A Candid Conversation about

CML

BY DON JEWLER

Oncology Issues interviewed Stuart Goldberg, MD, Chief, Division of Leukemia, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack N.J.

OI. *What is chronic myeloid leukemia?*

SG. CML is a clonal myeloproliferative disorder of hematopoeitic stem cells. CML accounts for about 15 percent of all adult leukemias. In 2009 an estimated 5,050 cases were diagnosed in the United States. Put in perspective, CML cases represent one-fortieth of the breast cancers or lung cancers that clinicians see. In 2009 an estimated 470 patients died from the disease. CML affects mostly adults (see Table 1, page 45). The median age at diagnosis is 66 years, but CML affects people at all ages.

OI. *What causes CML?*

SG. We don't know what causes CML. It is not smoking or drinking. It is just one of those unfortunate sporadic diseases. There was a small increase in CML cases following the atomic bomb blasts, so radiation exposure may play a small role.

OI. *What can community cancer care providers learn from this disease?*

SG. Chronic myeloid leukemia, or chronic myelogenous leukemia (CML), is a "small" cancer that teaches us about "big" cancers and much about the field of oncology in general. Many of the major breakthroughs in oncology have come about from studies of this small-population disease. For example, in the early 1960s, about a decade after James Watson and Francis Crick discovered the structure of DNA, investigators at the University of Pennsylvania in Philadelphia noted that patients with CML had a specific genetic break. For the first time we came to understand that when a chromosome is "abnormal" it can cause a disease such as cancer.

CML was the first human cancer associated with a specific genetic abnormality, the "Philadelphia chromosome" formed by a translocation between chromosomes 9 and 22. Treatment of CML with interferon, one of the first synthesized biologic therapies, led to improvements in survival and demonstrated the value of following cytogenetic responses (a first biomarker) in predicting survival.

CML also played a substantial role in marrow transplantation, becoming the first major use of transplantation. Observations of outcome data have taught us about graft-vs-leukemia effects and the power of donor lymphocytes in controlling relapse, leading to the modern reduced-intensity "mini-transplants." And, of course, CML is now treated with tyrosine kinase inhibitors, which were among the first rationally developed targeted therapies.

If you're going to learn only one disease in oncology, I tell my medical students, learn chronic myeloid leukemia, because the entire history of oncology can be summarized in the history of CML.

OI. *How do patients know if they have CML?*

SG. They don't. In the beginning CML is silent. About 40 percent of patients are asymptomatic, and those with symptoms usually complain of only minor fatigue, abdominal pain (from an enlarged spleen), or gout attacks (see Table 2, page 45). Most patients who walk into the family physician's office for a yearly check-up and are told they have CML come in feeling well. At least once or twice a year, I'm called down to our emergency room to see some young man who came in because he twisted his ankle playing basketball, for example, and he walks out with a diagnosis of leukemia.

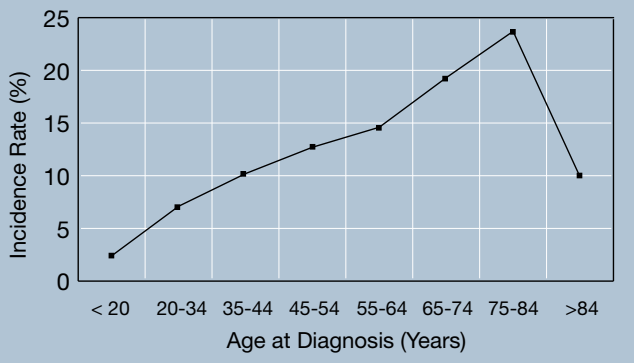
OI. *What is the progression of CML?*

SG. CML usually progresses through three phases: a largely asymptomatic chronic phase, a transitional accelerated phase, and a rapidly fatal blast phase also known as a blast crisis (see Table 3, page 46). If the disease is left untreated, the time to progression from chronic phase to blast phase is typically 3 to 5 years.

In the beginning, the chronic phase, bone marrow is turned on—too many cells are produced. For the most part, the cells work and look relatively normal under the microscope. Thus, the lack of symptoms is explained. However, like a factory operating at 200 percent of capacity for too many years, the machinery starts breaking down and making errors. In CML, the marrow starts to degenerate with new genetic alterations in addition to the Philadelphia chromosome (known as clonal evolution). This damaged marrow factory begins to make products that do not work so well—big ugly cells called blast, which are like weeds in a garden. They do not function—all they do is take up space. These new cells appear in the peripheral blood and

Table 1. Incidence of CML*

Cases Diagnosed Between 2002 and 2006



*Overall incidence rate is 1 to 2 cases per 100,000 people per year[1,2]

[1]SEER Stat Fact Sheets–Chronic Myeloid Leukemia. Available online at: *http://seer.cancer.gov/statfacts/html/cmyl.html*. Last accessed Nov. 18, 2010.
[2]Faderl S, Talpaz M, Estrov Z, O'Brien S, et al. The biology of chronic myeloid leukemia. *N Engl J Med.* 1999;341:164-172.

