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EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Identify the four major groups of leukemia
- Describe two diagnostic procedures required when first evaluating a patient with leukemia.
- Identify two classes of drugs used in the treatment of leukemia

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Leukemia: Understanding its types and treatments

Donald R. Fleming, MD

STATEMENT OF NEED/PROGRAM OVERVIEW

The main types of leukemia that affect most patients with the disease are classified by four characteristics: acute vs chronic and myeloid vs lymphoid. Each type of leukemia and its treatment has unique symptoms and risks. Oncology nurses should be able to distinguish these symptoms and educate patients appropriately. Chemotherapeutic agents and treatment regimens for the leukemias have changed dramatically in the past decade. Nurses need to regularly update their knowledge and understanding of the latest advances in leukemia treatment.

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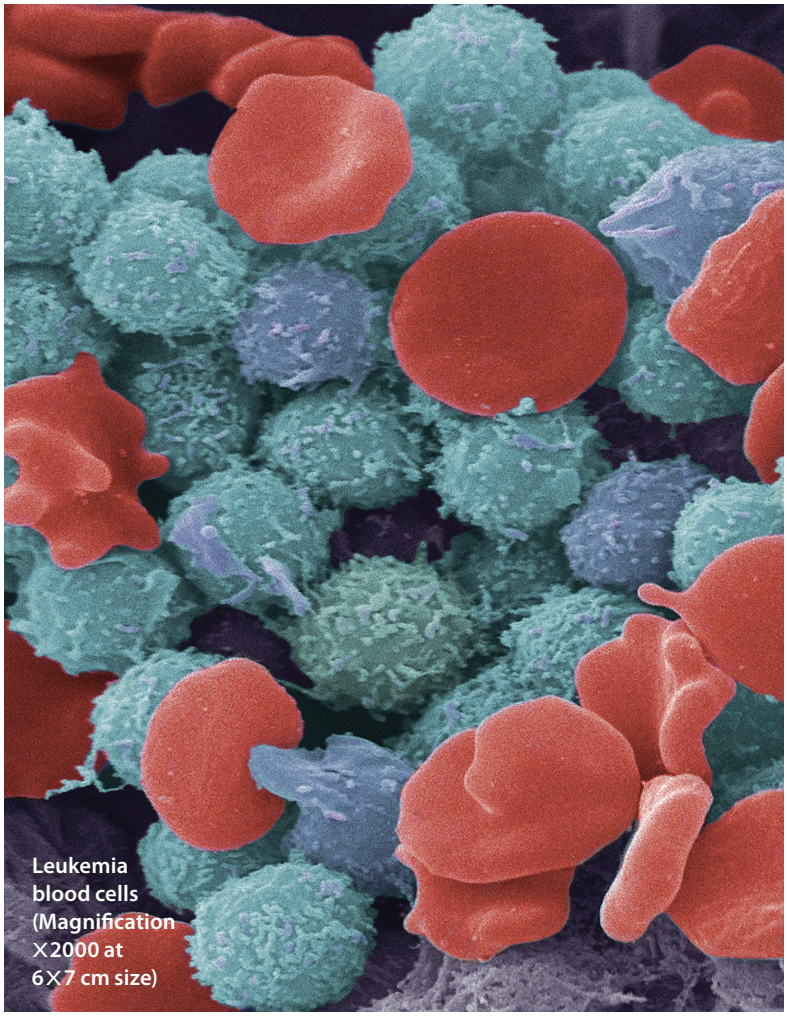
Leukemia: Understanding its types and treatments

This review describes the four major groups of leukemia, plus diagnostic tests and current and emerging treatment regimens for each group.



Leukemia blood cells (Magnification ×2000 at 6×7 cm size)

DONALD R. FLEMING, MD

Leukemia is a malignancy that develops in the bone marrow and affects hematopoiesis. It accounts for almost 10% of all malignancies diagnosed each year in the United States, with 40,000 to 50,000 new diagnoses annually.[1,2] Nearly half of patients with leukemia will die from the malady.[1,2] This review focuses on the four major classifications of leukemia with particular emphasis on acute versus chronic and myeloid-derived versus lymphoid-derived blood elements.

