CASE STUDY

86 CHRONIC MYELOGENOUS LEUKEMIA

For the Patient Case for this case study, see the printed book.

DISEASE SUMMARY

Definitions

Leukemia is a malignant (i.e., cancerous) disorder of the blood and blood-forming organs that results from a loss of cell division regulation and causes an accumulation of dysfunctional white blood cells (WBCs). There are four primary types of leukemia and each type is classified into multiple subtypes. The common pathologic feature of all forms of leukemia is an uncontrolled proliferation of abnormal leukocytes. The excessive proliferation of leukemic WBCs results in overcrowding of the bone marrow that causes decreased production and function of normal WBCs, red blood cells, and platelets.

The first description of a leukemic individual was by Valpreau in 1827. His patient, a 63-year-old florist and seller of lemonade "who had abandoned himself to the abuse of spiritus liquor and of women without, however, becoming syphilitic" became ill in 1825. The patient demonstrated significant swelling of the abdomen, fever, weakness, and symptoms related to kidney stones. On autopsy, the liver and spleen were enlarged, blood appeared the color of red wine, and pus resembled the color of yeast. Not until 1945, however, did the physiologist Bennett and the pathologist Virchow separately describe leukemia. Virchow first used the terms "white blood" (weissus blut) and later the term "leukemia." Virchow is largely credited with discoveries that have led to current knowledge of the pathology of leukemia.

Chronic myelogenous leukemia (CML) is a slowly progressive (i.e., chronic) type of cancer of the blood and bone marrow in which the bone marrow produces too many WBCs of the myeloid stem cell line known as granulocytes. For this reason, CML is also considered one of a number of *myeloproliferative disorders*. Although many of these leukemic cells differentiate morphologically, they remain immature functionally and are ineffective as inflammatory or immune response cells. With time, cancerous WBCs crowd out red blood cells and platelets in the bone marrow and, as is characteristic of cancer, spread through the blood and continue to divide in various organs.

Throughout the medical literature, CML is also known as *chronic myeloid leukemia*, *chronic granulocytic leukemia*, and *chronic myelocytic leukemia*.

Prevalence

More than 20,000 people in the United States have CML and the American Cancer Society estimates that 4,830 new cases (approximately 2,800 men and 2,030 women) will be diagnosed in 2008. CML affects 1–2 of every 100,000 people and the incidence is slightly higher in men

than in women. Most cases occur in middle-aged adults (the median age at presentation is 55 years), but up to 4% of patients are children. CML accounts for up to one in five cases of leukemia affecting adults today.

Significance

CML may have few symptoms for several years after onset, but multiple manifestations—including fatigue, weakness, loss of appetite, unintentional weight loss, excessive sweating (especially night sweats), bleeding, bruising, and left upper quadrant pain—eventually develop.

The American Cancer Society has estimated that approximately 450 deaths will occur nationally in 2008 from CML. The only known curative treatment is a bone marrow transplant from a suitable donor. However, even with a well-matched sibling donor, the probability of transplant-related mortality remains approximately 25%.

Unlike other forms of cancer, CML is not a solid tumor that can be eliminated in a relatively short period of time with surgery, chemotherapy, or radiation treatment. Many patients require long-term treatments that cause nausea, muscle cramps, and severe fatigue. This makes living with CML like living with a chronic—albeit very deadly—disease. Without treatment, CML is always fatal. On average, life expectancy without treatment is 3–4 years.

Causes and Risk Factors

Unlike other forms of cancer and leukemia, CML has few known causes and risk factors, but exposure to high doses of ionizing radiation has been implicated. Because of their relatively high turnover, WBCs are more susceptible to radiation-induced genetic damage and transformation into cancerous cells than are many other cell types. An acute whole-body exposure to radiation like that which has occurred with nuclear explosions is known to increase the risk for leukemia, including CML. Among Japanese survivors of the atomic bombings of Hiroshima and Nagasaki, the estimated lifetime risk for leukemia increased six-fold. There are substantial uncertainties about the risk of low-level, long-term exposure to radiation. The average annual exposure from cosmic rays and medical procedures is very low and estimated to account for $<5\%$ of all cases of leukemia. The majority of people treated for cancer with radiation, however, do not develop CML. Exposure to the organic chemical benzene is another possible cause of CML.

