

2005 CE Series - Lesson Nine

Advances in the Treatment of Chronic Myeloid Leukemia

ACPE Universal Program No. 406-000-05-009-H01

Expiration Date: 9/30/08

By Carroll L. Ramos, Ph.D., R.Ph.

Associate Professor, College of Pharmacy, Southwestern Oklahoma State University

Goals and Objectives

Goals: To provide the pharmacist with an understanding of the pathological and clinical features of chronic myeloid leukemia and the latest approaches to its treatment.

Objectives: After completing this program, the pharmacist will be able to:

1. Describe the general pathological and clinical features of leukemia, including the major types of leukemia.
2. Discuss the epidemiology, pathology, and clinical presentation of chronic myeloid leukemia.
3. Discuss treatment options for chronic myeloid leukemia, including the appropriate use of the drug imatinib mesylate (Gleevec).
4. Describe the role of the pharmacist in the management of patients with chronic myeloid leukemia.

According to estimates published in the American Cancer Society's *Cancer Facts & Figures*, 1,372,910 Americans will be diagnosed with cancer and 570,280 Americans will die from cancer in 2005, which makes cancer the second most common cause of death behind cardiovascular disease. Although leukemia is not as common as prostate, breast, lung, and colorectal cancer, this malignancy of blood-forming cells causes significant morbidity and mortality. About 35,000 new cases of leukemia will be identified in 2005 and an estimated 22,570 deaths will result from this form of cancer. Leukemia is projected to be the fifth and sixth most common cause of cancer death in males and females, respectively in 2005. Advances in the diagnosis and/or treatment of leukemia have resulted in a decline in the mortality rate from leukemia by approximately 0.5% each year since 1991 and an increase in the relative five-year survival rate for leukemia from 34% during the mid-1970s to 46% in 2000.

After a brief overview of leukemia, including the most common types of leukemia, this article will focus on chronic myeloid leukemia (CML) (also known as chronic myelogenous leukemia). One major reason for emphasizing CML is a relatively recent treatment advance known as imatinib mesylate (Gleevec) that utilizes specific molecular targeting. An understanding of this treatment will provide an opportunity for the community pharmacist to develop a working knowledge of the rapidly emerging field of molecular cancer therapeutics.

Leukemia: Definition, Pathology, and Clinical Features

Most textbooks of medicine define leukemia as a malignancy of hematopoietic (blood-forming) cells that involves overproduction or uncontrolled proliferation of either immature hematopoietic precursor cells (acute leukemia) or mature-appearing leukocytes (chronic leukemia). Acute leukemia is further differentiated from chronic leukemia by a more abrupt onset that is often described as stormy, whereas patients with chronic leukemia tend to present in a more gradual and insidious manner. The two major types of acute leukemia are *acute lymphoid leukemia (ALL)* and *acute myeloid leukemia (AML)*. The two major types of chronic leukemia are *chronic lymphocytic leukemia (CLL)* and *chronic myeloid (myelogenous) leukemia (CML)*. The exact cause of leukemia is largely unknown, although there is strong evidence for specific risk factors, such as exposure to ionizing radiation, chemicals, including chemotherapy drugs, and certain viruses. These factors cause molecular genetic alterations that trigger proliferation of specific hematopoietic cell types. As is typical with all cancers, the proliferation of these cell types is unable to be contained nor controlled by normal growth regulatory mechanisms.

Acute Lymphoid Leukemia (ALL)

Almost 4,000 new cases of ALL and approximately 1,500 deaths from this type of leukemia are expected in 2005. Most cases of ALL occur in children between the ages of 2 and 10 and ALL is the most common cause of cancer in children. In ALL, immature lymphoid cells known as lymphoblasts proliferate in an excessive manner in the bone marrow and thus crowd out and hinder the production of other blood cell lines, including red blood cells, normal leukocytes, and platelets. In addition, the cells can infiltrate distant organs and tissues, including the spleen and lymph nodes.

The most common signs and symptoms of ALL include fatigue and pale skin, secondary to a deficiency of functional red blood cells (anemia), unexplained bruising and nose bleeds, secondary to a deficiency of platelets (thrombocytopenia), fever and serious infections, secondary to a deficiency in normal leukocytes (leucopenia), and bone pain due to proliferation and accumulation of leukemic cells in the bone marrow.

