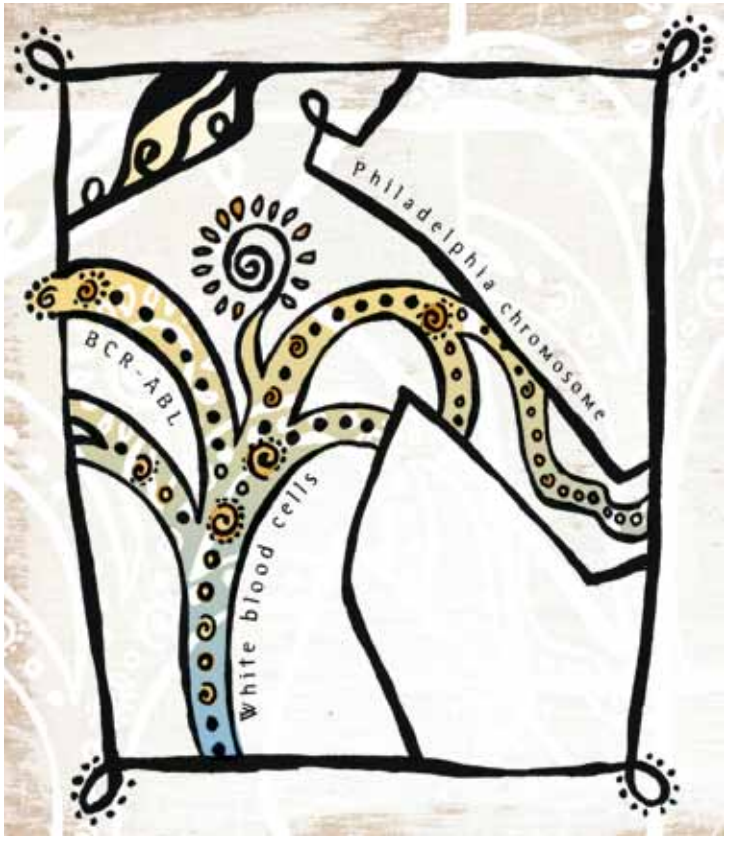
A Patient's Guide to CML



Molecular Biology ■ Diagnosis ■ **Stem Cell Transplant**
■ Monitoring ■ **New Drugs** ■ Questions to Ask ■ **and More**

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A Patient's Guide to CML

CHRONIC MYELOID LEUKEMIA (CML) is a relatively uncommon form of leukemia with an estimated 4,600 Americans diagnosed each year. The average age of CML diagnosis is around age 66, but about 2 percent of CML patients are children, according to the American Cancer Society. The disease is caused by the overgrowth of abnormal white blood cells in patients' bone marrow and bloodstream, which tends to crowd out red blood cells and platelets. Although most patients with CML have early-stage disease, when the disease progresses, anemia and recurring infections can occur.

MOST PATIENTS are symptom-free when the diagnosis is made, usually following a blood test for unrelated reasons. When patients do have symptoms related to CML, they often include fatigue, unexplained weight loss, fever, night sweats or pain on their left side under the ribs caused by the swelling of the spleen.

Although CML has no known common risk factors, patients who have been exposed to high doses of radiation do have a slightly increased risk. The most compelling link between radiation exposure and CML comes from the Life Span Study, which examined the late effects of Japanese survivors of the atomic bomb explosions in Hiroshima and Nagasaki in 1945.

Currently the initial treatment of choice for most, if not all, newly diagnosed CML patients is Gleevec® (imatinib), which entered clinical trials in 1998 and was approved by the Food and Drug Administration in a record 11 weeks in 2001—the fastest approved cancer drug at that time. Most of the patients who would have been offered a stem cell transplant now receive Gleevec as initial treatment. For patients who progress on Gleevec or are unable to tolerate its side effects, newer drugs such as Sprycel™ (dasatinib) and Tasigna® (nilotinib) look very promising.

