Lessons in Blood Cancer: How Far We Have Come – CML (Chronic Myeloid Leukemia)

TRANSCRIPT

Narrator
Doctors and researchers have been studying cancer for generations. Thanks to pioneers in science and tireless dedication, we have made great strides in diagnosis, treatment, and the quest for a cure.

But we need to understand where we started to learn how to get where we are headed.

Join us as we explore the history of blood cancer and highlight just how far we've come.

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Treating patients with CML in and of itself is very rewarding. You're taking a patient who's often very scared, very worried at the time of their diagnosis, and you're giving them a treatment that is usually successful, usually associated with a good quality of life and a great life expectancy.

What is CML?

CML stands for chronic myeloid leukemia. It is a leukemia, so that means it is a cancer of the bone marrow and in the blood. It is a chronic leukemia, which means that it is not as aggressive as some of the other types of acute leukemias. But it is a leukemia that typically presents with a very high white count; sometimes patients will also have an enlarged spleen.

CML is caused by a genetic abnormality found in the bone marrow, something called the Philadelphia chromosome, and that Philadelphia chromosome results in an abnormal gene product called BCR::ABL1. And because of that abnormal BCR::ABL1, that causes white blood cells in the bone marrow and in the blood to grow exponentially – to divide, to replicate without dying. And if that happens over a long period of time, that results in what we know as chronic myeloid leukemia.

The Evolution of CML Treatments

The first attempts at treating CML included compounds that contained arsenic. This was back in the late 19th century. Of course, arsenic wasn't very effective, and it was also very toxic, so it was quickly abandoned as a therapy for CML.

In the early 20th century with the advent of ionizing radiation as a therapeutic option, which was used to shrink spleens for patients who had very large and uncomfortable spleens.

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In the mid-20th century, we began to use chemotherapy drugs, medications such as busulfan, and later on hydroxyurea. And these are drugs that had some activity. They could lower the white count in patients with CML, but they didn't substantially change the course of the leukemia.

In the late 20th century, we began using a medication called interferon. It's an immunomodulatory agent. It did have some efficacy, but it only worked in a very small proportion of patients, so most patients did not benefit from interferon.

In the late 1970s going into the 1980s, it became evident that hematopoietic stem cell transplantation could be a very effective treatment for CML and some CML patients were cured. However, this was associated with a number of toxicities and risks, particularly in that time period. And maybe more importantly, most patients were not eligible for transplantation. So that still left a large majority of patients with a leukemia that was very difficult to treat.

In the 1990s, scientists began investigating the use of drugs that were able to inhibit directly the BCR::ABL1. The first candidate drug that they discovered was something called imatinib (Gleevec®). There was a physician scientist named Brian Druker who was and still is in Oregon, and he led some of the first clinical trials using imatinib for the use [in] CML, and they saw remarkable results. Imatinib worked extremely well, very quickly, and had an excellent safety and side-effect profile. So, when this drug was approved in 2001, it instantly became the standard of care for patients with CML and instantly transformed the disease into one that could be well-controlled in the large majority of CML patients.

Since imatinib was discovered, that became the standard of care for CML, but there were still some patients who did not respond well to imatinib. Their CML was resistant to imatinib, and therefore there was a need for additional drugs that were available for those patients. Fortunately, with imatinib, we had a blueprint for how to create a drug for CML. So they were able to use that blueprint and find other drugs that were similar to imatinib, had the same mechanism of action, but had a slightly different pharmacology to [them]. So, there were several of these drugs that then became tested in clinical trials and then became approved later on.

So nowadays, we have a total of six different tyrosine kinase inhibitors that we use for CML. In some ways, it is a wealth of riches because we have so many effective drugs for CML, but as a treating physician and as a patient, it is great to have these different choices because we try to find the drug that works the best for our individual patients.

In the other half of patients, however, we do see an increase in the BCR::ABL1 values and that means that we have to restart their CML medication. But it has been found to be a very safe and an effective treatment for a group of patients with CML.

The Role of TKIs

TKI stands for tyrosine kinase inhibitor. Tyrosine kinases are normal proteins that are found in all of our cells in the body. Some of these tyrosine kinases can become abnormal and become overactive, and that can lead to different types of cancers or contribute to different types of cancers. Tyrosine kinase inhibitors are small molecules. They are drugs that inhibit specifically tyrosine kinases and decrease their activity.

So, for example, imatinib is a tyrosine kinase inhibitor that was specifically developed to inhibit the BCR::ABL1 gene and the BCR::ABL1 protein and its tyrosine kinase. And by doing so, you shut off the tyrosine kinase activity and you kill leukemia cells.

Prior to the current era of tyrosine kinase inhibitors, patients with CML, first of all, had a disease that had very limited therapies. So, these patients had a life expectancy of about five years. There were some treatments available, many of them were not very effective. Some of them, like interferon, you had to give yourself injections that were sometimes painful every day of the week. With the advent of tyrosine kinase inhibitors, first of all, it is an oral medication, so it is easier to take. And because it is a targeted agent, it is associated with fewer side effects than other drugs. And so, most patients I would say, or the large majority of patients, have an excellent quality of life with these tyrosine kinase inhibitors. It is very important for patients as well as their physicians to determine whether patients are having side effects to these medications because they certainly are possible, and it is up to the physician and the patient to figure out how best to manage these side effects. Sometimes we think about reducing the dose of the drug and it can still be very effective. Sometimes we think about other adjunctive treatments to try to handle these side effects, and sometimes it is necessary to switch therapies (that is, switch to a different TKI for certain patients).

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A Cure for CML?

We're a little bit hesitant to use the word cure right now because in most patients with CML, if we looked hard enough and if we had the technology to do so, we would be able to find evidence of CML cells in the body and in the bone marrow.

However, with the advent of treatment-free remissions for some of our patients, this can be thought of right now as a potential functional cure.

Over the last 10 years, probably the biggest advance in our treatment for CML patients was the possibility of a durable treatment-free remission, meaning that some patients with CML could stop their CML medication and still remain in a very deep remission, long-term, probably indefinitely, hopefully for the rest of their lives.

Improved Quality of Life

Back in the day, when we were monitoring patients for CML, we would have to do bone marrow biopsies very frequently, perhaps every three months for patients, and they can sometimes be a difficult and painful procedure. Now we have a test called a BCR::ABL1 quantitative PCR. It is a simple blood test, and that is how we monitor patients with CML. And since we are just using simple blood tests to monitor CML, that is associated with a greatly improved quality of life compared to before.

A Hopeful Future

I would tell patients that for the large majority of patients with our currently available very effective therapies, first of all, that they can have an excellent quality of life. They can have their CML under very good control, and they can have a life expectancy that is similar to other people who don't even have CML. Even beyond that, we are hopeful that we can get to the point where we can have patients – a large number of patients – with CML, able to stop their tyrosine kinase inhibitors and have a prolonged treatment-free remission. So, I think a cure, or at least a functional cure, is definitely one of our goals for our patients in our lifetime.

How Far We Can Go...

So, it is an incredible time to be a practicing hematologist nowadays. The number of advancements that we have made just in the past 10 years that I've been practicing [has] really been extraordinary. That has translated to patients doing much, much better than before. And so I can say when I see patients in my clinic, there are a number of patients every day who are doing so well, who have maybe had a terrible prognosis before if they were diagnosed 10 to 20 years ago, and now we have been able to overcome those odds so that they are living healthy, productive lives.

Narrator
For more information about CML and other blood cancers, please contact an Information Specialist at 1-800-955-4572 or visit www.LLS.org/InformationSpecialists.

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