In children with ALL, chemotherapy can induce complete remission in almost 90% of patients. However, there is a high rate of relapse in ALL which necessitates a long-term chemotherapy maintenance regimen in most patients after initial remission is achieved. At least 50% of children with ALL who enter complete remission after induction chemotherapy remain in complete remission for 5 years, which in the eyes of many clinicians is a cure. Significant progress in the management of ALL is reflected by an 85% five-year survival rate for children with ALL, which is substantially greater than the 50-60% five-year survival rate recorded in the 1970s.

Acute Myeloid Leukemia (AML)

AML is the most common of the four major types of leukemia and is the most common type of adult leukemia. Almost 12,000 new cases of AML and approximately 9,000 deaths from this type of leukemia are estimated for 2005. The incidence of AML significantly increases with age and AML is much more common than ALL in middle-aged and older adults. The fundamental pathological feature of AML is uncontrolled proliferation of immature myeloid cells known as myeloblasts in the bone marrow. Similar to ALL, the rapid accumulation of malignant myeloblasts results in impaired synthesis of normal blood cells and thus the signs and symptoms of AML closely resemble those of ALL.

Although complete remission rates as high as 80% have been reported after induction chemotherapy of AML, the overall five-year survival rate for AML is only about 20%, the lowest of the four major leukemias. Older patients appear to have the poorest prognosis, whereas patients diagnosed with AML at younger ages have a better chance of long-term remission after treatment.

Chronic Lymphocytic Leukemia (CLL)

CLL is the second most common cause of leukemia in adults. Almost 9,800 new cases and 4,600 deaths from this type of leukemia will occur in 2005. CLL almost exclusively targets older adults. Most patients are greater than 60 years of age. The pathological hallmark of CLL is the uncontrolled proliferation of mature-appearing lymphocytes leading to a marked elevation of the peripheral blood lymphocyte count (lymphocytosis). In the vast majority of cases the malignant lymphocytes are of B-lymphocyte origin and in addition to crowding of normal bone marrow cells the lymphocytes can also infiltrate the spleen, lymph nodes, and even the liver. In contrast to the acute types of leukemia, CLL presents in a very insidious manner. In many cases, the only remarkable finding is an extremely elevated lymphocyte count. With advancing disease, patients are more likely to complain of enlarged lymph nodes (lymphadenopathy), fatigue, unexplained weight loss, fever, and night sweats.

The clinical literature indicates that patients diagnosed with CLL in the earliest stages do not significantly benefit from treatment. If these patients remain in a relatively early stage and do not display significant disease progression, then the long-term prognosis is more favorable compared to the relatively poor outlook for CLL patients with more advanced disease.

Focus on Chronic Myeloid (Myelogenous) Leukemia (CML)

Epidemiology of CML

About 4,600 new cases of CML and approximately 850 deaths from this type of leukemia are expected in 2005. As with most types of leukemia, a slightly greater number of males contract CML and die from this type of leukemia than females. The approximate median age range for initial presentation with CML is 45 to 55 years of age. Although CML is relatively uncommon in children, there appears to be a recent trend toward increased numbers of young adults diagnosed with CML.

Pathology and Cytogenetic Features of CML

The hallmark molecular genetic feature of CML is the presence of a single molecular defect in leukemic cells known as the *Philadelphia (Ph) chromosome*. The Philadelphia chromosome abnormality is present in leukemic cells of $\geq 95\%$ of CML patients. The Philadelphia chromosome results from a *translocation* of genetic material between chromosome 9 and chromosome 22. More specifically, a portion of the *abl* protooncogene on chromosome 9 is translocated to chromosome 22 where it fuses with the *bcr* gene, resulting in a hybrid *bcr-abl* gene: the molecular fingerprint of the Philadelphia chromosome. The product of the hybrid *bcr-abl* gene is an abnormal *tyrosine kinase*.

In normal hematopoiesis, tyrosine kinases play an important role in signal transduction for growth factors, such as colony stimulating factors, that closely regulate the differentiation and proliferation of stem cells within the bone marrow. In CML, expression of the hybrid *bcr-abl* gene leads to abnormal tyrosine kinase activity. The abnormal tyrosine kinase activity, and thus the Philadelphia chromosome, appears to originate primarily in stem cells of the myeloid cell

lineage, although the abnormality may also be present in stem cells for red blood cells, platelets, and monocytes.

As CML emerges and disease progression begins, the abnormal tyrosine kinase activity can lead to a markedly elevated white blood cell (WBC) count with a striking increase in neutrophils. The overproduction of Philadelphia chromosome-positive stem cells within the bone marrow can also result in a disturbance in normal hematopoiesis followed by infiltration and accumulation of leukemic cells in distant organs, such as the spleen.

