Abbreviations

# ADULT ACUTE LEUKEMIAS

Helen Wu, Pharm.D., BCOP

Reviewed by Joseph Bubalo, Pharm.D., BCPS, BCOP; and R. Chris Rathbun, Pharm.D., BCPS With Added Qualifications in Infectious Diseases

## Learning Objectives

1. Analyze a patient's case with the knowledge of pathophysiology, etiology and prognostic factors for acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL).
2. Given a patient's case, demonstrate how the patient's symptoms are associated with acute leukemias.
3. Develop a treatment plan for a patient with ALL based on patient-specific factors, such as disease classification, comorbidity, cytogenetics, and age.
4. Design a treatment plan for a patient with AML based on patient-specific factors, such as disease classification, comorbidity, cytogenetics, and age.
5. Evaluate the treatment response for a patient with ALL.
6. Assess the treatment response for a patient with AML.
7. Formulate monitoring plans for chemotherapy-related toxicities for both ALL and AML treatments.

## Introduction

Normal blood and bone marrow cells, being polyclonal, are heterogenous. The hematopoietic stem cells have the property of self-renewal, cell division, and differentiation. The stem cells are committed to the two main cell lines, myeloid and lymphoid. Leukemias are malignancies of hematopoietic stem cells in the bone marrow. Leukemia occurs when a monoclonal population is derived from a single hematopoietic stem cell. Leukemic cells demonstrate a growth advantage over normal cells either as a consequence of excess proliferation of a particular monoclonal population, apoptotic failure during the cell renewal process, or both.

In acute leukemia, clonal cells usually arrest at the level of myeloid or lymphoid lineage-committed progenitor cells called "blasts." As blasts build up in the bone marrow, they crowd out normal hematopoietic cells and cause bone marrow failure. This phenomenon is a hallmark feature of acute leukemia. Patients often present with "pancytopenia," which manifests as neutropenia, anemia, and thrombocytopenia. Patients with acute leukemia have high, normal, or low white blood cell counts, with or without circulating blasts in the blood. A normal bone marrow has less than 5% blasts. According to the World Health Organization classification, acute leukemia is present when greater than 20% myeloblasts (acute myeloid leukemia [AML]) or greater than 25% lymphoblasts (acute lymphocytic leukemia [ALL]) are present in the blood and bone marrow. Without treatment, patients with acute leukemias can die within weeks to months.

Most acute leukemias are idiopathic (*de novo*). Some are secondary to known mutagenic exposures (alkylating agents, organic aromatic compounds, or ionizing radiation), antecedent hematologic disorders (myelodysplasia, aplastic anemia, or myeloproliferative syndromes), or congenital predispositions (Down syndrome, Fanconi's Anemia, or monosomy 7).

There are two types of acute leukemias, myeloid and lymphoid. Myeloid leukemias are derived from the myeloid stem cells, which normally give rise to the myeloid cells (red blood cells, neutrophils, monocytes/macrophages, megakaryocytes/platelets, eosinophils, and basophils). Lymphoid leukemias are derived from the lymphoid stem cells, which normally give rise to the lymphocytes (B-cells, plasma cells, T-cells, natural killer cells, and dendritic cells). A variety of laboratory tests are performed to distinguish myeloid from lymphoid leukemia. Morphology is useful and basic. In AML, myeloid blasts tend to have multiple

Scheinberg DA, Maslak P. Weiss M. Acute leukemias. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:2404–32.

## Abbreviations in this Chapter

| | |
|---|---|
| ALL | Acute lymphocytic leukemia |
| Allo-SCT | Allogeneic hematopoietic stem cell transplantation |
| AML | Acute myeloid leukemia |
| APML | Acute promyelocytic leukemia |
| Ara-C | Cytarabine |
| ASCT | Autologous hematopoietic stem cell transplantation |
| ATRA | All-*trans* retinoic acid |
| CR | Complete remission |
| CVAD | Cyclophosphamide, vincristine, doxorubicin, and dexamethasone |
| FAB | French-American-British |
| HLA | Human leukocyte antigen |
| HiDAC | High-dose Ara-C |
| MTX | Methotrexate |
| Ph(+) | Philadelphia chromosome positive |

distinct nucleoli, more cytoplasm, and granularity in the cytoplasm. About 20% of the blast cells have needle-like cytoplasmic inclusions called Auer rods. The presence of Auer rods always means AML, but the absence of rods does not exclude AML. In ALL, lymphoid blasts tend to have indistinct nucleoli and have scant, agranular cytoplasm. Specific enzymes may be present in the lymphoid blast cells. Table 1-1 presents the distinctive features of AML and ALL. Immunophenotyping uses monoclonal antibodies to detect cell surface lineage-specific antigens by flow cytometry. Immunophenotyping identifies the cell type contributing to a patient's leukemia. Cytogenetics is a gross assessment of chromosomal changes. Some chromosome changes are myeloid-specific, some are lymphoid-specific, and some are lineage-nonspecific. However, the majority of leukemias have no detectable chromosome alterations, and therefore cytogenetic analysis is not useful for distinguishing myeloid from lymphoid.

# Acute Myelogenous Leukemias

The term "myeloid" means "pertaining to the bone." Myeloid leukemia may involve leukemia of the granulocytes, monocytes, erythrocytes, and platelets. The basic therapeutic approach to patients with AML has changed little during the past 20 years. The two major prognostic factors in newly diagnosed AML, patient age and chromosome status, form the basis of treatment decisions.

### Pathophysiology

#### Epidemiology

Acute myeloid leukemia, which accounts for 80% of adult acute leukemia, is a disease of older adults. In the United States, the median age of newly diagnosed AML is 68 years. The age-adjusted population incidence is 17.6 cases per 100,000 per year for people 65 years of age or older compared with an incidence of 1.8 cases per 100,000 per year for people younger than 65. It is estimated that 11,960 patients would be newly diagnosed with AML in the United States in 2005, and that about 9000 deaths would be attributed to AML.

#### Etiology

Most AML is idiopathic (*de novo*). Secondary AML occurs in patients with prior hematologic disorders such as aplastic anemia, myeloproliferative disorders, (chronic myeloid leukemia, myelofibrosis, polycythemia vera, essential thrombocytosis), myelodysplastic syndrome, or in patients with prior mutagenic exposure. Mutagenic exposure can include chemotherapy, ionizing radiation, and organic solvents. Anticancer drugs are the leading cause of treatment-associated AML. Alkylating agent-associated leukemias occur on average 4–6 years after exposure, and affected individuals have aberrations of chromosomes 5 and 7. Topoisomerase II inhibitor-associated leukemias occur 1–3 years after exposure, and affected individuals often have aberrations involving chromosome 11q23. Chloramphenicol and phenylbutazone can result in bone marrow failure that can evolve into AML. *De novo* AML has a much better prognosis than secondary AML.

#### Clinical Presentation

Acute myeloid leukemia develops and progresses quickly. Most patients are usually asymptomatic until several weeks before the diagnosis is made. Patients with AML have signs or symptoms of anemia (e.g., fatigue, shortness of breath, pallor, tachycardia, and tachypnea), thrombocytopenia (e.g., epistaxis, gingival bleeding, petechiae), neutropenia (resulting in bacterial or fungal infections), and/or leukocytosis (e.g., elevated white blood count, shortness of breath, and altered cognition). Meningeal involvement with AML can cause asymmetric cranial nerve abnormalities. Acute myeloid leukemia can metastasize to the skin and manifest as purplish subcutaneous nodules.