ACUTE LEUKEMIAS

Acute myelogenous leukemia (AML) The incidence of AML in the United States is approximately three cases per 100,000 persons.[1,3] The risk of developing AML increases with age, the same as with most nonhematologic malignancies. Frequently, patients will have no preexisting hematologic condition; however, patients who had myelodysplasia (formerly referred to as *preleukemia* and common in the elderly) have an increased risk of developing AML.[1-3] Exposure

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to previous chemotherapy (particularly alkylating agents), industrial chemicals, and radioactive material also increases this risk. Most cases of AML develop in adults, but children, particularly those born with genetic abnormalities such as Down syndrome, Bloom syndrome, or Fanconi anemia, are also susceptible to this disease.[3]

The signs and symptoms of AML manifest as a result of the disease's effect on normal blood cell production. While the bone marrow is overwhelmed with leukemic cell production, a corresponding decrease in normal platelets, red blood cells (RBCs), and leukocyte production increases the risk of bleeding, causing fatigue from anemia and infection due to neutropenia. Occasionally, bone pain can manifest due to cell turnover in the bone marrow. In addition to easy bruising caused by thrombocytopenia and pallor caused by anemia, some patients present with hepatosplenomegaly and lymphadenopathy, but this is rare in AML. Occasionally, patients can have central nervous system (CNS) involvement; however, this also is a rare situation and happens more often in patients with acute lymphoblastic leukemia (ALL).[4,5]

When AML is suspected, routine laboratory studies such as CBC are obtained, followed by a bone marrow biopsy. Lumbar puncture is performed to evaluate the spinal fluid for leukemic cells if CNS involvement is suspected.

AML is classified into several subtypes, identified as M0 through M8[2-3] (Table 1). AML classifications are based on levels of myeloid maturation, with M0 reflecting difficulty in delineating whether the disease is truly a myeloid-type versus lymphoid-type malignancy, as it lacks both myeloid and lymphoid markers. Some unique types such as M6, M7, and M8 are classified according to the erythroid, megakaryocyte, and basophilic series, respectively, involved in the malignancy. These subtypes are extremely rare.[1-3]

The most efficient, and currently most often used, method for identifying the type of acute myelogenous leukemia is flow cytometry. Cytogenetic tests can help identify the type of leukemia as well as determine prognosis in many cases, but it can take up to 2 weeks for test results to be obtained and may not be clinically practical patient management.[3] Fluorescence in-situ hybridization (FISH) can accelerate the evaluation process for nonrandom cytogenetic abnormalities, which represent mutations that are consistent enough to be identified with a particular malignancy.[2,3]

Acute myelomonocytic leukemia (M4 type, with both myeloid and monocytoid cell lineages and inversion of chromosome 16) is associated with a good prognosis. AML M2, associated with t(8;21) (translocation in chromosomes 8 and 21), also carries a good prognosis. Deletions in chromosomes 5 or 7 often occur in patients who had a preexisting myelodysplastic syndrome. In cases where there are no chromosomal abnormalities or chromosome 8 abnormalities, the prognosis is considered as intermediate risk.[2,3]

An important determination to make is whether the patient has M3 type (*acute promyelocytic leukemia* [APL]). This type has a very specific treatment associated with it. Due to a translocation in chromosomes 15 and 17, the chromosomal abnormality t(15;17), APL is uniquely responsive to the agent all-trans retinoic acid (tretinoin [Vesanoid]).[6,7] Prior to this product's use, patients often succumbed to disseminated intravascular coagulation (DIC) during induction chemotherapy. More recently, a very good outcome has been achieved when treating this leukemia with arsenic trioxide (Trisenox), an arsenic derivative.

APL treatment is unique due to its the molecular traits, whereas the approach for the remaining forms of AML is quite homogenous.[5,6] Not much has changed over the past two decades in regard to treatment methods for AML. The treatment regimen uses cytarabine (Ara-C; Cytosar-U, Depocyt) as a base combined with an anthracycline (daunorubicin or idarubicin [Idamycin PFS, generics]). The anthracycline used is based primarily on professional preference and clinical outcome. The usual cycle is cytarabine for 7 days and the anthracycline for 3 days; hence, it is referred to as the *7/3 regimen*.[8,9]

Clinical interest is increasingly toward foregoing the traditional regimen in older patients with AML in favor of using hypomethylating agents.