The Clinical Presentation of the CML Patient

Similar to CLL, CML can emerge clinically in a very insidious manner. It is not unusual for CML to be diagnosed after detection of an abnormally high or even a marginally elevated white blood cell (WBC) count during the course of a routine physical examination. In many cases the patient will fail to report any additional signs or symptoms indicative of leukemia.

Patients presenting initially with more advanced disease are more likely to complain of a history of worsening fatigue, unexplained weight loss, and pain localized to the upper left quadrant of the abdomen secondary to an enlarged spleen. The peripheral blood WBC count is often $>20 \times 10^3$ cells/ 3 cells/ in the neutrophil count, immature neutrophil precursors (myeloblasts) and other cells of the myeloid lineage, such as basophils, can also be elevated. Interestingly, despite extreme elevations in numbers, leukocyte function appears to be normal and thus infections are not a common component of the initial clinical presentation of CML.

The Phases of Progression of CML

Chronic Phase-The vast majority of patients are initially diagnosed in the chronic phase of CML. The chronic nature of this phase results from the relatively stable and predictable profile of signs and symptoms. Patients can remain in this phase for many years. Chronic phase patients have the most favorable response to treatment.

Accelerated Phase-After a number of years in the chronic phase, almost all CML patients begin to experience significant disease progression. Patients are more likely to complain of abdominal pain, secondary to an enlarged spleen and even an enlarged liver, fever, and weight loss. The WBC count returns to an abnormally elevated level and the fraction of myeloblasts in the peripheral blood and bone marrow is significantly increased from chronic phase levels. The burden of Philadelphia chromosome-positive cells in the bone marrow and blood is also increased. The accelerated phase typically lasts only months (usually < 1 year).

Blast Crisis-The accelerated phase is often the prelude to blast crisis. In this phase, there is a dramatic increase in the severity of signs and symptoms. Complications not typically observed in the chronic phase, such as anemia, bleeding secondary to thrombocytopenia, and infections, are common in blast crisis. The fraction of myeloblasts in the blood and/or bone marrow exceeds 30%. Patients in blast crisis generally do not respond well to treatment and the prognosis is extremely poor. Most patients will die within months.

The New Standard of Therapy for CML: Imatinib Mesylate (Gleevec)

Imatinib mesylate (Gleevec), a product of Novartis, was approved by the FDA in 2001 for the treatment of CML. The primary indication of imatinib is the treatment of adults with early chronic phase, Philadelphia chromosome-positive CML. Imatinib is also indicated for the

treatment of Philadelphia chromosome-positive CML patients in the accelerated phase or blast crisis, as well as chronic phase patients who have failed historical treatments, such as interferon. Imatinib is approved for pediatric patients with Philadelphia chromosome-positive CML who have relapsed after previous treatments, including stem cell transplantation.

Pharmacology of imatinib

An understanding of the molecular and cytogenetic basis of many cancers has fostered the development of a number of *molecular cancer therapeutic agents*. Unlike traditional chemotherapeutic agents which often have broad cytotoxic actions, molecular cancer therapeutic agents have highly specific and targeted mechanisms of action. Imatinib is an excellent example of this new approach to cancer therapeutics.

Imatinib is a specific inhibitor of a select group of tyrosine kinases. The drug potently inhibits the activity of the tyrosine kinase coded by the hybrid *bcr-abl* gene of the Philadelphia chromosome. Since this tyrosine kinase is responsible for the abnormal signal transduction that drives the overproduction of bone marrow stem cells in CML, inhibition of this tyrosine kinase activity effectively diminishes or eliminates the excessive proliferation of these cells.

Efficacy and clinical impact of imatinib

Data from one of the largest and most extensive clinical trials with imatinib clearly demonstrates the impressive efficacy of imatinib in CML. This Phase III, multi-center trial, known as IRIS (International Randomized Interferon Versus STI571 (experimental designator for imatinib)), was initiated in 2000-2001 and compared imatinib with the combination treatment of interferon and cytarabine (Ara-C). The trial utilized a crossover design that allowed patients to switch treatments if there was intolerance or treatment failure.

The primary endpoint of the study was time to disease progression, which was defined as the period of time before the patient failed to maintain either a *complete hematologic response* to treatment (essentially a normalization of blood cell counts) or a *major cytogenetic response* to treatment (either a complete absence of Philadelphia chromosome-positive leukemic cells in the bone marrow and blood or a substantial reduction in the numbers of these cells). The findings of the IRIS trial are summarized below.