Table 2. Common Characteristics of CML Patients at Presentation[1-3]

Approximately 40 percent of patients are asymptomatic[1]

Clinical Presentations
- Fatigue, abdominal fullness, weight loss
- Splenomegaly
- Purpura, bleeding

Peripheral Blood Findings
- Increased white blood cell count
- Increased platelet count
- Decreased red blood cell count
- Basophilia, eosinophilia
- Low leukocyte alkaline phosphatase
- Peripheral blood smear shows granulocyte differentiation

Bone Marrow Findings
- Hypercellular
- Elevated myeloid:erythroid ratio
- Elevated megakaryocytes
- Myeloblasts usually <5%

[1]Sawyers CL. Chronic myeloid leukemia. *N Engl J Med.* 1999;340:1330-1340.
[2]Faderl S, Talpaz M, Estrov Z, O'Brien S, et al. The biology of chronic myeloid leukemia *N Engl J Med.* 1999;341:164-172.
[3]DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practices in Oncology.* Vol 2. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

in the bone marrow in what is called the accelerated phase. Shortly after, these blast cells feed off each other and fill up the bone marrow. Basically, the bone marrow shuts down. The disease ends in what is called the blast-crisis.

To put it simply, patients with this disease are sitting on a time bomb with a long fuse of 4 and a half to 5 years during which time they feel completely normal. While the fuse is burning, they feel fine, but without treatment the bomb eventually explodes.

OI. *Can we lengthen the fuse?*

SG. Let's go back a little in history and talk about the biologic agent interferon. Interferon is a natural chemical, but it has nasty side effects. It makes people feel achy, like they have a flu, because indeed your body gives off this chemical when you fight a virus. Interferon not only fights viruses, but it can also suppress CML. It can lengthen that fuse before the bomb goes off.

We found, however, that not everybody benefited from interferon. If most patients lived 5 years before interferon, with interferon most patients were living 7 years, and they were feeling lousy during these years.

Every tenth patient that we treated did live very long and maybe was cured. The biologic modifier interferon suppressed expression of the Philadelphia chromosome and improved survival in a small proportion of patients. We could identify which patients were likely to become long-term survivors by treating patients for one year and then repeating a marrow evaluation to examine chromosomal changes. Those individuals who suppressed or lost the Philadelphia chromosome at the one-year evaluation were likely to become survivors.

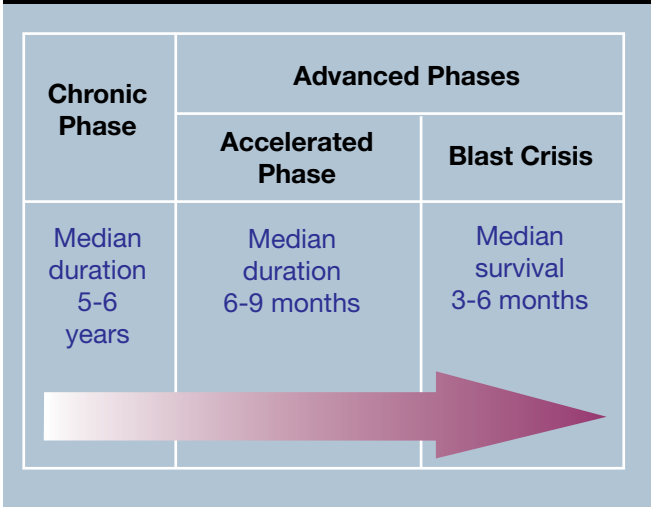
Since most patients did not respond to interferon, marrow transplantation emerged as the treatment of choice for CML. In fact, the most common reason to undergo an allogeneic transplant in the 1990s was CML. Transplants could cure 60 to 70 percent of patients, but unfortunately treatment-related morbidity and mortality were formidable. Today transplants are principally used in patients not responding to tyrosine kinase inhibitors (TKIs).