#### Laboratory Examination and Diagnosis

In patients with AML, the complete blood cell count shows pancytopenia or leukocytosis. A bone marrow biopsy is required for diagnosis. The blood and/or bone marrow must show greater than 20% blasts. Cytogenetic analysis should be performed with the initial bone marrow biopsy because chromosome alterations offer important prognostic information and often dictate treatment decisions.

Stone RM, O'Donnell MR, Sekeres MA. Acute myeloid leukemia. Hematology (Am Soc Hematol Educ Program) 2004:98–117. Review.

American Cancer Society. Cancer Facts and Figures 2005. Available at *www.cancer.org/docroot/STT/stt_0.asp*. Accessed January 9, 2006.

Mauritzson N, Albin M, Rylander L, et al. Pooled analysis of clinical and cytogenetic features in treatment-related and *de novo* adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976–1993 and on 5098 unselected cases reported in the literature 1974–2001. Leukemia 2002;16(12):2366–78.

**Abbreviations**

**Table 1-1. Laboratory Tests Used to Distinguish Myeloid From Lymphoid Leukemias**

| | Myeloid | Lymphoid |
|---|---|---|
| Morphology | Auer rods in cytoplasm (in 20% of blast cells) | |
| Cytochemical phenotyping | Myeloperoxidase (granulocytes)<br>Non-specific esterase (monocytes) | |
| Immunophenotyping | CD13/33<br>CD 14 (monocytes)<br>CD 61 (megakaryocyte)<br>Glycophorin (erythrocytes) | TdT<br>CD19, 19 (B-cell)<br>CD 2, 3, 5, 7 (T-cell) |
| Cytogenetics | Myeloid-specific abnormalities | Lymphoid-specific abnormalities |

AML = acute myeloid leukemia; TdT = terminal deoxynucleotidyl transferase.

### Prognosis

Several features at diagnosis are prognostic in AML. The strongest prognostic tool is cytogenetic analysis for chromosome status. The human somatic cell contains 23 pairs of chromosomes. The letters "p" and "q" are used to refer to the short and long arms of the chromosomes, respectively; translocations are indicated by "t," followed by the chromosome bands involved in a set of parentheses. "Inv" indicates an inversion, "ins" is an insertion, and "del" is a deletion. Cytogenetic abnormalities that indicate a good prognosis for AML include t(8,21), inv16, and t(15,17). Deletions of the long arms or monosomies of chromosomes 5 or 7, translocations or inversions of chromosome 3, t(6,9), t(9,22) or abnormalities of chromosome 11q23 signify a poor prognosis. Younger age (younger than 60 years old) is a favorable prognostic factor. Normal cytogenetic results are neither a poor prognostic nor a favorable prognostic factor for patients with AML.

### Classification

The French-American-British (FAB) classification has been widely adopted and has promoted uniformity of diagnosis of morphologic subtypes of AML. The classification is useful in identifying certain biologic subtypes but does not account for all subtypes. The evolution of the classification system in AML from morphology to a cytogenetic-based system reflects the recognition of the importance of subtype-specific biology Table 1-2.

## Quality Pharmaceutical Care of Acute Myeloid Leukemia

### Treatment Overview

The goal of treatment is to obtain remission to prolong survival (by 1–3 years). In general, only patients with *de novo* AML who are under 60 years of age are potentially curable with chemotherapy alone. Patients with secondary AML have a lower remission rate than patients with *de novo* AML, but can only be cured with an allogeneic hematopoietic stem cell transplantation (allo-SCT) whereby donor allo-reactive T-cells recognize and destroy primitive host leukemic cells (graft versus leukemia effects). The allo-SCT is also performed in patients younger than age 60 with *de novo* acute leukemia and poor cytogenetics as this increases the cure rate. The leukemia-free survival in patients older than age 60 is under 5%, so the goal of therapy in this age group is palliation, not cure.

Treatment modalities of AML include cytotoxic chemotherapy, autologous hematopoietic stem cell transplantation (ASCT), and allo-SCT. Cytotoxic chemotherapy produces a 3–5 log reduction in acute leukemia cells and is usually delivered over 6–7 days. This therapy results in bone marrow aplasia for about 2–3 weeks during which time patients must be supported with antibiotic drugs and red blood cell and platelet transfusions. Recombinant growth factors (filgrastim or sargramostim) can help speed neutrophil recovery.

Autologous hematopoietic stem cell transplantation can be thought of as super-chemotherapy. Patients must be in complete remission to receive ASCT. Autologous hematopoietic stem cells are mobilized into the blood stream with colony-stimulating factors with or without chemotherapy. Peripheral blood stem cells are collected using leukapheresis and frozen in liquid nitrogen with dimethylsulfoxide as a cell protectant. Myeloablative therapy is delivered, and patients are then "rescued" by re-infusion of the previously collected autologous peripheral blood stem cells. Engraftment takes 10–14 days. Many hematologists consider ASCT superior to conventional chemotherapy for patients with good prognostic factors.

Allogeneic hematopoietic stem cell transplantation involves both myeloablative therapy and immunotherapy. Hematopoietic stem cells are mobilized in the donor's blood with growth factors and collected using leukapheresis. These fresh donor hematopoietic stem cells are infused intravenously into the patient following myeloablative therapy. Engraftment takes about 14 days. Alloreactive donor T-cells may recognize human leukocyte antigen (HLA) discrepancies in the recipient, setting off an immune response against the recipient. This response is primarily in the recipient's oral or gastrointestinal mucosa, skin, and/or liver, and is called graft-versus-host disease, which can be fatal. To minimize graft-versus-host disease, the patient and donor need to be a complete or nearly complete (11/12 or 12/12) HLA match and preferably be siblings. Patients with moderate to severe graft-versus-host disease have a lower incidence of leukemia relapse than those with none or mild because of the concurrence of the graft-versus-leukemia effect.

### Treatment Plan

#### *Induction Therapy*

The goal of induction chemotherapy is to achieve complete remission (CR). A CR is defined as neutrophils greater than 1 x $10^9$ cells/L in the peripheral blood, less than 5% bone marrow blasts and normal cytogenetics. Chemotherapy is given to "empty" the bone marrow of all hematopoietic cells (both benign and malignant) and to

## Abbreviations

**Table 1-2. French-American-British (FAB) Classification of Acute Myeloid Leukemia**

| FAB | Common Name | Cytogenetic Associations | Clinical Characteristics | Prognosis |
|---|---|---|---|---|
| M0 | Acute myeloid leukemia, minimally differentiated | inv(3q26), t(3;3) | | |
| M1 | Acute myeloblastic leukemia without maturation | | | |
| M2 | Acute myeloblastic leukemia with maturation | t(8,21) | Myeloblastomas or chloromas | Good |
| M3 | Acute promyelocytic leukemia | t(15,17) | Disseminated intravascular coagulation | Good |
| M4 | Acute myelomonoblastic leukemia | 11q23, inv3, t(3,3), t(6,9) | Hyperleukocytosis<br>CNS involvement<br>Skin and gum infiltration | |
| M4Eo | Acute myelomonoblastic leukemia with abnormal eosinophils | inv16 | | Good |
| M5 | Acute monoblastic leukemia | 11q23, t(9,11) t(8,16) | Hyperleukocytosis<br>CNS involvement<br>Skin and gum infiltration | Poor |
| M6 | Erythroleukemia | del5, del7 | | Poor |
| M7 | Acute megakaryoblastic leukemia | t(1,22) | Down syndrome | Poor |

CNS = central nervous system.
National Cancer Institute. Available at *www.cancer.gov/cancertopics/pdq/treatment/adultAML/healthprofessional* and *www.cancer.gov/cancertopics/pdq/treatment/adultALL/healthprofessional*. Accessed March 13, 2006.

allow the marrow to repopulate with normal cells, thereby yielding remission.