Typically, remission is achieved in more than half of patients who receive treatment for AML. This remission, however, is often short-lived unless consolidation treatment or, in cases in which high doses of cytarabine are administered, intensification is given. Usually a series of four to eight cycles of the previous medication, most often cytarabine, is administered and at higher doses to lengthen the duration of remission. Unfortunately, relapse eventually occurs in most patients and they succumb to their leukemia.[2,3,8] This is often due to limited treatment options, especially in older patients. If cytogenetic tests indicate an extremely poor prognosis or when relapse occurs, stem cell transplant from a histocompatible (HLA-matched) or a matched unrelated donor is considered. However, stem cell transplantation is not an option for many patients with AML because of their

age and comorbidities. It is generally reserved for relatively young and otherwise healthy patients.

Clinical interest is increasingly directed toward foregoing the traditional cytarabine/anthracycline regimen in older patients with AML in favor of using hypomethylating agents, which are often used to treat myelodysplastic syndromes. Decitabine (Dacogen) and azacitidine (Vidaza) have been used in these patients with similar success and less toxicity compared with more aggressive treatments used in younger patients.[2,9,10] Unfortunately, not many advances have been made in conventional therapies for AML. A previously available drug, gemtuzumab ozogamicin (Myelotarg), was discontinued because toxicity-related issues outweighed its benefits. This monoclonal antibody targeted CD-33-expressing myeloid precursors and was indicated for older patients after relapse. The drug was also very effective in relapsed APL.[7,11]

Acute lymphoblastic leukemia (ALL) Incidence of ALL is about half that of AML; the disease is diagnosed in approximately 1.5 per 100,000 people per year in the United States.[5] ALL, as in AML, is classified according to the maturation of the leukemic cells (ie, precursor vs acute mature lymphoblastic leukemia) and by the type of lymphocyte (B cell or T cell). An additional form is a unique biphenotypic (*mixed-type*) leukemia that has both myeloid and lymphoid markers present, which can make determining the optimal treatment difficult. Biphenotypic leukemia is often treated similar to AML.[1,12] Whereas AML is more prevalent in older persons, ALL occurs in younger age groups. Fortunately, outcomes are improved in this patient population. Risk factors for ALL often do not exist; however, as with AML, some relative increase in incidence can occur in a single family, giving some credence to a genetic predisposition.[4,5,13]

TABLE 1. WHO classifications for AML subtypes

Type	Name
M0	Minimally differentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia (t(8;21)(q22,q22))
M2	Acute myeloblastic leukemia (t(6;9))
M3	Acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
M4eo	Myelomonocytic leukemia with bone marrow eosinophilia
M5	• Acute monoblastic leukemia (M5a) • Acute monocytic leukemia (M5b)
M6	Acute erythroid leukemias, including —Erythroleukemia (M6a) —Very rare pure erythroid leukemia (M6b)
M7	Acute megakaryoblastic leukemia
M8	Acute basophilic leukemia

Key: AML, acute myeloid leukemia; t, translocation; WHO, World Health Organization.

Source: Acute myeloid leukemia classification. News-Medical.net Web site. http://www.news-medical.net/health/Acute-Myeloid-Leukemia-Classification.aspx. Accessed March 9, 2012.

ALL is treated similarly in most patients. The induction regimen involves a series of chemotherapeutic agents and may vary slightly according to institution protocols. The regimen used in the induction phase includes an anthracycline (such as daunorubicin), a vinca alkaloid (such as vincristine), and L-asparaginase (Elspar). Consolidation, as with AML, is achieved by adding cytarabine and etoposide to the induction regimen.[14-16] However, unlike AML, maintenance therapy often includes low doses of methotrexate, 6-mercaptopurine (6-MP), and glucocorticoids (such as prednisone). Typically, AML treatment is completed within 1 year; however, ALL treatment can easily continue for 2 to 3 years. The induction and consolidation therapies are administered for 6 months, and maintenance therapy is administered for up to 2 years. In addition, patients with ALL often need CNS prophylaxis, which involves methotrexate or cytarabine infusions directly into the spinal fluid, to prevent relapse in the CNS.[4,15]

