieves complete remission in 80%-95% of patients.[87,88] To reduce toxicity, only an anthracycline and ATRA were used, which demonstrated a CR rate was 91%.[89] Most recently, regimens using ATRA and ATO are being evaluated, with promising results. When possible, after induction therapy, consolidation with ATO and 2 cycles of an anthracycline should be administered. Following this, maintenance therapy with ATRA combined with daily

low-dose 6-mercaptopurine and weekly oral methotrexate can be administered to reduce relapse.[90] Referral for alloHCT should be considered as salvage therapy in patients who relapse and achieve CR2.

Conclusions

There have been recent advances in understanding the molecular biology of acute leukemia. This has resulted in a more specific leukemia classification and guide for treatment. The future direction, using this knowledge, is to provide therapies targeted against specific leukemia molecular abnormalities and tailored for patients to achieve higher cure rates and long-term survival.

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