Is CML Curable?

We've been asked lately if CML is curable. Yes, CML is curable and here is why we think this is so.

**First, a Little History**

Did you know that the first case of CML was first diagnosed in Scotland in 1845 and then a second case was reported a few weeks later in Berlin? In 1872, it was observed that leukemic stem cells come from the bone marrow. However, it was in a lab in Philadelphia in 1962 that two researchers working together, Lowell and Hungerford located the Philadelphia Chromosome. This was a very significant event as it showed that cancer, and CML in this case, could be traced to a problem in the DNA. In 1972 Janet Rowley showed that there was a translocation, or exchange of gene material, between chromosomes 9 and 22 associated with leukemia, and specifically CML. Through the decades a variety of treatments have been helping most patients extend their lives. But it was a significant breakthrough by Alexander Levitzki who showed that ABL inhibitors could be effectively used in inhibiting tyrosine kinases and blocking cancer. Today we have three approved Tyrosine Kinase Inhibitors and another one far advanced in clinical trials (M. Deininger, ASH 2008, CML Educational Session). Most important thanks go to Dr. B. Druker for his tenacity while working with Signal Transductions Inhibitors, or STI 571, now known as Gleevec or Glivec, that proved the concept of targeted therapies and greatly improved the lives of CML patients. Dr. Druker’s worked rallied the entire CML community of scientist, doctors and patients as never before.

Simply put, tyrosine Kinase inhibitors block the function of ATP, which is like an energy cell. Blocking the function of ATP in turn blocks the function of the protein generated by BCR ABL, which slows proliferation (which is what any cancer really is, over proliferation of cells that go un-checked by the body’s immune system) of CML. This is a very simple description of it; there are other more technical and much more eloquently stated descriptions. Don’t hesitate to google and find the one that helps you understand the best.

Before Tyrosine Kinase Inhibitors there was Interferon. Interferon is a biological immune modifier. Interferon on its own had a very difficult time to combat CML and BCR ABL outsmarted and overwhelmed it. Consequently many patients had to take incredibly high doses of Interferon to try to stop CML from progressing to its more deadly accelerated phases. A high dose of interferon induces an incredible amount of side effects that are very difficult to deal with and greatly diminish a patient’s quality of life. However, there was some good news; some patients, a small percentage, close to 12% by some reports, could be successfully treated with interferon and were able to stop taking the drug without relapsing. Some of these patients have been tracked for more than 20 years without relapse. These results added to the data of the patients who responded to an allogenic bone marrow transplant, suggest to us that CML is curable.

We were all quite fortunate when Gleevec™, the world’s first Tyrosine Kinase Inhibitor started in Phase I trials and successfully went on to Phase II and expanded access programs. I am not going to expound too much on the success of these drugs, the data shows us that lives have been extended and with the newer drugs, quality of life is improving as well. For those who have the misfortune of developing resistance to one drug or another, we are lucky that there are second-generation drugs such as Sprycel™ and Tasigna™ as well as additional drugs in trials.
But what about the cure?

At ASH 2008 there was an update on the study that was started by Dr. Mahone in France and it is quite exciting. There were 15 patients in France who decided to stop treatment with Gleevec™ for one reason or another, so the opportunity was taken to observe what would happen to them. 7 of the patients relapsed within 6 months, however, 8 of the patients in this very small cohort pilot study, did not relapse. These patients have been followed for more than 37 months. Interestingly it was noted that these patients had been “pre-treated” with interferon. Could it be that pretreatment with interferon confers some advantage? That was the hypothesis, but the hypothesis would need further testing, so they enrolled another 69 patients from 22 different centers in France. The criterion was that they had to have been in a complete molecular remission and PCR undetectable for two years consecutively, before being allowed to stop Gleevec™. Of these 69 patients, 27 patients have relapsed; 13 were pretreated with IFN, and 14 were only treated with Gleevec™.

The big news is that at 9 months follow up 46% (or approximately 31) of these patients are still in remission, of those 46% patients, 53% were pretreated with interferon and 39% are “de novo” patients (have only been treated with Gleevec™). Earlier we mentioned that on Interferon alone, some sources reported up to 12% of patients could be taken off the drug. Added with this new information, we can explore the hypothesis that the early results with interferon alone could be greatly improved with the addition of a targeted therapy like Gleevec™. The other good news is that most patients who relapsed after stopping Gleevec™ quickly regained their molecular response: “Dr. Mahon also emphasized that all of the patients who relapsed were sensitive to Imatinib after it was restarted. Some of the relapsed patients went back into remission very quickly, but for others, it is a slower process. Although the follow-up in this particular study (69 patients, 22 centers) is short, patients in the pilot study have now been followed for several years. “The results from both of these trials confirm that complete molecular response can be sustained after Imatinib is discontinued. This is particularly true for patients who have been pretreated with interferon, said Dr. Mahon”.

It seems possible that the combination of both Gleevec™ and other Tyrosine Kinase Inhibitor’s for that matter, with something like Interferon can improve the potential for patients to enjoy a relapse free and drug free remission. Not sure if that is the exact same thing as a cure, but we would like to see what it is like to not have to think about one drug or another, wouldn’t you?

Earlier in this essay, it was mentioned that CML could be traced to a problem in the DNA. This is very good news, because now we know that our DNA doesn’t exactly “seal our fate” as we once thought it did. There is new research about epigenomes. The really basic take away about epigenes is that they can be switched one way, and that means that they can be switched back too! Read the really cool article about this here: Whew! Your DNA Isn’t Your Destiny

There are now more centers participating in allowing patients to try to stop Gleevec™ and we think that this is very exciting. Importantly, there is research going on in many areas that helps us all to learn more about this disease. This is vitally important to us as these drugs are very expensive and are creating a significant socioeconomic hardship for CML patients and their families. This was evident with the results of the international CML patients survey presented at a satellite symposium at a ASH in December 2008. Visit the CML Society website for the video presentation.

Saying CML isn’t curable would be ignoring the great successes we have had in helping people with CML to enjoy improved survival rates. So stay healthy, continue to learn along with us and importantly, stay informed.

Is CML Curable? We can certainly say we are counting on it!

Disclaimers: Please note the clinical trial data presented here was from a relatively small cohort of patients who were good responders to therapy. While the results seem quite positive, do not attempt to stop your therapy. If you have any questions about your current treatment, please discuss them with your doctor.

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