OI. *Is inhibiting tyrosine kinase the key to successful treatment?*

SG. BCR-ABL-targeted therapy was a game changer. Since the Philadelphia chromosome is the key driver of the disease, in the late 1990s investigators began to develop treatments focusing on this abnormality. The Philadelphia chromosome is formed when a piece of genetic material from chromosome 9 breaks off and attaches to chromosome 22, and a piece of 22 breaks off and moves to chromosome number 9 (a "balanced translocation") (see Figure 1, page 47). But it is not an even swap. Nine gives a small piece. Twenty-two gives a big piece, and chromosome 22 appears smaller than normal. This small 22 chromosome can be identified as the Philadelphia chromosome.

What is really happening in CML is quite interesting. Chromosomes are made of DNA base pairs, like letters of the alphabet. They spell out words that get translated into proteins; between words are spacer letters. The ABL gene on number 9 and the BCR gene from 22 when separated on respective chromosomes do not do much. But smash them

Table 3. Clinical Course: Phases of CML



together—it's like putting half a sentence next to another half sentence, and, now you have a whole sentence that means something. On the new Philadelphia chromosome we have the BCR and ABL genes next to each other. This produces a new protein (bcr-abl1) that normally does not exist in people. This protein functions as a "tyrosine kinase," actively telling the cell to grow. Important for treatment, only the cancers' bone marrow cells have the cancerous gene protein, while healthy blood cells do not. Thus, we have a unique change and target in the cancerous CML cell.

Imatinib (Gleevec) revolutionized the treatment of CML, bringing hope of prolonged survival to most patients without the need for transplantation. By selectively targeting the causative BCR-ABL fusion protein, imatinib induced deep cytogenetic and molecular remissions that can be monitored using sensitive PCR-based assays. More than 70 percent of CML patients achieved a cytogenetic response within the first year of treatment with imatinib, and by two years of treatment, cytogenetic response rates approached 90 percent. Most of these CML patients are projected to have long-term survival.

Imatinib, unlike traditional cytotoxic chemotherapy, targets the cancerous cell while sparing the healthy cells. The medication is usually well tolerated with minimal side-effects. However, an important clinical issue is imatinib resistance—a failure to achieve early, time-based milestones or a loss of prior responses.

During the past decade we learned to pick out those patients early who were not responding, so that we can change treatment before the "fuse" burns out. The approvals of two additional TKIs, dasatinib (Sprycel) and nilotinib (Tasigna) offer options for patients with CML who experience imatinib failure. Both dasatinib and nilotinib achieve responses in the range of 40 to 50 percent when given to patients progressing on imatinib. Because both agents have different spectrums of side effects, both work very well in intolerant patients. This year, major randomized clinical trials have demonstrated that the newer "second generation" tyrosine kinase agents are able to get more newly diagnosed CML patients into remission than imatinib, thus leading to new first-line indications for both medications.

OI. *Can you say a few words about the PCR test?*

SG. Modern techniques allow us to look at the Philadelphia chromosome. We can look at it by either doing a bone marrow test (classical karyotype) that patients do not like, or we can do peripheral blood studies where we can look at the chromosomal break by a technique called FISH, fluorescence *in situ* hybridization. Both tests sample only a few cells (20-200 average). Alternatively we can look for the protein formed by the Philadelphia chromosome (bcr-abl1) using a test called PCR, or the polymerase chain reaction-based assay. PCR tests can be performed on the blood and examine over 10,000 cells. They can be used repeatedly to follow a patient's response to treatment.

An international collaborative effort has been underway to standardize this sensitive test. Under the current system, the "average" amount of bcr-abl1 protein in a newly diagnosed patient is defined as an IS (international standard) value of 100 percent. A major molecular response (MMR) from which most patients will not relapse is achieved at an IS of 0.1 percent (or a three-log reduction in the amount of cancerous protein). Most current treatment recommendations advise following blood PCR values on CML patients every 3 to 6 months, and if the values are low (below 1 percent) and stable and/or falling to continue treatment, whereas a rising PCR value may indicate a loss of response and the need to change therapies.

OI. *How can physicians keep up with rapidly changing treatment options when they see just a few patients with CML a year?*

SG. Keeping up with the research on "small population cancers" is tough. These cancers are common enough to see every year in a typical oncology practice and rare enough to make it hard to devote substantial learning time at meetings when other disease updates on breast, colon, and lung cancer are being presented.