A relatively rare form of ALL, previously known as L-3, and also referred to as Burkitt lymphoma in its lymphomatous presentation, has a completely different treatment approach. High doses of alkylating agents are utilized in a series very similar to the treatment regimen for aggressive non-Hodgkin lymphoma. Patients are often CD-20 positive and are treated with rituximab (Rituxan), a monoclonal antibody, in conjunction with high-dose alkylating agents such as anthracyclines, glucocorticoids, and vinca alkaloids.[4,5]

The prognosis for children with ALL is fairly good; however, outcomes for adult patients with ALL are not as optimistic, primarily due to cytogenetic abnormalities such as Philadelphia chromosome-positive ALL. Other chromosome abnormalities, such as those involving the fourth and 11th chromosomes, have a higher incidence in older patients and adversely affect patient prognosis.[5-16]

CHRONIC LEUKEMIA

Chronic myelogenous leukemia (CML) This form of leukemia is diagnosed in approximately two persons per 100,000 population.[17] CML is diagnosed often in persons aged 50 to 60 years; however, the disease can develop in persons at extreme variations in age. [17] Risk factors are uncertain but past exposure to radiation is believed to increase the risk. CML often manifests with symptoms very similar to acute

leukemia. A predominance of leukemic cells in the bone marrow often cause anemia and fatigue, but in contrast to AML, platelets are often elevated as CML has some features of a myeloproliferative disorder. The white blood cell count (WBC) is also typically elevated, just as you might see in a patient with AML, but with a very limited number of circulating myeloid cells or *myeloblasts*. The spleen may be enlarged, producing symptoms of early satiety and abdominal fullness due to occupation of space in the left upper quadrant of the abdomen.[18]

Most patients with CML present in the chronic phase. Occasionally, an accelerated phase develops whereby the number of circulating blast cells increases to almost 30% in the marrow, which is by definition acute leukemia. Platelet counts may be lower, and the patient may become more anemic and eventually enter the blast phase, typically defined as having at least 30% myeloid or lymphoid blasts in the bone marrow. This definition was recently reduced to 20%.

In the late 1990s, a major paradigm switch in the approach to this disease occurred based on the presence of the classic Philadelphia chromosome.

Unlike the acute leukemias, the prognosis for CML has changed abruptly in the last decade.[18,19] Prior to approximately 10 years ago, oral chemotherapy agents such hydroxyurea (Droxia, Hydrea, generics) or busulfan (Busulfex, Myleran) were used to control the disease hematologically without much focus on the degree of molecular remission. Alfa-interferon was used for a brief period; but in the late 1990s, a major paradigm switch in the approach to this disease occurred based on the presence of the classic Philadelphia chromosome abnormality, which is known as the BCR/ABL translocation with chromosomes 9 and 22. Unlike most malignancies, CML seems to have a very "lock and key" predominant mutation that drastically affects the disease process once altered.

The tyrosine kinase inhibitors (TKIs) have significantly improved outcomes for patients with this leukemia. Imatinib (Gleevec) received FDA approval in the late 1990s, and since then, two newer agents (dasatinib [Sprycel] and nilotinib [Tasigna]) were approved.[20-22] More than 90% of patients experience not only a hematologic remission, but also a molecular remission if treated with a TKI during the chronic phase. Bosutinib, another TKI, may offer additional therapeutic options with a more acceptable side effect profile.[23] Occasionally patients develop mutations in addition to t(9;22). The most treatment-refractory mutation is the T315I mutation; however, ponatinib, a recent possible newcomer to the treatment arsenal for CML, has addressed this issue.[24,25] Nevertheless, patients occasionally progress to accelerated, and even blast phases, and require stem cell transplantation. With the newer medications, this treatment is used less frequently.