This CML pocket guide will help you to better understand and live with the disease, while learning about new treatments and research. Additional information and patient support can be found through organizations such as **The Leukemia & Lymphoma Society (www.lls.org) and the American Cancer Society (www.cancer.org).**

Molecular Biology & Diagnosis

ONCE AN EXCESS OF WHITE BLOOD CELLS IS FOUND through a simple blood test, CML is relatively easy to diagnose by identifying an abnormal chromosome called the Philadelphia chromosome, which is present in 95 percent of CML cases and about 25 percent of acute lymphoblastic leukemia (ALL) cases.

The Philadelphia chromosome is created when the long arms of chromosomes 9 and 22 break off and switch places, called translocation. The abl gene, which is normally located on chromosome 9, becomes situated next to the bcr gene on chromosome 22, resulting in a fused gene called bcr-abl, now considered to be the initiating event in CML. Much has been learned of the molecular basis of CML and it was this knowledge that led scientists to develop Gleevec to effectively target the initiating event in CML.

Not all cases of CML are identical, so doctors use a variety of scoring systems to assess stage and risk of a newly diagnosed CML patient. Instead of dividing progression into stages like many other cancers, CML is defined as chronic phase, accelerated phase or acute phase (often referred to as blast crisis). The phase of CML is based on the percentage of immature white blood cells (called blast cells) compared with other blood cells in the bone marrow. (Although a CML diagnosis can be made by blood tests, examination of the bone marrow is useful in providing information that can be used for assessing the individual risks and helping the doctor tailor treatment.)

In the chronic phase, blast cells comprise no more than 5 percent of blood cells in circulating blood or bone marrow. Approximately 90 percent of people diagnosed with CML are in chronic phase because the disease is usually caught early. Most of these patients have no symptoms and are often diagnosed during a routine blood test. An increase in white blood cells in the bloodstream may be a sign of chronic phase CML.

When the blast cells reach between 6 to 30 percent in the blood or bone marrow, CML enters the accelerated phase. Patients will usually have an enlarged spleen, and fatigue and weight loss become more noticeable.

During blast crisis, the leukemia becomes more aggressive. In the bone marrow and the bloodstream, the blast cells make up more than 30 percent of blood cells. Because the blast cells crowd out red blood cells and functioning white blood cells, anemia and recurring infections become common. The cancer is hard to treat at this phase and survival is usually less than six months.

Though most patients are diagnosed with chronic phase CML, if left untreated or if the cancer is resistant to treatment, it can progress into the more advanced phases over a period of two to 10 years. This progression is thought to be due to acquisition of newer genetic abnormalities by the CML cell. Gleevec is currently considered part of the initial treatment of patients who present with CML in advanced phase, but stem cell transplant may also be considered.

The Sokal score, the most widely used prognostic scoring system, uses a combination of the patient's age, spleen size, platelet count and the percentage of immature white cells in the peripheral blood to calculate an overall score that is useful in predicting outcome of patients on Gleevec.

Gleevec: A Turning Point

A BETTER UNDERSTANDING OF the molecular biology of CML in the late 1980s and early 1990s led scientists to investigate the notion that a small molecule could be designed specifically to block the activity of bcr-abl and thereby block the initiating event in CML. STI571, today known as Gleevec, was soon developed and became the first molecularly targeted drug designed to interfere with the bcr-abl protein in CML cells.

Gleevec entered human testing in 1998, and data from three early-phase trials produced such positive results that the FDA granted accelerated approval to Gleevec in May 2001 for CML that either relapsed or failed to respond to interferon, and for patients unable to tolerate interferon's side effects.

A global phase III trial called IRIS compared Gleevec with a combination of interferon and Cytosar® (cytarabine), the standard treatment at the time, in newly diagnosed chronic phase CML patients. Thanks to excellent early results from the IRIS study, Gleevec was given full approval in December 2002 for the treatment of newly diagnosed CML, and became the preferred initial treatment. The immediate implication was that many patients who would have been offered a stem cell transplant, a risky procedure, could now receive Gleevec.