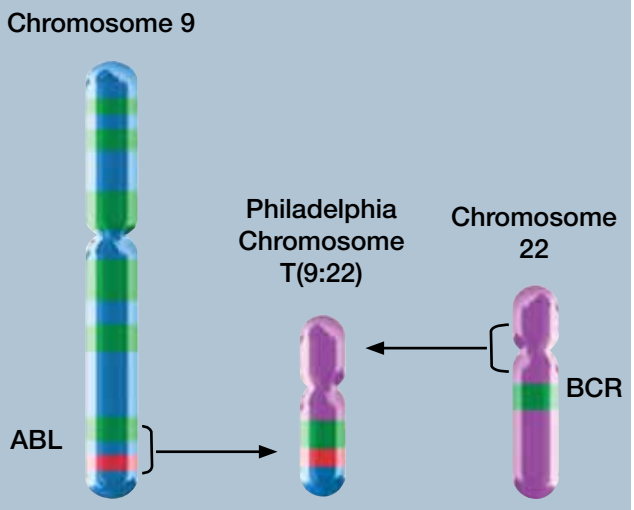
My first recommendation is to read the clinical guidelines when a patient is evaluated. We all have access to the NCCN guidelines online. The European LeukemiaNet guidelines are also quite good. Unlike the "big cancers," we do not have to commit this information to memory; we just need to know where to find it when the patient comes in.

Do not throw away the educational books you receive from the ASH and ASCO annual meetings. I put them on my shelf. They are also available on the Internet. A quick scan from the most recent annual meeting review will keep most physicians up to date. I often put articles or a copy of the guideline flow sheet in my charts as reminders.

My next recommendation is for physicians to use the experts in their community. They should use mentors when

Figure 1. Philadelphia Chromosome—Hallmark of CML

- CML is characterized by the presence of the Philadelphia (Ph) chromosome
- Created by reciprocal translocation between the breakpoint cluster region (*BCR*) gene (located on chromosome 22) and the *ABL* gene (located on chromosome 9)



they see a rare disease. Use them even if they are the "competition." I receive calls every day from physicians who are my competition. Some may say, "The PCR did not drop as much. Do I have to worry about this?" Answers to these questions in a ten-second phone call may save a patient's life.

Note that the availability of newer agents, coupled with the benefit of administering second-line therapy before disease progression to advanced stages, places new responsibilities on clinicians to monitor patients carefully to ensure that non-responders are identified and switched to the appropriate therapy as early in the disease process as possible.

OI. *As an expert and consultant, have you seen community physicians make mistakes in treatment of CML patients?*

SG. One of the biggest mistakes I have seen is that physicians measure PCRs either too often or not enough. A PCR every month is of little benefit especially if the patient has achieved a complete cytogenetic remission. Even more concerning is that some physicians may forget to measure PCR at all. Remember, it is the cytogenetic response and *not* the peripheral blood counts that predicts survival. If a patient's PCR values for the bcr-abl1 fusion protein start going up, this $200 to $300 test can tell you the patient is at risk for relapsing and that new therapies might be needed.

OI. *Can you speak to the economic impact of CML?*

SG. Due to the improvements in frontline treatment since the 1970s, the majority of people with CML are now living at least 5 years after their diagnosis. When a 30- or 40-year-old patient becomes a long-term survivor and a contributing member to society, the positive economic implications are significant. At the same time, CML presents economic challenges because current TKIs are extremely expensive and must be taken at this point for a lifetime. The success of the tyrosine kinase inhibitors is leading to more long-term survivors. Some estimates suggest that this "small" disease of 4,000 cases per year may reach a quarter million by 2050. With so many patients on expensive medications the cost to society may be daunting.

OI. *What interests you most about CML?*

SG. CML remains an exciting disease for the development of new ideas and treatment paradigms in cancer management. I believe the next big breakthrough in oncology, the next new idea, will come from this disease, because it is so simple and elegant. Tyrosine kinase-targeted therapy, biomarkers, molecular monitoring, transplantation, and donor lymphocytes to change the immunologic response—these are all expanding beyond CML into other more common diseases. For a small cancer, CML cancer has taught us a great deal.

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The Association of Community Cancer Centers (ACCC) has launched an educational program to provide community-based cancer care providers the tools they need to improve the quality of care for patients with small-population cancers. This educational project has been initiated with a focus on chronic myeloid leukemia (CML).

ACCC seeks to understand the barriers to treatment and to assess the most effective practices for treating CML within the community setting. To that end, we surveyed members about CML and are in the process of conducting extensive interviews to identify effective practices in treating patients with small-population cancers such as CML. Results will be presented and disseminated in early 2011.

Check out our CML online resource at: *www.accc-cancer.org/education/education-CML-resourcepage.asp.*

The project is made possible by an educational grant from Novartis Oncology and will take two years to complete.