The most commonly used regimen for induction chemotherapy is combination therapy of cytarabine (Ara-C) plus an anthracycline. Daunorubicin 45–60 mg/m$^2$/day as an intravenous bolus for 3 days, and Ara-C 100 mg/m$^2$/day by continuous intravenous infusion for 7 days are administered. This regimen is known as the "7+3" regimen, and is one of the most successful induction treatments for AML. Idarubicin appears to be more effective than daunorubicin, although the doses of idarubicin and daunorubicin may not have been equivalent. In general, there is no significant difference in CR rate among regimens using daunorubicin, idarubicin or mitoxantrone. Higher doses of Ara-C of 200 mg/m$^2$/day for 7 days have also shown a similar CR rate compared with 100 mg/m$^2$/day for 7 days. The CR rate is about 65% across different studies.

Because Ara-C is one of the most active drugs for the treatment of AML, high-dose Ara-C (HiDAC) has been studied for AML induction. High-dose Ara-C has been studied given as 2 g/m$^2$/dose every 12 hours for 12 doses, or 3 g/m$^2$/dose every 12 hours for eight doses on alternate days, together with an anthracycline. The results have shown CR rates similar to the "7+3" regimen. However, a longer duration of CR and longer disease-free survival were reported among patients receiving HiDAC therapy as induction or consolidation. Nevertheless, HiDAC therapy was associated with increased hematological and more toxicity, including such as worse nausea, emesis, and ophthalmologic toxicity. Patients receiving HiDAC are predisposed to cerebellar toxicity, especially if they have renal dysfunction.

Adding drugs to the Ara-C and anthracycline combination for induction therapy has also been studied. One study showed that adding etoposide 75 mg/m$^2$/day for 7 days to the "7+3" regimen improved CR duration and survival in patients younger than 55 years of age. Older patients experienced significantly more toxicity with no benefit in outcome. However, in younger patients, intensified induction may improve CR duration and overall survival without necessarily improving the CR rate.


Rai KR, Holland JF, Glidewell OJ, et al. Treatment of acute myelocytic leukemia: a study by cancer and leukemia group B. Blood 1981;58(6):1203–12.

Wiernik PH, Banks PL, Case DC Jr, et al. Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. Blood 1992;79(2):313–9.

Dillman RO, Davis RB, Green MR, et al. A comparative study of two different doses of cytarabine for acute myeloid leukemia: a phase III trial of Cancer and Leukemia Group B. Blood 1991;78(10):2520–6.

Bishop JF, Matthews JP, Young GA, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood 1996;87(5):1710–7.

Bishop JF, Lowenthal RM, Joshua D, et al. Etoposide in acute nonlymphocytic leukemia. Australian Leukemia Study Group. Blood 1990;75:27–32.

### *Assessment of Treatment Response*

A complete blood cell count and bone marrow biopsy are used to assess treatment response. About 60%–70% of patients achieve CR after receiving induction chemotherapy. Remission rates are inversely related to age. Increased morbidity and mortality during induction therapy appear to be directly related to age. Duration of CR may be shorter in older patients. Long-term disease-free survival occurs in only 20%–30% of patients who achieve CR. The majority of patients with AML still die of their disease. Patients aged 55 or older showed a much lower disease-free survival rate than patients younger than 55 years of age. Among patients younger than age 55, both disease-free survival and overall survival increase with more intensive post-remission strategies. More chemotherapy may be given if a day 14 (i.e., 14 days from the first dose of chemotherapy) bone marrow biopsy shows residual disease.

### *Post-Remission Therapy*

Once remission is achieved, additional therapy is required to eradicate remaining leukemia cells so that long-term disease-free survival (i.e., cure) might be possible. Postremission therapy will prolong remission in most patients and is indicated for patients with potentially curable AML. Current approaches to post-remission therapy include consolidation chemotherapy, high-dose chemotherapy rescue with ASCT, and allo-SCT.

Consolidation chemotherapy usually includes HiDAC alone or in combination with one or more drugs, such as mitoxantrone, daunorubicin, or etoposide. Consolidation chemotherapy using HiDAC-containing regimens has yielded disease-free survival rates from 20% to 50%. In a large randomized study published in 1994, three different Ara-C-containing consolidation regimens showed a benefit in survival to patients younger than age 60 who received HiDAC. Three treatment regimens were studied: Ara-C 100 mg/m$^2$/day continuous intravenous infusion for 5 days, 400 mg/m$^2$/day continuous intravenous infusion for 5 days, and 3 g/m$^2$/dose as a 3-hour intravenous infusion 2 times/day on days 1, 3, and 5. The disease-free survival rate was 21% in the 100-mg arm, 25% in the 400-mg arm, and 39% in the 3-g HiDAC arm. Results were most significant in patients with favorable cytogenetics. However, high rates of central nervous system toxicity were observed in patients older than age 60 randomized to the high-dose regimen.

Another commonly used consolidation chemotherapy regimen includes 1–3 cycles of conventional dosing Ara-C 100 mg/m$^2$/day continuous intravenous infusion for 5 days plus daunorubicin 45–60 mg/m$^2$/day for 2 days for 1–3 cycles (the "5+2" regimen). The "5+2" regimen yielded only 15%–20% survival; therefore, younger patients generally are treated with more aggressive therapy. Intensification of Ara-C dose or duration of consolidation chemotherapy with conventional dose Ara-C did not improve disease-free survival or overall survival in patients age 60 or older. The duration of consolidation chemotherapy has ranged from one cycle to four or more cycles. The optimal doses, schedules, and duration of consolidation chemotherapy have not been determined.

Autologous stem cell transplantation is an important treatment modality for AML. In the earlier days, bone marrow cells were used instead of peripheral stem cells. Phase II and III studies demonstrated that patients with favorable-risk cytogenetics benefited from ASCT, with reduction in relapse and improvement in disease-free survival. Patients with poor-risk cytogenetics do not appear to benefit significantly from ASCT and should preferentially be treated with allo-SCT. Many Phase II studies of ASCT for AML in patients who achieved their first CR have shown an overall disease-free survival range of 40%–60% and treatment-related mortality of 5%–15%. Phase III trials have shown similar results of disease-free survival of 35%–54% with ASCT compared with the parallel chemotherapy arm of 30%–40%. The preparative regimen used in ASCT can include total body irradiation plus cyclophosphamide, busulfan plus cyclophosphamide, or busulfan plus etoposide. Autologous stem cell transplantation involves the administration of high chemotherapy doses, but it is limited by the lack of the graft-versus-leukemia effect associated with allogeneic transplantation. Furthermore, there is a theoretical risk of infusion of occult residual leukemic cells. It is generally an option for patients with favorable-risk cytogenetics in their first or second CR. The optimal amount and type of consolidation therapy before ASCT remains to be determined; however, several studies have suggested patients who received greater than or equal to two courses of consolidation therapy had longer disease-free survival.