Five-year results of the IRIS study recently showed that 97 percent of chronic phase CML patients in the Gleevec arm achieved a complete hematological response (normalization of white blood cell counts) and 82 percent achieved a complete cytogenetic response (elimination of the Philadelphia chromosome). The overall survival at five years was 90 percent, and progression-free survival in advanced phases of CML was 92 percent. The survival of patients achieving a complete cytogenetic response was also noted to be significantly better than survival of patients treated in previous clinical trials with interferon alone or in conjunction with Cytosar.

Since all but 3 percent of the combination-treated patients switched over to the Gleevec arm of the IRIS study after progressing on interferon plus Cytosar—and subsequently responded to the drug over time—no long-term data exist for the interferon plus Cytosar arm.

In general, Gleevec is well tolerated at the standard daily dose of 400 mg. By binding to the bcr-abl protein on the leukemia cell, Gleevec shuts down the enzyme's activity, causing leukemia cells to die. Since healthy cells don't have the abnormal bcr-abl protein, they are unaffected by Gleevec, which spares patients from having to deal with side effects found with traditional chemotherapy drugs that damage healthy cells. Side effects with Gleevec can include low blood count, bone pain, rash, diarrhea, nausea and water retention. Rare cases of cardiac toxicity have been reported, so patients are closely monitored.

Currently, patients who do not respond to the standard dose are usually treated with higher doses of Gleevec (600 mg or 800 mg), which are currently being tested in clinical trials with various combination therapies. Side effects appear to increase with higher doses of Gleevec, particularly nausea, weight gain and muscle cramps. Patients who do not respond to high-dose Gleevec are considered to have Gleevec-resistant CML and are usually offered a "next-generation" drug.

Treatment for Gleevec-Resistant CML

DESPITE THE REMARKABLE EFFECTIVENESS OF GLEEVEC, about 15 percent of patients with chronic phase CML and almost all patients with advanced phase CML eventually progress on the drug. The risk of resistance increases with the number of years the patient received prior treatment and severity of the disease.

In mid-2006, an international panel met to develop guidelines on defining Gleevec resistance, which was then published in the journal *Blood*. The panel outlined the following goals of treatment:

- At three months, blood counts should begin to normalize.
- Within six months, blood counts should return to normal (a complete hematologic response) or at least show some cytogenetic response (percentage of Philadelphia chromosome-positive cells begins to decrease).
- At one year, the Philadelphia chromosome-positive cells should make up less than 35 percent of blood cells (partial cytogenetic response).
- At 18 months, no Philadelphia chromosome-positive cells are found using the most sensitive screening method available (a complete cytogenetic response; see "How to Monitor CML").

If these goals are not met, the patient's CML is considered Gleevec resistant. In addition, if new mutations arise or if the hematological or cytogenetic response is eventually lost while the patient remains on Gleevec, it's considered resistance.

To counter Gleevec-resistant CML, scientists have developed two novel drugs, Sprycel and Tasigna, both of which have shown benefit in clinical trials. Like Gleevec, both drugs turn off bcr-abl, but each work in a slightly different way.

Laboratory studies found Sprycel to be about 300 times more active than Gleevec, and the new agent blocks not only the enzyme related to bcr-abl but also a different enzyme called SRC tyrosine kinase, the precise role of which remains unclear in CML. Sprycel entered clinical trials in 2003 and received approval in June 2006 for the treatment of all phases of Gleevec-resistant CML. The current data for Sprycel in Gleevec-resistant chronic phase patients suggest a 90 percent complete hematological response and a 40 percent complete cytogenetic response. The response rates for patients with CML in advanced phases are also encouraging at up to 34 percent.

All side effects associated with Sprycel appear to be reversible and can include bone marrow suppression, rash, joint pain, headache and fluid retention, which can be problematic in about 10 to 15 percent of patients, particularly those who develop large fluid collections around the lung, heart or both.

Tasigna is about 30 times more potent than Gleevec, and current studies in Gleevec-resistant chronic phase CML patients demonstrated a 69 percent complete hematological response and a 32 percent complete cytogenetic response. In patients with advanced stages of CML, the hematological responses reached up to 45 percent, and cytogenetic responses neared 17 percent. The side effects of Tasigna can include bone marrow suppression, rash, joint pain, constipation, generalized itching and abnormal liver function tests, all of which

were found to be reversible in clinical trials. The drug is anticipated to gain FDA approval for Gleevec-resistant CML in 2007.