Pathophysiology

The bone marrow normally produces immature cells known as *stem cells* and *blast cells* in a controlled manner. These cells mature, differentiate (i.e., become specialized), and are released into the peripheral blood. When these cells grow old, they are eliminated from the blood by macrophages and replaced by new cells in a continuous cycle. ***The basic mechanism of malignant transformation (i.e., conversion of a normal cell to a cancerous one) involves genetic injury to cells that disrupts growth control and differentiation pathways.*** In CML, blast cells in the myeloid cell lineage that are developing into WBCs called granulocytes (e.g., neutrophils, basophils, and eosinophils) are specifically injured and do not fully mature. As the disease progresses, granulocytes accumulate in large numbers within the bone marrow and blood and eventually crowd out healthy components of the blood (i.e., red cells, other WBCs, and platelets). This predisposes patients with CML to anemia, infections, and easy bleeding and bruising. CML, therefore, is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line. The peripheral blood profile shows an increased number of granulocytes and their immature precursors (i.e., myeloblasts).

Deoxyribonucleic acid (DNA) acts as a set of instructions for cell function that directs cells to grow and divide. Specific genes within DNA known as *oncogenes* promote cell division when activated. Other genes known as *tumor suppressor genes* slow down cell division and instruct cells to die at appropriate and natural times. Leukemia occurs when damage to DNA activates oncogenes and deactivates tumor suppressor genes. The precise DNA mutation that causes CML was first identified by Nowell and Hungerford and is known as the *Philadelphia chromosome* (Ph chromosome), named after the city in which it was discovered. This unique mutation is not transmitted from parent to child; rather, it is an acquired mutation that develops during

the routine process of cell division. Exposure to ionizing radiation may cause this chromosome abnormality. The Ph chromosome is a hallmark of CML and is present throughout the clinical course of the disease until a cure has been achieved.

The Ph chromosome is an abnormally short chromosome 22 caused by a reciprocal translocation (i.e., an exchange of DNA between two chromosomes) between the long arms of chromosomes 9 and 22 and is denoted by t(9;22). This translocation relocates the proto-oncogene (i.e., gene that has the potential to evolve into an oncogene) *abl* (named for the Abelson murine leukemia virus) from chromosome 9 to chromosome 22 into the segment occupied by the *bcr* (break point cluster) gene. The *abl* gene normally encodes for the enzyme *tyrosine kinase*. The exchange of genetic material results in fusion of *abl* and *bcr* into an oncogene with enhanced tyrosine kinase activity with respect to *abl*. It has been proposed that the close proximity of the *abl* and *bcr* genes in WBCs during interphase may favor translocation between the two chromosomes. Excessive tyrosine kinase activity is a property of oncogenes that can transform normal cells into cancerous ones. The expression of this enzyme induces a phosphorylation process that allows WBCs to bypass signals that control normal cell differentiation and division. The ultimate result is an increase in white blood cell division, a decrease in natural cell death (i.e., *apoptosis*), and the development of CML.

It is generally believed that CML develops when a single stem cell acquires a Ph chromosome carrying the *abl-bcr* fusion gene. Evidence that this fusion gene can transform a normal WBC into a leukemic one is provided by mouse models in which introduction of the gene almost invariably leads to leukemia. The presence of the *abl-bcr* rearrangement is a hallmark of CML, although this gene arrangement is also associated with other diseases. It is considered diagnostic when present in a patient with other typical clinical signs and symptoms of CML.

Early CML does not behave like leukemia in that normal bone marrow function is retained. White blood cells differentiate normally and are able to combat infection. However, the disease is inherently unstable and progressive. Progression is often associated with additional mutations superimposed on the Ph chromosome (e.g., deactivation of tumor suppressor genes) and probably caused by random mutations in genetically unstable and rapidly proliferating WBCs.

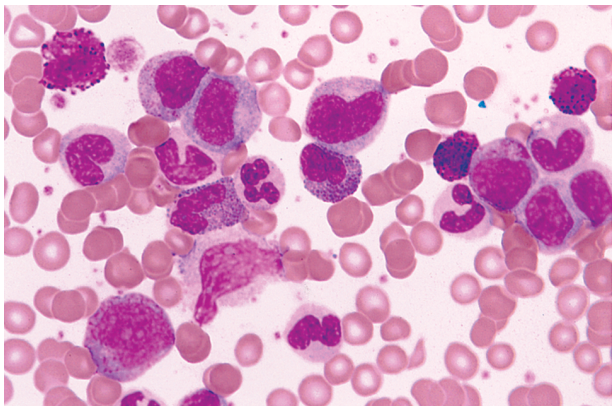
Diagnosis: Clinical Manifestations and Laboratory Tests

The diagnosis of CML is based primarily on four tests:

1. complete blood count (CBC)
2. examination of a bone marrow sample aspirated from the posterior iliac crest (i.e., hipbone) or sternum (i.e., breastbone)
3. fluorescence in situ hybridization (FISH) assay (a rapid and sensitive means of detecting numerical and structural chromosome changes)
4. polymerase chain reaction to detect the presence of the *abl-bcr* gene in cells within the peripheral blood

The bone marrow is characteristically hypercellular with expansion of the myeloid cell line (i.e., neutrophils, eosinophils, and basophils). The patient is typically a middle-aged adult.