Allogeneic hematopoietic stem cell transplantation is the primary treatment modality for patients with leukemia who are younger than 60 years old failing induction therapy, patients with *de novo* AML who have poor cytogenetics, or secondary acute leukemia. In poor-risk patients, disease-free survival is 20%–40% with allo-SCT. The poor-risk group is unlikely to be cured with consolidation chemotherapy, and allo-SCT in first CR is a reasonable option for patients with an HLA-identical sibling donor. Allogeneic hematopoietic stem cell transplantation results in the lowest incidence of leukemia relapse. Disease-free survival rates using allo-SCT as primary post-remission therapy is limited by the need for an HLA-matched donor and the mortality from allo-SCT. The mortality from allo-SCT that uses an HLA-matched sibling donor ranges from 20% to 40%. Nevertheless, in high-risk patients with AML, the outcome is poor even with allo-SCT; 5-year disease-free survival ranges from 8% to 30% for patients with secondary AML or myelodysplasia.

### *Therapeutic Considerations*

Older patients (older than 60 years) do not tolerate intensive HiDAC chemotherapy as well as younger patients, which may be due to concomitant diseases and compromised organ function. In addition, older adults with AML usually have poor prognostic factors. Leukemic cells in older patients often express the multiresistant-drug

Mayer RJ, Davis RB, Schiffer CA, et al. Intensive post-remission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. N Engl J Med 1994;331(14):896–903.

Linker CA. Autologous stem cell transplantation for acute myeloid leukemia. Bone Marrow Transplant 2003;31(9):731–8.

marker, which renders their cells more resistant to chemotherapy. Intensive chemotherapy yields a better CR rate than low-dose Ara-C; the CR duration and event-free survival are relatively short (months). Therefore, when selecting chemotherapy for this age group, a less intensive regimen should be considered to diminish the impact on quality of life.

The overall survival rate for allo-SCT and ASCT is not different due to higher relapse rates with ASCT and higher treatment mortality rates with allo-SCT. In consideration for quality of life issues, allo-SCT is usually reserved for patients with poor risk factors, relapsed disease, or secondary leukemia.

### Recurrent AML

Many drugs are useful in treating recurrent AML. A study with mitoxantrone and Ara-C was successful in 50%–60% of patients who experienced relapse after initially obtaining CR. Other studies using idarubicin and cytarabine or high-dose etoposide and cyclophosphamide reported similar results. To avoid the toxic effect of retreatments, allo-SCT can be considered in treating early first relapse after re-induction therapy. Allogeneic hematopoietic stem cell transplantation can be used to treat some patients whose disease fails to go into remission with intensive chemotherapy.

Because of the inability of older patients to tolerate more intensive chemotherapy, a less toxic therapy would be preferred. Antibody-targeted chemotherapy is expected to be less toxic than conventional chemotherapy and has been developed for the treatment of CD33-positive AML. The immunotoxin gemtuzumab ozogamicin has been reported to have a 30% response rate in patients with relapsed AML expressing CD33. Although gemtuzumab ozogamicin is considered less intensive than most re-induction chemotherapy regimens, it can still induce profound bone marrow aplasia and it also has substantial hepatic toxic effects, including hepatic venoocclusive disease.

### Acute Promyelocytic Leukemia

Tretinoin (all-*trans* retinoic acid [ATRA]) is approved in the United States for use in treating acute promyelocytic leukemia (APML). Acute promyelocytic leukemia is associated with t(15,17), where the promyelocyte leukemia gene on chromosome 15 is juxtaposed to the retinoic acid-alpha receptor gene on chromosome 17. Tretinoin binds to the chimeric gene product of this translocation and causes the leukemic clone to mature and undergo apoptosis. Patients with APML have bleeding tendencies due to the release of cytoplasmic granules into the blood causing disseminated intravascular coagulation. Tretinoin added to chemotherapy reduces disseminated intravascular coagulation and increases the CR rate to 80% and leukemia-free survival to 70% compared with conventional dose chemotherapy alone. A combination of tretinoin and anthracyclines cures about 70% of adult patients with APML. However, tretinoin can cause significant toxicities, including hyperleukocytosis and the "retinoic acid syndrome" or "ATRA syndrome." The ATRA syndrome may include fever, dyspnea, pleural effusions, pulmonary capillary leak, and peripheral edema. If ATRA syndrome develops, dexamethasone 10 mg 2 times/day for at least 3 days should be initiated and ATRA discontinued. Tretinoin also causes dryness of the lining of the mouth and skin, and skin rash. Headache is another common side effect with tretinoin. Close monitoring for ATRA syndrome and other side effects is required while patients receive tretinoin therapy.

Arsenic trioxide, an agent with both differentiation-inducing and apoptosis-inducing properties against APML cells, has a high rate of successful remission induction in patients with relapsed APML. Daily arsenic trioxide administration yields a CR rate of 85%, with a median time to CR of 59 days. Actuarial 18-month relapse-free survival was 56%. Induction with arsenic trioxide may be complicated by APML differentiation syndrome (similar to ATRA syndrome), prolongation of QT interval, and neuropathy.

# Acute Lymphocytic Leukemia

## Pathophysiology

Acute lymphocytic leukemia is a malignant disorder resulting from the clonal proliferation of lymphoid precursors. The disease can originate in lymphoid cells of

Paciucci PA, Dutcher JP, Cuttner J, et al. Mitoxantrone and ara-C in previously treated patients with acute myelogenous leukemia. Leukemia 1987;1:565–7.

Sievers EL, Larson RA, Stadtmauer EA, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. J Clin Oncol 2001;19(13):3244–54.

Larson RA, Boogaerts M, Estey E, et al. Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). Leukemia 2002;16(9):1627–36.

Mandelli F, Diverio D, Avvisati G, et al. Molecular remission in PML/RAR alpha-positive acute promyelocytic leukemia by combined all-*trans* retinoic acid and idarubicin (AIDA) therapy. Gruppo Italiano-Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed Oncologia Pediatrica Cooperative Groups. Blood 1997;90(3):1014–21.

Tallman MS, Andersen JW, Schiffer CA, et al. All-*trans* retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. Blood 2002;100(13):4298–302.

De Botton S, Dombret H, Sanz M, et al. Incidence, clinical features, and outcomes of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood 1998;92(8):2712–8.

Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol 2001;19(18):3852–60.

Shen ZX, Chen GQ, Ni JH, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood 1997;89(9):3354–60.

different lineages, thus giving rise to B-cell or T-cell leukemias, or sometimes to mixed-lineage leukemia.