Mutations affecting more than 40 different amino acids have been described in patients receiving Gleevec. It is of interest to researchers that some mutations might actually be present prior to Gleevec therapy and do not necessarily reflect the patient's likelihood to respond to Gleevec. In contrast, some mutations, such as the T315I mutation and those involving the so-called "P loop" mutations, often carry a worse prognosis. Sprycel and Tasigna appear to work against all known Gleevec-resistant mutations except the T315I mutation. Scientists are now developing drugs that can work in Gleevec-resistant patients with T315I. Several candidate drugs are currently in clinical trials and early results are encouraging.

Because not all mutations carry a bad prognosis, debate has focused on the merits of subjecting a patient to a mutation analysis test except when there is evidence of emerging resistance to Gleevec. Mutations usually work by interfering with the way Gleevec binds to bcr-abl. Resistance to Gleevec can also arise from a number of other causes, such as the activation of alternate molecular signaling pathways, some of which might involve the SRC tyrosine kinase family, which may be why Sprycel works so well in some cases of Gleevec-resistant CML.

Currently, all newly diagnosed patients receive initial treatment with Gleevec, and then if resistance occurs, patients are offered Sprycel. Once approved, Tasigna may also be offered for such patients. Since both of these so-called second-generation drugs appear to be more potent than Gleevec, some researchers are looking at the potential of these drugs as first-line treatment. Ongoing studies with Sprycel in untreated CML patients are comparing it to two different doses of Gleevec, but data has not yet been published.

Once stronger drugs are given, there are few remaining options for patients who develop resistance. These patients can receive an allogeneic stem cell transplant, which is why doctors give treatment in a step-ladder approach, starting with Gleevec before moving on to stronger CML drugs. Add the possibility of combination regimens and newer drugs in clinical testing, and scientists believe that CML, if not cured, can become a chronic disease with minimal decrease in quality of life.

Stem Cell Transplant

THE SUCCESS OF GLEEVEC INITIALLY posed an enigma in terms of deciding the best initial therapy for chronic phase patients. This is important because the results of a stem cell transplant are best when the procedure is done as early as possible following diagnosis. The positive results obtained with Gleevec led to major revisions in the standard treatment for CML, but if a patient is identified as having a less-than-optimal response to Gleevec, transplant should be considered.

It is crucial to note that as drug therapy for CML has improved, so has transplantation. Improvements in the supportive care of CML patients, better conditioning treatments before transplantation and better donor selection techniques, among other things, have all contributed to better outcomes. There were initial concerns that prior Gleevec therapy might harm the success of a subsequent transplant, but that effect remains unconfirmed.

Allogeneic stem cell transplantation, a procedure where stem cells can be harvested from the bone marrow or blood of a donor, remains the only curative therapy for CML, but it comes with a caveat. The procedure can cause serious complications in at least one-third of patients and even result in death in about 10 percent of patients. One of the potential complications to transplant is graft-versus-host disease—when the new donor cells (the graft) recognize the patient's existing cells (the host) as foreign, which causes both acute and chronic side effects. Particular graft cells called T cells may attack the host cells. It usually begins as a rash on the hands and feet and progresses to diarrhea, liver damage and damage to other organs.

Whether from a related or unrelated donor, stem cells must be from a person with the same human leukocyte antigens (HLAs) on their cells. HLAs are unique protein markers found on nearly all cells in the body, but higher numbers of HLAs are found on white blood cells. The greater the number of matching HLAs, the better the chance the patient's body will accept the donor's stem cells. Patients who do not have an HLA-matched relative may be able to find an unrelated donor from organizations like the National Marrow Donor Program (see "Resources").

During an allogeneic transplant, the patient is given a conditioning treatment, which includes high doses of chemotherapy and sometimes radiation therapy. The principal goal is to prevent rejection of the donor cells by suppressing the host's immune system and to eradicate the cancer cells. Scientists have learned that the immunosuppressive effects are critical and make a large contribution to success or failure. These observations led to the minitransplant for older patients that uses lower doses of chemotherapy and radiation, making the treatment considerably less toxic.