CML progresses through three worsening phases or stages of disease—an initial *chronic phase* of variable length, a short and unstable *accelerated* or *transitional phase*, and a highly aggressive and terminal *blast crisis phase*. The onset of the chronic phase is usually slow with non-specific symptoms such as weakness, lack of energy, poor exercise tolerance, and unintentional weight loss. Most patients are diagnosed during the chronic phase of CML. ***The most characteristic laboratory finding is leukocytosis with immature granulocyte cell types in the peripheral blood.*** This is illustrated in Disease Summary Figure 86.1. During this chronic phase of the disease, 5% or less of WBCs are blast cells (normally, 3–5%). Anemia and, eventually, thrombocytopenia (i.e., low platelet count) develop. Anemia is mild to moderate, normochromic and normocytic, and causes weakness, easy fatigability, and dyspnea (i.e., shortness of breath) with exertion. Splenomegaly is often present at the time of diagnosis, hepatomegaly is less common, and lymphadenopathy is rare. ***Splenomegaly is the most common physical finding in patients with CML, and the size of the spleen is directly related to the WBC count.*** Although patients in the early chronic phase of CML generally are asymptomatic and may live for years unaware of the disease, without effective treatment most will enter the accelerated phase within 4 years. Some patients who respond well to chemotherapy have remained in the chronic phase for more than 9 years.



DISEASE SUMMARY FIGURE 86.1
Peripheral blood smear from a patient with chronic myelogenous leukemia. The most characteristic laboratory finding is leukocytosis with excessive numbers of neutrophils, basophils, and immature granulocytes in the blood. (Reprinted with permission from McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

The accelerated phase is characterized by further enlargement of the spleen and progressive symptoms of anemia and thrombocytopenia. Splenomegaly often causes a feeling of abdominal fullness and discomfort or pain under the left ribcage. An increase in basophil count (i.e., basophilia) that may exceed 20% of the differential WBC count and more immature cells in the blood and bone marrow confirm transition to the accelerated phase. In accelerated phase CML, 6–30% of the cells in the blood are blast cells. During this phase, low-grade fever in the absence of infection, night sweats, bone pain, and unintentional weight loss develop from the accumulation of leukemic WBCs, which results in a hypermetabolic state. Bleeding and easy bruising may arise from a low platelet count (often <100,000/cu mm). Generally, the accelerated phase lasts 1–3 months.

The terminal blast crisis phase of CML represents evolution to acute leukemia, is characterized by an increasing number of blast cells, and typically lasts for 3–6 months before the patient's demise. More than 30% of cells in the blood are blast cells. In approximately two thirds of patients, the blasts are myeloid (i.e., evolution to acute myelogenous leukemia). However, in the remaining one third of patients, blasts exhibit a lymphoid phenotype (i.e., evolution to acute lymphoblastic leukemia). ***This phenomenon provides further evidence for the stem cell origin of this disease.*** Other symptoms become more pronounced and splenomegaly may increase significantly. Isolated infiltrates of leukemic WBCs can be found in the skin, lymph nodes, and central nervous system. With extremely high WBC counts (>500,000/cu mm), symptoms of leukostasis and hyperviscosity of the blood may occur (e.g., blurred vision from stasis in retinal capillaries, respiratory distress from stasis in pulmonary capillaries, or priapism). Fever secondary to infection is common. Chromosomal abnormalities in addition to the Ph chromosome are usually found at the time of blast crisis. These include trisomies 8, 9, 19, or 21 and deletion of the Y chromosome. The prognosis for patients who progress to the blast crisis phase is poor and survival is, at best, 6 months.

Disease Summary Question 1. Define *priapism.*

Disease Summary Question 2. Why are patients with chronic myelogenous leukemia often hyperuricemic?

Disease Summary Question 3. Why are infiltrates of leukemic white blood cells found in the skin, lymph nodes, and central nervous system of patients with chronic myelogenous leukemia?

Disease Summary Question 4. Distinguish the pathophysiology of splenomegaly in patients with chronic myelogenous leukemia from those patients with right heart failure and portal hypertension due to cirrhosis.