### Epidemiology

Adult lymphocytic leukemia is rare, with just 1.6 cases per 100,000 individuals per year in the United States. Adult lymphocytic leukemia accounts for about 20% of adult acute leukemia. The estimated number of new cases in 2005 is 3970, with an estimated 1490 deaths.

### Etiology

Unlike AML, virtually all ALL is *de novo*. Prior mutagenic exposures or prior hematologic disorders do not predispose to ALL. The one notable exception is chronic myeloid leukemia, which can transform into ALL. Patients with ALL that arises from chronic myeloid leukemia need an allo-SCT to obtain a cure.

### Clinical Presentation

Adult lymphocytic leukemia develops and progresses quickly. Most patients are usually asymptomatic until several weeks before the diagnosis is made. Patients with ALL and patients with AML have similar clinical presentations with the exception that there is a much greater chance that ALL cells will involve the meninges and testicles (chemotherapy sanctuary sites) compared with AML. Like patients with AML, patients with ALL often present with symptoms of anemia, thrombocytopenia, neutropenia and/or leukocytosis. Skin involvement with ALL is rare. Lymphadenopathy is found in up to 80% of patients with ALL, and hepatomegaly or splenomegaly in up to 75% of those patients.

### Laboratory Examination and Diagnosis

A bone marrow biopsy is required for diagnosis. Cytogenetic analysis should also be sent for determining prognosis and appropriate treatment. Acute lymphocytic leukemia is defined as an abnormal bone marrow with greater than 5% clonal lymphoid blasts. Patients present with various abnormalities in white blood cells and differential, abnormal hematocrit and platelet counts. The total white blood cell count is greater than 10 x $10^9$ cells/L in 50%–60% of patients with ALL at diagnosis, and greater than 100 x $10^9$ cells/L in 10%; 30%–40% have total white blood cell counts less than 10 x $10^9$ cells/L. Absolute neutrophil counts are usually low. Despite high white blood cell count, symptoms of hyperleukocytosis are seldom observed. More than 90% of patients present with thrombocytopenia. Anemia is nearly universal in patients with ALL. The bone marrow is commonly hypercellular; rarely, it is hypoplastic or aplastic.

### Classification

Acute lymphocytic leukemic cells have been categorized based on morphologic characteristics by the FAB classification system. Using this system, lymphoid malignancies of small uniform blasts (e.g., typical childhood ALL) are called L1, larger and more variable size cells are designated L2, cells with basophilic and sometimes vacuolated cytoplasm are called L3 (e.g., typical Burkitt's lymphoma cells). Acute lymphocytic leukemic cells have also been categorized based on immunologic (i.e., T-cell or B-cell) and cytogenetic abnormalities. Major cytogenetic subgroups include the t(9,22) (e.g., Philadelphia chromosome-positive [Ph(+)]) and the t(8,14) found in the L3 or Burkitt's leukemia.

### Prognosis

The strongest prognostic feature for ALL is cytogenetics, followed by age. Childhood ALL has a higher cure rate than adult ALL. Patients with hyperploid ALL, particularly those with more than 50 chromosomes, have the best prognosis. The favorable outcome in patients with hyperploidy may be due to an increased sensitivity to drugs. Hyperploidy is present in about 10%–20% of adult patients with ALL. The Philadelphia chromosome, t(9,22), is present in more than 30% of adult patients with ALL. Philadelphia chromosome positive-ALL is associated with older age, high leukocyte counts, and L2 morphologic type. It is associated with a higher frequency of expression of CD10 and CD34. Nearly 50% of patients with Ph(+) ALL may have additional chromosomal abnormalities, particularly monosomy 7. Positivity for the Philadelphia chromosome is a poor prognostic factor. Patients with Ph(+) ALL have significantly lower rates of CR (50%–70%) and of long-term disease-free survival (less than 10%). Another poor prognosis factor is t(4,11). In addition to t(9,22) and t(4,11), patients with deletion or ablation of chromosome 7 have been reported to have a lower probability of survival at 5 years compared with patients with a normal karyotype.

## Quality Pharmaceutical Care of Acute Lymphocytic Leukemia

### Treatment Overview

The four components to therapy are remission induction, consolidation/intensification, maintenance, and central nervous system prophylaxis. The average length of treatment of ALL ranges from 1.5 to 3 years. The primary goal of induction treatment is to achieve CR; once CR is achieved, therapy must be continued for an extended period to eliminate subclinical disease to prevent relapse. Treatment strategies are based on risk factors. Patients with no poor prognostic factors can be treated with chemotherapy alone. For patients with poor prognostic factors, allo-SCT is the optimal treatment after initial induction and consolidation chemotherapy. Selection of therapy is more dependent on the immunophenotype rather than FAB classification. For patients with ALL under age 60, the goal of treatment is cure. For those older than age 60, the goal is palliation and prolongation of survival.

### Treatment Plan

About 35%–40% of patients can survive 2 years with aggressive induction combination chemotherapy. Most induction regimens for ALL include prednisone, vincristine, and an anthracycline. Some regimens also add other drugs,

Cortes JE, Kantarjian HM. Acute lymphoblastic leukemia. A comprehensive review with emphasis on biology and therapy. Cancer 1995;76(12):2393–417.

such as asparaginase or cyclophosphamide. Current multidrug induction regimens result in CR rates that range from 60% to 90%.

One of the most frequently used regimens to treat ALL is the Linker regimen. The treatment schema is as presented in Table 1-3.

Another commonly used regimen for ALL is hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), a regimen originated at the University of Texas M.D. Anderson Cancer Center. The treatment schema is presented in Table 1-4. The dose-intensive phase includes eight cycles of intensive therapy with hyper-CVAD (cycles 1, 3, 5, and 7) alternating with high-dose methotrexate (HD-MTX) and Ara-C (cycles 2, 4, 6, and 8). See Table 1-4 for the complete hyper-CVAD regimen.

For CNS prophylaxis, the number of MTX doses and Ara-C and their administration schedule are based on a patient's risk for central nervous system disease. The need for maintenance therapy is determined by the patient's disease subtype. Maintenance therapy is required by all patients except those with mature B-cell ALL or Ph(+) ALL. Duration of maintenance therapy is 2 years.

### Assessment of Treatment Response

The criteria that must be met for remission include the following: the bone marrow is normal with less than 5% blasts; there are no signs or symptoms of the disease, no signs or symptoms of central nervous system leukemia or other extramedullary infiltration; and all blood counts (white blood cell count, hematocrit, hemoglobin, and platelets) are within normal limits. About 60%–80% of adult patients with ALL can be expected to attain CR following appropriate induction therapy. About 35%–40% of patients can be expected to survive 2 years with aggressive induction therapy and effective supportive care.

### Post-Remission Therapy

Post-remission therapy includes the options of consolidation chemotherapy followed by maintenance therapy, ASCT, or allo-SCT. Consolidation chemotherapy usually includes the drugs that are used to induce remission plus additional drugs. Unlike AML, central nervous system prophylaxis is necessary and includes injections of MTX and/or Ara-C, with or without hydrocortisone, directly into the spinal fluid. Depending on the patient's disease subtype and risk factors, maintenance chemotherapy may be given over 2–3 years following consolidation chemotherapy. In adults with no poor risk factors, the leukemia-free survival is about 50%.