Time to Disease Progression-At 12 months, 97% of imatinib-treated patients displayed no evidence of disease progression compared to 80% with combination interferon and Ara-C treatment. The authors of the trial noted that a significant number of patients initially treated with interferon and Ara-C switched to imatinib during the 12-month period, for reasons such as inadequate response or toxicities, and thus the data for interferon and Ara-C may actually be overestimated. At 30 months, 88% of imatinib-treated patients were free of disease progression compared to 68% for combination interferon and Ara-C treatment.

Complete hematologic response rates-At 30 months, 95% of imatinib-treated patients demonstrated a complete hematologic response compared to 55% for combination interferon and Ara-C treatment.

Major cytogenetic response rates-At 30 months, 83% of imatinib-treated patients demonstrated a major cytogenetic response compared to 16% for combination interferon and Ara-C treatment.

At least three clinical trials have addressed use of imatinib in patients with Philadelphia chromosome-positive chronic phase CML who have failed interferon therapy, patients in

accelerated phase CML, and patients in blast crisis. The findings of these trials are summarized below.

Complete hematologic response rates-After ≥ 4 weeks of imatinib therapy, a complete hematologic response was identified in 95% of chronic phase patients who previously failed interferon, 38% of accelerated phase patients, and 7% of patients in blast crisis.

Major cytogenetic response rates- After ≥ 4 weeks of imatinib therapy, a major cytogenetic response was identified in 60% of chronic phase patients who previously failed interferon, 21% of accelerated phase patients, and 7% of patients in blast crisis.

Return to chronic phase-After ≥ 4 weeks of imatinib therapy, 20% of accelerated phase and 18% of blast crisis patients reverted to chronic phase.

Overall, results from clinical trials indicate that imatinib substantially advances the treatment of CML compared to previous standards of care, such as interferon. CML patients treated with imatinib have better overall hematologic and cytogenetic responses and significantly longer periods of disease-free survival. Follow up studies of patients enrolled in the IRIS trial are still ongoing and thus updated five-year survival rates for CML in light of imatinib therapy are pending. Preliminary calculations suggest that imatinib treatment provides a significant long-term survival advantage compared to interferon.

Adverse effects and safety profile of imatinib

Imatinib therapy appears to be tolerated by most patients. In the IRIS trial, only 1% of imatinib patients discontinued treatment compared to 31% of patients treated with interferon and Ara-C. Based on clinical trial findings and other literature reports, the most common adverse effects of imatinib are fluid retention and edema, nausea, muscle cramps, musculoskeletal and joint pain, diarrhea, rash, fatigue, and headache. The incidences of many of these adverse effects are relatively high. For example, depending on the study and the patient population, fluid retention and edema may be present in 50-70% of patients, while the remaining adverse effects listed above range from 30-50% of patients. Rates of adverse effects appear to be dose-dependent and are greater in patients with more advanced disease, such as blast crisis, and elderly patients. Additional adverse effects that are reported to occur in 10-30% of patients include abdominal pain, hemorrhage, vomiting, dyspepsia, cough, dizziness, fever, weight gain, insomnia, and depression.

Many antineoplastic drugs have the potential for bone marrow suppression. This is particularly true of the traditional chemotherapeutic agents. Imatinib patients appear to experience a lower rate of hematologic toxicity than patients treated with a combination of interferon and Ara-C. For example, in the IRIS trial, neutrophil deficiency (neutropenia) was reported in 12% of imatinib patients compared to 21% of patients treated with interferon and Ara-C. Platelet deficiency occurred in 8% of imatinib patients compared to 16% of patients treated with the interferon and Ara-C combination. Anemia was relatively low and comparable in both groups with 3% of imatinib patients displaying evidence of anemia. Similar to other adverse effects, hematologic toxicity of imatinib is dependent on dose and the overall phase of disease.

Drug interactions with imatinib

Hepatic metabolism followed by elimination in the feces largely determines the 18 hour elimination half-life of the imatinib parent compound and the 40 hour half-life of a major active metabolite after an oral dose. Since imatinib and its metabolites are not eliminated through renal

mechanisms, there generally is no need to adjust dose in patients with renal insufficiency. Although it would be expected to adjust the dose in liver disease patients, there is little or no clinical experience to guide this decision.

The major cytochrome P450 enzyme involved in imatinib metabolism is CYP3A4. Therefore, any drug that interacts with CYP3A4, whether through inhibition, induction, or as a substrate, should be used with caution in patients treated with imatinib.