Long-term remission has been reported in more than 80 percent of patients who receive stem cell transplants using a matched sibling donor. The results using a matched unrelated donor have also improved substantially, with long-term remission rates slightly lower than those achieved with transplants from related donors.

How to Monitor CML

NEW THERAPIES THAT PRODUCE complete cytogenetic responses in the vast majority of patients have necessitated a revision in the methods that were used to monitor CML patients in the pre-Gleevec era. A decade ago, regular blood counts and bone marrow tests to quantify the number of Philadelphia chromosome-positive cells were the principal methods employed to monitor recurrence or disease progression.

In the 1990s, learning from the few patients who achieved complete cytogenetic remissions but still relapsed, it became clear that such patients may harbor minimal residual disease. Efforts were then directed to understand the relationship between the type of response, the potential number of CML cells and the level of molecular disease.

In patients who achieve a complete hematologic response, defined as white blood cell counts returning to normal and regression of a large spleen to its normal size, patients may still harbor many CML cells in their blood. And patients achieving a complete cytogenetic remission may still have as many as a billion CML cells with the Philadelphia chromosome. In contrast, patients who achieve complete molecular remission, CML cells may number fewer than a million. Although it can be considered remission, many patients are told to continue therapy to prevent recurrence. The more cells a test can examine for the Philadelphia chromosome (called sensitivity), the better it can define a complete response.

There are several screening methods for detecting the abnormally short Philadelphia chromosome. However, the sensitivity of the molecular tests may vary substantially.

Fluorescent in situ hybridization (FISH) is more sensitive than the conventional chromosome analysis in detecting the Philadelphia chromosome and can detect up to one abnormal cell in 100. FISH uses labeled chromosome probes to locate the positions of bcr and abl genes. If the two genes are fused together, their presence near each other can be detected. False positives may occur if the two genes happen to be close together. Recently, laboratories started employing a FISH technique that uses double fusion probes to score the presence of bcr-abl twice in each cell. This increases the sensitivity and decreases the number of false-positive results. If no CML cells are found using FISH, the patient has achieved a complete cytogenetic response.

The most sensitive method for detecting specific bcr-abl mutations is reverse transcriptase polymerase chain reaction (RT-PCR). This technique amplifies a specific DNA sequence in a drop of blood and reads the pattern of the bcr-abl protein. Its high sensitivity can detect a single leukemia cell among a million normal white blood cells. The test can detect any residual CML disease after a stem cell transplant or monitor the response to a targeted therapy. If no cells are found to contain the bcr-abl gene in the blood during RT-PCR, it is considered a complete molecular response, the highest possible response.

Drugs in the Pipeline

ALTHOUGH THE OUTLOOK for the next-generation CML targeted agents is hopeful, researchers are still looking for newer drugs that will provide longer remissions and hopefully a cure for the thousands of patients living with CML.

Ceflatonin® (homoharringtonine), a chemotherapy drug, has been found in clinical trials to be useful in treating patients with relapsed disease when used alone or in combination with other agents, such as interferon. The FDA recently granted fast-track status to Ceflatonin, which will expedite its review of the drug.

Other candidate drugs include Zarnestra™ (tipifarnib), a drug being developed for acute leukemia that may have activity in CML and strengthen the effectiveness of Gleevec when used in combinations. Because these new medicines are targeted therapies designed to block one or more cellular proteins, scientists hope they can combine the drugs without greatly increasing side effects. Other drugs like Zolinza® (vorinostat), which was just recently approved to treat a rare type of non-Hodgkin's lymphoma, and Dacogen® (decitabine) are also in clinical testing for CML.

The T315I mutation in abl kinase makes CML cells resistant not only to Gleevec, but also to Sprycel and Tasigna. A new class of drugs called aurora kinase inhibitors appears to be effective in treating Gleevec-resistant patients with this T315I mutation. MK-0457 (also called VX-680) is an aurora kinase inhibitor that can overcome the effects of the T315I mutation. It is currently in phase I studies for Gleevec-resistant CML and has shown activity in patients with the T315I mutation. AT9283 is another drug in early-phase testing from this class that inhibits cell division.