Autologous hematopoietic stem cell transplantation has not proven to be better than consolidation chemotherapy in ALL. Autologous hematopoietic stem cell transplantation is now used in an investigational manner for patients with ALL with poor risk features who do not have an allogeneic stem cell donor.

**Table 1-3. Linkers' Regimen for Acute Lymphocytic Leukemia**

Induction IA (DVPAsp)
- Daunorubicin 60 mg/m$^2$/day intravenously on days 1–3 (and day 15 if on day14 bone marrow had residual leukemia).
- Vincristine 1.4 mg/m$^2$ intravenously on days 1, 8, 15, and 22 (maximum of 2 mg if age older than 40 years).
- Prednisone orally 60 mg/m$^2$/day on days 1–28.
- L-Asparaginase 6000 units/m$^2$ subcutaneously on days 17–28.

Consolidation IB, IIB (HiDAC/etoposide)
- Cytarabine (Ara-C) 2 g/m$^2$/day intravenous infusion on days 1–4.
- Etoposide 500 mg/m$^2$/day intravenous infusion on days 1–4.

Consolidation IIA (DVPAsp)
- Daunorubicin 60 mg/m$^2$/day intravenously on days 1–3.
- Vincristine 1.4 mg/m$^2$ intravenously on days 1, 8, and 15 (maximum of 2 mg if age older than 40 years).
- Prednisone 60 mg/m$^2$/day orally on days 1–21.
- L-Asparaginase 12,000 units/m$^2$ subcutaneously six dosages over 2 weeks.

Consolidation IC, IIC, IIIC (HD-MTX/6-MP)
- Methotrexate 220 mg/m$^2$ intravenous bolus, then 60 mg/m$^2$/hour for 36 hours on days 1–2 and 15–16 (rescued with leucovorin 50 mg/m$^2$ intravenously every 6 hours for three dosages, then oral leucovorin until methotrexate less than 0.05 micromolar).
- Mercaptopurine 75 mg/m$^2$ orally on days 1–28.

Maintenance
- Methotrexate 20 mg/m$^2$/week orally.
- Mercaptopurine 75 mg/m$^2$/day orally until patients were in CR for 30 months. At that point, all treatment is stopped.

CNS prophylaxis
- Intrathecal methotrexate 12 mg/week for six dosages.

6-MP = 6-mercaptopurine; CNS = central nervous system; CR = complete remission; DVPAsp = daunorubicin vincristine, prednisone, asparaginase; HiDAC = high-dose cytarabine; HD-MTX = high-dose methotrexate.
Reprinted with permission from the American Society of Clinical Oncology. Linker C, Damon L, Ries C, Navarro W. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. J Clin Oncol 2002;20:2464–71.

Allogeneic hematopoietic stem cell transplantation is used as post-remission therapy in patients with ALL with poor risk features or in adults under age 65 years who have relapsed. Allogeneic hematopoietic stem cell transplantation results in the lowest incidence of leukemic relapse. The improvement in disease-free survival by allo-SCT as primary post-remission therapy is offset by the increased morbidity and mortality from graft-versus-host-disease and other allo-SCT-related mortalities. In a prospective trial, adults with ALL in remission who were younger than age 40 received allo-SCT if a sibling donor was available or they were randomly assigned to either ongoing chemotherapy or ASCT. There was no advantage of allo-SCT for the group of patients without poor prognostic factors. There was,

Linker C, Damon L, Ries C, Navarro W. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. J Clin Oncol 2002;20(10):2464–71.

Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 2004;101(12):2788–801.

**Table 1-4. Hyper-CVAD Regimen for Acute Lymphocytic Leukemia**

Hyper-CVAD cycle
- Cyclophosphamide 300 mg/m$^2$ intravenously every 12 hours for six dosages on days 1–3, mesna 600 mg/m$^2$ is given together with cyclophosphamide.
- Vincristine 2 mg intravenously on days 4 and 11.
- Doxorubicin 50 mg/m$^2$ intravenously on day 4.
- Dexamethasone 40 mg/day orally on days 1–4 and 11–14.

HD-MTX-Ara-C cycle
- Methotrexate 1 g/m$^2$ intravenously over 24 hours on day 1 (leucovorin rescue is initiated 12 hours after methotrexate infusion is completed until methotrexate level is less than 0.1 µm/L).
- Ara-C 3 g/m$^2$ intravenously every 12 hours for four dosages on days 2–3.
- Methylprednisolone 50 mg intravenously twice daily on days 1–3.

CNS prophylaxis
- Methotrexate 12 mg and Ara-C 100 mg intrathecally (alternating doses).

Oral maintenance therapy
- Mercaptopurine 50 mg orally 3 times/day.
- Methotrexate 20 mg/m$^2$/week orally.
- Vincristine 2 mg/month intravenously.
- Prednisone 200 mg/day orally for 5 days/month (with vincristine).

Ara-C = cytarabine; CNS = central nervous system; CVAD = cyclophosphamide, vincristine, doxorubicin, and dexamethasone; HD-MTX = high-dose methotrexate.
Reprinted with permission from John Wiley & Sons. Kantarjian H, Thomas D, O'Brien S, et al. Long-term Follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regiment in adult acute lymphocytic leukemia. Cancer 2004;101(12):2788–801.

however, a significant survival benefit by allo-SCT in patients with poor prognostic factors. The long-term survival of patients receiving chemotherapy and ASCT was identical.

Allogeneic hematopoietic stem cell transplantation as the primary post-remission therapy is limited by the need for an HLA-matched sibling donor and the increased mortality from allo-SCT in older patients (older than 60 years). The transplant-related mortality from matched-sibling allo-SCT ranges from 20% to 40%. Allogeneic hematopoietic stem cell transplantation should be reserved as primary post-remission therapy for adult patients with ALL with poor prognostic factors.

### Imatinib in Philadelphia Chromosome Positive ALL

Imatinib is a drug that blocks the adenosine triphosphate-binding domain of the chimeric tyrosine kinase produced from the Philadelphia chromosome. The Philadelphia chromosome is present in about 30% of adults with B-lineage ALL. Imatinib is being tested as adjunctive therapy (with chemotherapy and with allo-SCT) in patients with Ph(+) ALL. In a small study done at M.D. Anderson Cancer Center, 20 patients received imatinib with chemotherapy for Ph(+) ALL. Patients received allo-SCT if they were eligible. Patients ineligible for allo-SCT received imatinib and chemotherapy as the treatment modality. Results at 20 months showed better outcome using imatinib with chemotherapy to treat Ph(+) ALL than conventional chemotherapy regimens. In a small Japanese study of 24 patients, the combination of imatinib with chemotherapy was promising and produced CR in most of the newly diagnosed patients with Ph(+) ALL. This result is especially useful because it provides patients with a better chance to receive a post-remission allo-SCT.

## Chemotherapy Toxicity Monitoring

### Cytarabine

Cytarabine exhibits an adverse effect profile similar to many other chemotherapy drugs, with effects such as myelosuppression, nausea/vomiting, mucositis and stomatitis. At low doses (i.e., 100–200 mg/m$^2$/day), fever and skin rash can occur. At high doses, skin toxicity can manifest as a rash covering most of the body, or as plantar-palmar erythema. Desquamation of the palms and soles can occur, causing significant pain, and appropriate skin care must be provided during the treatment period. Frequent showers and skin moisturizing therapy are warranted during HiDAC infusion days. If severe skin rash occurs, short-term systemic corticosteroid therapy can be used to alleviate symptoms and prevent further complications.