Disease Summary Question 5. Is pallor (i.e., pale skin) in a Caucasian patient a clinical sign of a subnormal red blood cell count, thrombocytopenia, or dysfunctional white blood cells caused by chronic myelogenous leukemia?

Disease Summary Question 6. Are frequent and severe nosebleeds a complication of a subnormal red blood cell count, thrombocytopenia, or dysfunctional white blood cells caused by chronic myelogenous leukemia?

Disease Summary Question 7. In which tissue of the body does chronic myelogenous leukemia originate?

Appropriate Therapy

The primary goals of treatment for CML today are three-fold:

1. achieve a *hematologic* remission (i.e., normal CBC and physical examination with no organomegaly)
2. achieve a *cytogenetic* remission (i.e., elimination of all Ph chromosome-positive cells)
3. achieve a *molecular* remission (i.e., negative polymerase chain reaction for the *abl-bcr* fusion gene)

Once a patient achieves a hematologic remission, the goals of treatment are to achieve a cytogenetic remission and, hopefully, also a molecular remission (i.e., complete cure) and significantly prolong the patient's lifespan.

Treatment decisions are complicated, options are always changing, and there are few documented long-term results for newer treatments. In general, however, treatment of CML depends on the age and overall health of the patient, the specific phase of the disease, and the availability of a suitable donor for bone marrow transplantation (BMT). Options include treatment with imatinib mesylate, hydroxyurea chemotherapy, BMT, stem cell transplantation, donor lymphocyte infusion, and a variety of experimental treatments.

For most patients with CML, drug therapy with imatinib mesylate is standard initial therapy. Imatinib specifically inhibits the activity of *abl-bcr* tyrosine kinase, the enzyme that is responsible for the accumulation of leukemic WBCs in the bone marrow and peripheral blood. The drug was approved by the U.S. Food and Drug Administration in 2001, inhibits proliferation and induces apoptosis of cells positive for the Ph chromosome, and has proved highly effective in treating patients with the chronic phase of CML. Imatinib has few serious side effects and has substantially changed treatment guidelines in recent years. For patients with chronic-phase CML, imatinib at 400 mg/day orally is the best treatment because it induces hematologic remission in almost all (98%) patients, has a high cytogenetic remission rate of 70%, and carries a 94% 3-year survival rate. The molecular remission rate has been as high as 50%. At this time, with some patients out 5 years from start of imatinib therapy, 100% of patients with a cytogenetic remission and a significant reduction in the *abl-bcr* oncogene remain disease-free. Fewer than 5% of patients discontinue the drug because of unacceptable side effects. Treatment results with imatinib during the accelerated or blast crisis phases have been dismal, and positive responses have been less frequent and sustained for much shorter periods of time. Although imatinib has become the gold standard for treating CML, it is still unknown whether the therapeutic effects of the drug last longer than 5 years and that it actually provides a cure for CML. Resistance of CML cells to imatinib is emerging through multiple mechanisms, such as increased expression of the *abl-bcr* oncogene. Dasatinib become available in mid-2006 and has been shown to produce a positive response in a high proportion of patients whose disease has become resistant to imatinib.

Chemotherapy uses chemical agents to kill leukemic white blood cells and reduce the WBC count (i.e., induce *myelosuppression*). Chemotherapy may be taken orally or intravenously. It is a systemic treatment for cancer because drugs enter the bloodstream and kill cancer cells throughout the body, but they also kill healthy (especially rapidly dividing) cells in the process. Chemotherapy is often used when other treatments have been unsuccessful. A 1–2-month treatment period is required.

Hydroxyurea, an inhibitor of deoxynucleotide synthesis, is the most common chemotherapy agent used to achieve hematologic remission. This drug was formerly the standard treatment for CML and can be used for patients who do not tolerate imatinib. Most patients achieve hematologic remission within 2 months, but use of this drug rarely results in a cure.

Myelosuppression effects last, at most, 1 week (i.e., rapid WBC rebound) and are easier to control than with other myelosuppressive drugs.

Bone marrow transplantation is a procedure that allows patients with CML to re-establish their healthy stem cell population by replacing their leukemic bone marrow with leukemia-free marrow. Patients first receive high doses of chemotherapy or radiation to destroy all leukemic cell-producing bone marrow. The marrow is then replaced with marrow from a compatible donor (i.e., *allogenic BMT*). ***Allogenic BMT is currently the only known treatment with the potential to cure CML*** and should ideally be performed when the patient is in the chronic phase of the disease. However, BMT has life-threatening risks and is not an option for all patients. Some patients are not healthy enough to tolerate the high doses of chemotherapy or radiation used before transplantation. The mortality rate associated with BMT may be as high as 25% with a matched sibling donor and 40% if the donor is unrelated. Approximately half of all patients with CML who undergo BMT achieve a cure. The best results (80% cure rate) are achieved in patients who are younger than 40 years of age and transplants are performed from a matched sibling within 1 year of diagnosis. Results of BMT with unrelated donor marrow are inferior but still provide a cure rate of 40–60% for an otherwise invariably fatal disease.