Chronic lymphocytic leukemia (CLL) CLL is the most prevalent form of leukemia in the western hemisphere. Incidence approaches four per 100,000 population in the United States.[26] The patient ratio is approximately 2:1 male to female. CLL is associated with the older population, as the median age of patients is 72 years. However, some evidence indicates the median age has decreased to the late 60s. More frequent blood testing, including testing outside health care providers' offices such as at health fairs where CLL is often detected in asymptomatic persons, may contribute to earlier diagnosis.[26] Often this leukemia is indolent and does not require treatment, but patients occasionally present with symptomatic splenomegaly, lymphadenopathy, and more seriously, low-blood-count disorders such as anemia and thrombocytopenia. These features indicate more severe disease. The Rai or Binet classification systems are used to classify severity. The Rai system is used in the United States; stage 0 indicates a diagnosis of CLL and only a lymphocytosis. The disease is classified as Rai-1 and Rai-2 after the patient develops lymphadenopathy or splenomegaly, respectively.[26] Anemia and thrombocytopenia, classified as Rai-3 and Rai-4, respectively, indicate more severe disease; but, an important determination to make is that the condition is due to marrow involvement and not an autoimmune form of either condition. Autoimmune forms of anemia and thrombocytopenia have less severe prognoses and are often treated with corticosteroids alone to reduce the destruction of the red cells or platelets as opposed to directly treating the leukemia.[26]

As with other leukemias, CLL can be diagnosed via bone marrow biopsy. Many physicians forego this procedure, however, because the disease is readily diagnosed and managed with flow cytometry of peripheral blood. In addition, classification of disease is also achieved with this test. As with other forms of leukemia, cytogenetic tests can play an important role in determining the prognosis for these patients. Partial deletion of the 13th chromosome has been associated with a very benign disease course, whereas deletions in chromosome 11 and, even more severe, chromosome 17 (p53 mutation), indicates a very poor prognosis.

A duplication of the 12th chromosome (trisomy 12 abnormality), indicates an intermediate prognosis.[26]

Other prognostic features such as the absence of mutations in the variable heavy chain regions of the immunoglobulin-producing genes have been associated with a poor prognosis, whereas patients with mutations in this gene region have a better prognosis. Chromosome abnormalities can often be detected in the peripheral blood using the FISH technique.

Treatment options for CLL have changed quite drastically over the years. Prior to the 1990s, patients were treated with oral alkylating agents such as cyclophosphamide (Cytoxan, generics), often in conjunction with a glucocorticoid such as prednisone. Today, more intense treatments—combinations using purine analogues such as fludarabine (Fludara, Oforta, generics) or, more recently, bendamustine (Treanda), which is unique in that it may have some additional alkylating agent properties—are utilized, often in conjunction with the monoclonal antibody rituximab (Rituxan), because these tumors typically express CD-20.[27-29]

With the exception of those patients with p53 mutation, CLL often goes into remission. Patients with chromosome 13 deletion abnormality are seldom treated. These patients are the eldest elderly and are not aggressively treated. Patients are often not treated until they become symptomatic or in later stages of disease such as Rai-3 and Rai-4.[26,29,30]

Despite the very effective treatments for this disorder, patients frequently experience a series of relapses and require repeat treatments. This can result in a decrease in their functional performance status. It is therefore important to consider comorbidities and the patient's performance status when designing treatment.

Despite the effective treatments for CLL, patients frequently experience a series of relapses and require repeat treatments.

Treatments for CLL have progressively drifted from cytotoxic chemotherapeutic approaches to biologic therapies. Other monoclonal antibodies such as the humanized form of anti CD-20 monoclonal antibody ofatumumab (Arzerra), and the anti-CD 52, alemtuzumab (Campath) have been used. Alemtuzumab may be especially helpful in the resistant chromosome 17 deletion forms of CLL.[26,28-30] A diversely applied medication for hematologic malignancies is lenalidomide (Revlimid), an immunomodulatory agent with efficacy in numerous refractory lymphoproliferative disorders, including refractory CLL.[31] Biologic agents such as Bruton tyrosine kinase inhibitors and PI3K inhibitors are effective in cases of refractory CLL with very limited side effects. Nevertheless, patients experience repeated relapses with this disorder and eventually succumb to infections resulting from the effects of treatment on the immune system, as well as from the disease.[32,33]

CONCLUSION

Classification of the leukemias is based on four characteristics: acute or chronic condition and myeloid- or lymphoid-derived disease. A significant majority of patients with leukemia have one of these types. Treatment approaches to the acute leukemias have limited success. However, major changes in the treatment approaches for the chronic leukemias, especially CML, have dramatically improved outcomes for patients with these diseases. Hopefully, further research and clinical investigation will generate similar treatment advances for patients with the acute leukemias. ■

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