Ocular toxicity is also associated with HiDAC therapy, which results from damage to corneal epithelium due to Ara-C secretion into the tears. Symptoms can include conjunctivitis, excessive lacrimation, photophobia, blurred vision, and eye pain. Corticosteroid eye drops should be administered concurrently with HiDAC therapy to prevent ocular toxicity.

Cerebellar dysfunction is another toxic effect of HiDAC therapy. Cerebellar dysfunction is characterized by ataxia, dysarthria, dysdiadochokinesia, coordination difficulties and slurring of speech. Studies have shown that compromised renal function is the major risk factor for developing cerebellar toxicity of Ara-C. According to the studies, 76% of patients with estimated creatinine clearance below 60 mL/minute developed neurotoxicity. However, only 8% of patients with good renal function developed neurotoxicity. Dose reductions are warranted in patients

Sebban C, Lepage E, Vernant JP, et al. Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. J Clin Oncol 1994;12(12):2580–7.

Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. Blood 2004;103(12):4396–407.

Towatari M, Yanada M, Usui N, et al. Japan Adult Leukemia Study Group. Combination of intensive chemotherapy and imatinib can rapidly induce high-quality complete remission for a majority of patients with newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia. Blood 2004;104(12):3507–12.

with renal insufficiency receiving HiDAC therapy. Studies suggest that the accumulation of the deaminated metabolite, uracil arabinoside, a known neurotoxin, causes the neurotoxicity.

### L-asparaginase

Hypersensitivity reactions are common (15%–35%) with L-asparaginase, and anaphylactoid reactions can be life-threatening. Symptoms include hypotension, laryngeal constriction, edema, and loss of consciousness. Because anaphylactoid reaction is common, patients should receive close medical supervision during administration. Most serious hypersensitivity reactions occur after several doses have been administered; however, anaphylactic reactions have also been noted with the first dose.

Hepatic toxicity is also common with L-asparaginase. Liver function tests (aspartate transaminase, alanine transaminase, alkaline phosphatase, and bilirubin) can be abnormally elevated within days of therapy. Hepatic protein synthesis can be depressed, which can result in hypoalbuminemia and decreased hepatically derived clotting factors (prothrombin, fibrinogen, and factors V, VII, VIII, and IX). Laboratory tests should be closely monitored.

Pancreatic dysfunction has also been reported with L-asparaginase and may reflect drug-induced acute pancreatitis. Blood glucose, amylase, and lipase levels should be closely monitored during treatment.

### Anthracycline

In common with many other cytotoxic drugs, anthracyclines (daunorubicin, doxorubicin, and idarubicin) cause myelosuppression, nausea/vomiting, mucositis, and stomatitis. Anthracyclines are also known to cause transient elevations in serum bilirubin and other liver enzymes. Because anthracyclines and their metabolites are excreted in the bile, drug elimination is impaired in patients with hepatobiliary dysfunction; therefore, doses must be reduced to prevent severe toxicity. In patients with significant elevations of serum bilirubin (greater than 1.5 mg/dL), the dose must be reduced by 75%.

Anthracyclines are also associated with extravasation. Extravasation can lead to painful soft tissue ulcerations. Surgical excision of evolving necrotic lesions is needed to prevent progressive ulceration of adjacent tissues. A central-line catheter is recommended but not necessary to avoid extravasation.

Another significant toxicity associated with anthracyclines is cardiomyopathy. Cardiomyopathy with anthracyclines is a potentially irreversible, cumulative dose-related toxicity. The risk increases when the cumulative delivered dose of doxorubicin is greater than 550 mg/m$^2$ (or equivalent daunorubicin or idarubicin dose). The mechanism of cardiac toxicity appears to involve excessive intracellular production of free radicals by anthracyclines within the myocardium. Patients usually present with symptoms of congestive heart failure. Cardiac examinations such as electrocardiogram or multiple-gated acquisition scan should be performed routinely to prevent cardiomyopathy.

### Vincristine

Neurotoxicity is the dose-limiting toxicity of vincristine. Jaw pain (secondary to trigeminal neuralgia) may occur in some patients but is usually limited to high doses of the drug; analgesics may help the pain. Constipation and paralytic ileus can also occur after vincristine administration. A prophylactic bowel regimen, such as stool softeners or stimulants, can be used to prevent this complication. Paresthesias (numbness and tingling) involving the feet or hands has also been reported to be a significant toxicity of vincristine. The peripheral neuropathy associated with vincristine is usually bilateral and symmetric. It is either partially or completely reversible, but recovery often takes several months. Vincristine can also extravasate; therefore, clinicians must be cautious when administering the drug. Rarely, vincristine can cause the syndrome of inappropriate secretion of antidiuretic hormone, resulting in hyponatremia. Because vincristine is excreted through the biliary route, doses must be adjusted when patients have hepatobiliary dysfunction.

Intrathecal vincristine administration is known to be fatal. In patients given accidental intrathecal injections, the clinical course proceeds rapidly from headache and backache to generalized muscle weakness and loss of deep tendon reflexes, apnea, loss of brain wave activity, and death. Special pharmacy labeling of vincristine syringes is important to avoid inadvertent intrathecal injection.

### Methotrexate

Methotrexate is mainly excreted renally. Because of extensive renal clearance, various guidelines for MTX dose adjustment are available, and adjustment should be considered in patients with impaired renal function. In general, high-dose MTX (greater than 1 g/m$^2$) should be avoided in patients with creatinine clearances less than 50 mL/minute. Dose reduction is warranted for patients with creatinine clearances less than 80 mL/minute. To ensure appropriate MTX clearance, adequate hydration and urine alkalization are required during high-dose MTX dosing. The urine pH should be greater than or equal to 7, and urine output should be 100 mL/hour before, during, and after the MTX infusion.

Patients with effusions should be treated cautiously because third-space fluids increase the risk for MTX toxicity. When deposited into third-space fluids, MTX slowly distributes from this compartment back into the plasma, increasing overall systemic exposure and the risk of toxicity. The prolonged MTX clearance leads to a higher chance of systemic toxicity such as myelosuppression and mucositis. Whenever possible, pleural or any third-space fluids should be drained before MTX dosing.

Many drug-interactions are associated with MTX. Probenecid is known to block MTX tubular secretion; weak acids such as drugs in the penicillin family, salicylates, and nonsteroidal anti-inflammatory drugs compete with MTX

Smith GA, Damon LE, Rugo HS, Ries CA, Linker CA. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. J Clin Oncol 1997;15(2):833–9.

for renal tubular secretion. Drugs causing nephrotoxicity can hinder MTX clearance. Sulfonamides can displace MTX from protein-binding sites and decrease renal clearance of MTX. All the interactions described above can result in decreased MTX clearance or increased toxicity. Because cotrimoxazole is commonly used for *Pneumocystis jiroveci* pneumonia prophylaxis for a patient with ALL, pharmacists must pay close attention to the patient's drug list to avoid a drug-drug interaction.