The azole antifungals, ketoconazole and itraconazole, and the macrolide antibiotics, erythromycin, azithromycin, and clarithromycin, are known inhibitors of CYP3A4 and thus co-administration may significantly increase imatinib plasma levels and increase risk of adverse effects. In contrast to CYP3A4 inhibitors, inducers of CYP3A4 can significantly increase the metabolism and elimination of imatinib, reduce plasma levels, and diminish the effectiveness of the drug. CYP3A4 inducers include carbamazepine, phenytoin, phenobarbital, dexamethasone, and rifampin.

Drugs that are primarily metabolized through CYP3A4 are also likely to interact with imatinib. CYP3A4 substrates include statins and dihydropyridine calcium channel blockers. Co-administration with imatinib may raise the plasma levels of the interacting drug. One example of this interaction is the ability of imatinib to increase plasma levels of the lipid-lowering statin, simvastatin, by at least two-fold. Elevated plasma levels of statins could increase risk of statin-induced myopathy. Since warfarin is also metabolized in part by CYP3A4, clinicians should consider an alternative strategy for imatinib patients that require anticoagulation.

There is evidence that co-administration of imatinib and acetaminophen can result in elevation of acetaminophen plasma levels. Although there is a relatively low rate of liver enzyme elevations and hepatotoxicity with imatinib therapy, concomitant use with acetaminophen may increase risk of such complications.

Dosage and administration of imatinib, patient information, and precautions

Gleevec brand tablets of imatinib are available in 100 mg and 400 mg strengths. The most commonly prescribed regimens of imatinib are 400 mg/day for adult, chronic phase CML patients and 600 mg/day for accelerated phase or blast crisis patients. Since Gleevec tablets are scored, the manufacturer recommends use of the 400 mg tablets in most regimens. Based on this recommendation, a physician is most likely to prescribe one and one-half tablets of the 400 mg strength for patients requiring 600 mg/day of imatinib. The 100 mg strength tablets may be more commonly employed in customized pediatric dosing.

It is recommended that patients take imatinib with a meal and a full glass of water to minimize gastrointestinal upset. Patients should avoid grapefruit juice due to the ability of active components in the juice to possibly alter the metabolism of imatinib and raise plasma levels. Since animal studies have demonstrated teratogenic effects of imatinib, it is recommended that female patients of reproductive age be cautioned to avoid pregnancy during imatinib treatment.

Role of the Pharmacist

A major role of the community pharmacist in the care of CML patients treated with Gleevec is to help the patient receive their medication in a timely and regular manner. The prescribing and distribution process for Gleevec is slightly more complicated than most drugs because of the high cost of Gleevec treatment. A recent AWP for thirty Gleevec 400 mg tablets was about \$2,600. Annual costs of Gleevec therapy may range between \$25,000 and \$35,000 for the 400

mg/day regimen and substantially more for the 600 mg/day regimen. The expense is further compounded by the fact that most patients will receive long-term treatment with Gleevec (at least many months and perhaps years).

In respect to patients that have prescription benefit coverage, the manufacturer requests that the *prescribing physician* contact the pharmacy benefit manager to verify coverage of Gleevec and obtain prior authorization before a new prescription is brought to a pharmacy provider. When this process is completed, the pharmacist is recommended to order Gleevec from the wholesaler on an as needed basis.

For patients without pharmacy benefit coverage, the manufacturer recommends that healthcare professionals encourage patients to call the *Gleevec Reimbursement Hotline* (1-877-Gleevec), which will attempt to find resources that may fund at least part of the cost of Gleevec treatment. If a funding source is not identified, then the hotline staff will consider the patient's eligibility for a patient assistance program. The Novartis web site for Gleevec (www.gleevec.com) has extensive information, including downloadable documents, for both healthcare professionals and patients

By acting as a guide and a valuable information resource, the community pharmacist can help facilitate the transition between the initial diagnosis of CML and long-term treatment with Gleevec.

BIBLIOGRAPHY

American Cancer Society, *Cancer Facts & Figures*, 2005.

Appelbaum FR: The Acute Leukemias and Keating MJ, Kantarjian H: The Chronic Leukemias, in *Cecil Textbook of Medicine*, 22nd ed., Goldman L and Ausiello D, eds., Saunders, 2004.

Gleevec (imatinib mesylate) Prescribing Information, Novartis Pharmaceuticals, 2005.

Goldman JM, Melo JV. Mechanisms of disease: Chronic myeloid leukemia-advances in biology and new approaches. *New England Journal of Medicine*, 349(15):1451-64, 2003.

O'Brien SG et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *New England Journal of Medicine*, 348(11):994-1004, 2003.