Autologous BMT (in which the patient's own bone marrow is used) is currently being studied as a treatment for patients who achieve a remission and then relapse. Healthy bone marrow is harvested from the patient during remission, frozen, then thawed and infused following relapse. Since this treatment for CML is new, there are no data showing its long-term effectiveness.

Stem cell transplantation is similar to BMT, except that stem cells are collected from the blood (rather than from the bone marrow) following a drug-induced increase in the release of stem cells into the blood. As with BMT, the cells can be harvested from the patient during remission or they can be collected from a compatible donor. This procedure is used more frequently than BMT because of its shorter recovery time and less risk for infection. Stem cell transplantation may also be performed with stem cells collected from the umbilical cord blood of newborn infants.

Before imatinib came onto the market, *interferon-α* therapy was standard treatment for patients who were too old for BMT or who did not have a matched bone marrow donor. This agent reduces the number of leukemic WBCs by stimulating the patient's immune system to specifically target cancerous WBCs for elimination. *Interferon-α* is still used when other treatments fail or are not an option (such as during pregnancy). However, it causes major side effects, including severe mood disturbances, psychoses, bone pain, and headache. Up to 2 years of therapy may be required before a remission is achieved. Complete elimination of the Ph chromosome has been observed in only one of five patients treated with this medication.

With *donor lymphocyte infusion*, lymphocytes are collected from a compatible donor and infused into the bone marrow of the patient with CML. Donor lymphocytes perceive leukemic WBCs as foreign, and attack and destroy them. This type of treatment is typically employed to supplement stem cell or bone marrow transplantation and is also known in the medical literature as *biological therapy*, *biological response modifier therapy*, or *immunotherapy*. This type of treatment leads to long-term remission in 50–70% of cases.

Some people with CML choose to enroll in clinical trials to try experimental treatments or new combinations of known therapies. In the rare instances in which symptoms of leukostasis and hyperviscosity of the blood result from extreme hyperleukocytosis, emergency leukapheresis is performed. With this procedure, a cell separator is used to temporarily lower WBC count rapidly and safely in patients with counts >300,000/cu mm.

As a palliative measure, splenectomy (i.e., surgical removal of the spleen) has been employed in some patients with large spleens that have been causing severe pain. This approach is rarely necessary, however, in patients whose disease is well controlled. Splenectomy is associated with high perioperative morbidity and mortality rates due to bleeding and clotting complications.

Disease Summary Question 8. If imatinib treatment fails and the patient is too old or a suitable donor is unavailable for bone marrow transplantation, what would you expect is the drug of choice for chronic myelogenous leukemia?

Serious Complications and Prognosis

The most serious complications of CML develop during the blast crisis phase and include infections and bleeding episodes. In addition, respiratory distress may result from extremely high numbers of circulating leukemic WBCs that cause blood to become viscous and slow-moving. Potentially serious complications may also arise from treatment; for example, BMT carries a high mortality rate and therapy with interferon-α may cause severe psychiatric disorders.

The probability for recovery from CML depends on a number of factors including the phase of the disease at diagnosis, the number of blast cells in the blood and bone marrow, the size of the spleen at diagnosis, the patient's health, and the patient's age. Poor prognosis is associated with several patient factors including older age, African-American descent, hepatomegaly, splenomegaly, anemia, thrombocytopenia, thrombocytosis, and basophilia. Several therapy-associated factors may also indicate a poor prognosis. These include:

- longer-than-usual time to hematologic remission with myelosuppressive therapy
- short duration of response to hydroxyurea
- poor suppression of Ph chromosome-positive cells by chemotherapy or interferon-α treatment

In the recent past, median survival with treatment was 3–4 years. However, in the era of imatinib therapy, >80% of patients remain alive and in remission at 4 years. It cannot be reliably predicted at this time to what extent long-term survival will be impacted by new treatment guidelines, but results have been very encouraging. At the current time, allogenic BMT remains the only treatment for CML with an established record for producing a cure.

Disease Summary Question 9. Propose a reasonable explanation for a finding of thrombocytosis in patients with chronic myelogenous leukemia.

Disease Summary Question 10. Explain why kidney stones are a potential complication of chronic myelogenous leukemia.

Suggested Readings

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