High-dose MTX can occasionally cause acute encephalopathy. The risk increases with higher cumulative doses of MTX and concomitant cranial radiation therapy. When given intrathecally, MTX can cause chemical meningitis. Patients receiving intrathecal MTX or high-dose MTX should be monitored carefully for signs and symptoms associated with neurotoxicity.

The toxic effects of MTX can be reversed by administration of leucovorin. Leucovorin "rescue" has been used with high-dose MTX therapy to rescue normal cells while leaving the tumor cells subject to its cytotoxic action. Intravenous leucovorin therapy is usually started 24 hours after the beginning of high-dose MTX infusion, and continued until the MTX concentration is less than 0.1 µmol/L. The bioavailability of oral leucovorin at doses greater than 50 mg is not 100%. Therefore, intravenous and oral leucovorin are not interchangeable at doses greater than 50 mg. If a patient has persistent high MTX levels over a prolonged time period, the oral leucovorin dose may need to be increased to provide adequate "rescue."

# Conclusion

The treatment of leukemia involves multiple considerations. With the advancement of molecular biology, cytogenetics has become the No. 1 prognostic factor in selecting optimal treatment. A patient's age and other comorbidities often determine the patient's ability to tolerate therapy. Leukemia treatments are often complex and carry significant toxicity. The success of treatment depends on careful analysis of disease information, appropriate supportive therapies, close monitoring of toxic chemotherapy, and patient compliance.

Pharmacist contributions, such as close monitoring of therapy and educating patient on drug therapy, definitely play a role in the outcome of therapy. The clinical pharmacy program in the inpatient leukemia and bone marrow transplantation service at the University of California, San Francisco Medical Center, has demonstrated pharmacists' invaluable contribution to patient care and medical/nursing staff. Under the practice guideline developed by the committee on interdisciplinary practice, the pharmacists are authorized to monitor the patient's chemotherapy toxicity, antiemetic therapy, antibiotic drug therapy, pain management, total parenteral nutrition, electrolyte supplements, and other ancillary drug therapy. In addition, pharmacists take active roles in educating patients and arranging appropriate discharge drugs. Pharmacists have provided continuity of care in this tertiary care setting, which affects patient care tremendously. Pharmacists have also generated significant cost savings for the institution and have improved work efficiency for the medical/nursing staff. Pharmacists can make an invaluable contribution to patient care with their clinical expertise.

# Annotated Bibliography


1. National Cancer Institute. Adult Acute Myeloid Leukemia (PDQ) and Adult Acute Lymphoblastic Leukemia (PDQ): Treatment Health Professional Version. Available at *www.cancer.gov/cancertopics/pdq/treatment/adultAML/healthprofessional* and *www.cancer.gov/cancertopics/pdq/treatment/adultALL/healthprofessional*. Accessed March 13, 2006.

   This National Cancer Institute (NCI) Web site provides a comprehensive review of adult acute myeloid leukemia (AML) and adult acute lymphoblastic leukemia (ALL). The Web site provides updated information and contains detailed information on various aspects of AML and ALL, such as epidemiology, diagnosis, classification, and treatments. The information is evidence-based. The classification section is molecular-biology based, which indicates the current trend of classifying AML and ALL subtypes. The treatment section, which provides good reviews of old and new studies, is helpful for pharmacists who wish to learn about the evolutionary development of AML and ALL treatments or to be updated on the current treatments of AML and ALL. However, because the information is so detailed, it might not be the most suitable reading material for a pharmacist with limited knowledge of leukemia.

2. Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. N Engl J Med 1999;341(14):1051–62.

   This is an easy-to-read review article for pharmacists with either basic or advanced knowledge of leukemia. The photographs included in the article are good visual aids to help readers understand leukemia morphology. The illustrations of genetic transcription emphasize the importance of molecular biology in understanding the disease. This article, a shortened version of the review on the NCI Web site, is brief, concise, and easy to follow. It gives readers scientific perspectives of the disease. However, the article was published before arsenic trioxide and gemtuzumab ozogamicin were available and does not provide the most updated treatment options.

3. Linker CA, Levitt LJ, O'Donnell M, Forman SJ, Ries CA. Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: a follow-up report. Blood 1991;78(11):2814–22.

   This is one of the most frequently cited articles in the field of ALL. The regimen studied in this report is known as the "Linker regimen," one of the most frequently used regimens in treating ALL. The complete remission (CR) rate with this regimen was 88%, with a 5-year survival rate of 40%. Since this article's publication, the regimen has been modified significantly. Although follow-up studies of the "Linker regimen" have been published in recent years, this 1991 article is regarded as a landmark study for the treatment of ALL. This study provides historical perspective on how the combination therapy of anthracycline, corticosteroid, vinca


Wu HT, Graff LR, Yuen CW. Clinical pharmacy in an inpatient leukemia and bone marrow transplant service. Am J Health-Syst Pharm 2005;62:744–7.

alkaloid, and L-asparaginase originated and on its successful use to treat patients with ALL without poor risk factors.

4. Hoelzer D, Thiel E, Loffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. Blood 1988;71(1):123–31.

This article, one of the most cited publications for treatment of ALL, discusses the "German regimen." Although the CR rate is not as good as with the Linker regimen, the overall survival rate at 5 years is comparable. This trial was much bigger than the Linker study. Many ALL treatments use either the "German regimen" or the "Linker regimen" as their backbone. Similar to the Linker article, this article does not provide the most updated information on treatment of ALL, but it does provide good historical perspective. The history helps pharmacists understand why certain drugs are used in ALL treatments.

5. Smith SM, Le Beau MM, Huo D, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood 2003;102(1):43–52.

Secondary leukemia due to treatment is an important issue in patients with cancer. Pharmacists should have a thorough understanding of the etiology and characteristics of cytotoxic therapy-induced leukemia. The authors performed a large-scale, retrospective review of patients who received radiation therapy, chemotherapy therapy, or combination of radiation therapy and chemotherapy (1972–2001). This article provides a comprehensive review of the 306 patients identified with treatment-induced AML and myelodysplastic syndrome, whether from chemotherapy, radiation, or combination therapy. Cytogenetic characteristics, latency intervals, and overall survival were analyzed and reported. This article alerts clinicians to the seriousness of cytotoxic treatment-induced AML and myelodysplastic syndrome. Patients need to be informed of such risks before receiving any cytotoxic treatments. The characteristics of chemotherapy-induced secondary leukemia are discussed in detail in this article.

6. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood 2005;105(7):2640–53.

A drug earning much attention in recent years is imatinib. This novel, interesting drug represents a paradigm shift in treatment for chronic myeloid leukemia and has also shown promising result in Philadelphia chromosome positive ALL. Because imatinib is the first tyrosine-kinase inhibitor, one should understand the mechanism and application of this drug. Topics covered in this article include the development of tyrosine kinase inhibitors; in vitro and in vivo profiles of imatinib; and summaries of clinical studies, drug resistance, dosing strategies, and adverse effects. Despite the article's focus on using imatinib to treat chronic myeloid leukemia, it is a useful reference because tyrosine kinase inhibitors have great potential in treating other cancers.