A vaccine called GVAX that is currently being tested against various solid tumors has also found its way to CML. GVAX is an immunotherapy agent that has been shown to induce long-term remissions in Gleevec-resistant CML. Although the phase II CML trial only included 19 patients who progressed on Gleevec after at least one year, five patients had a complete molecular response and another five had a 90 percent reduction in bcr-abl. With a median follow-up of 14 months, nine patients continue to respond to the vaccine, although one patient has developed cytogenetic progression. Treatment with GVAX was well tolerated.

Another promising drug in development is SKI-606, which, like Sprycel, inhibits both bcr-abl and SRC enzymes. Early-phase trials found the drug to be very active in CML, and it appears SKI-606 has the ability to overcome most mutations, although it is not clear if it will be active against the T315I mutation. The drug appears to be well tolerated in patients with various cancers.

Resources

American Cancer Society
800-227-2345
www.cancer.org

Caitlin Raymond International Registry
800-726-2824
www.crir.org

The Leukemia & Lymphoma Society
800-955-4572
www.lls.org

Leukemia Research Foundation
847-424-0600
www.leukemia-research.org

National Bone Marrow Transplant Link
800-546-5268
www.nbmtlink.org

National Cancer Institute
800-422-6237
www.cancer.gov

National Marrow Donor Program
800-627-7692
www.marrow.org

QUESTIONS TO ASK

- What phase is my CML in?
- What treatment choices do I have?
- Which treatment do you recommend and why?
- Should we think about a stem cell transplant at this time?
- What side effects are there to the treatments you recommend?
- What can I do to help reduce the side effects I may have?
- What are the chances that my leukemia will come back once I am in remission?

Adapted with permission from the American Cancer Society (www.cancer.org).

Glossary

Accelerated phase: Blast cells comprise between 6 and 30 percent of circulating blood cells in the bloodstream and bone marrow.

Allogeneic stem cell transplant: A procedure where stem cells from a healthy donor are removed and transfused into the patient. The patient usually receives conditioning therapy before the transplant consisting of high doses of chemotherapy or radiation to kill cancer cells.

Bcr-abl: The abnormal gene created from the translocation of chromosomes 9 and 22 (called the Philadelphia chromosome); the marker of CML for 95 percent of patients.

Blast cell: An immature white blood cell.

Blast crisis: Resembles acute leukemia in that more than 30 percent of blood in the bloodstream and bone marrow are blast cells; also called acute phase.

Bone marrow: Located in the center area of the bones, bone marrow is where the various blood cells are made from stem cells.

Chronic myeloid leukemia: A slow-progressing cancer that causes the body to produce too many cancerous myeloid white blood cells.

Chronic phase: Blast cells comprise no more than 5 percent of blood cells in the bloodstream or bone marrow; early-stage CML.

Cytogenetic response: A change in the course of a patient's disease when treatment reduces the number of cells carrying the abnormal Philadelphia chromosome.

Fluorescent in situ hybridization: A method to identify cells in which the nucleus contains the Philadelphia chromosome; also used to determine if treatment is working by revealing the number of CML cells in the blood.

Hematologic response: A decrease in the number of white blood cells in the circulation to a normal level after treatment.

Molecular response: A complete molecular response signifies that no CML cells with the bcr-abl gene are detected using the most sensitive technology.

Philadelphia chromosome: The chromosome created after translocation of genetic material of chromosomes 9 and 22 that is responsible for CML.

Polymerase chain reaction: A sensitive test that amplifies specific DNA and makes it possible to detect the alteration in DNA caused by chromosome translocation in CML; can detect a single cell positive for bcr-abl in a population of 500,000 normal cells.

Stem cell: An undifferentiated cell that matures into various types of cells, including blood cells.

Translocation: When genes or sections of chromosomes are switched between two different chromosomes; the translocation can be harmless or produce abnormal results depending on the information exchanged.

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