CML: Updates from the American Society of Hematology (ASH®) Annual Meeting

David L. Porter, MD
January 26, 2012

Slide 1: CML–Updates from the American Society of Hematology (ASH®) Annual Meeting
OPERATOR:
Hello, everyone, and welcome to *CML–Updates from the American Society of Hematology (ASH®)* Annual Meeting, a free telephone/web education program. It is my pleasure to introduce your moderator Mabel Maia of The Leukemia & Lymphoma Society.

Slide 2: Welcome and Introductions
MABEL MAIA:
Thank you. Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you and a special thanks to Dr. Porter for sharing his time and expertise with us today.

We have over 800 individuals participating today from across the United States and many international participants from Bangladesh, Canada, Egypt, France, Greece, Guatemala, India, Mexico, Pakistan, Uruguay and Ireland. We welcome all of you.

We would also like to acknowledge and thank Novartis Oncology and Bristol-Myers Squibb for their support of this program.

Following Dr. Porter's presentation we will take questions from the telephone and Web audiences.

I am now pleased to introduce Dr. David Porter, Professor of Medicine Director, Blood and Marrow Transplantation Hospital of the University of Pennsylvania in Philadelphia. Dr. Porter, we are so privileged to have you with us today and now I turn the program over to you.

Slide 3: CML 2012
DR. DAVID PORTER
Thank you very much, Mabel. This is my pleasure indeed.

I do want to also thank The Leukemia & Lymphoma Society for asking me to participate in what I hope is going to be an interesting, informative and hopefully important program today.

I'd also like to say at the beginning of my presentation how much I truly believe the LLS does wonderful things for so many patients. These educational sessions are just one example of the remarkable support and the resources that they can provide.

I want to thank all of you for taking the time out today to listen and to join today's program. And I find the interest from so many participants particularly impressive.

As Mabel mentioned, my presentation is going to be with the assistance of slides that many of you have access to. I'm going to try and make the points from the slides in the presentation as clear as I can, so that those of you who are listening without the slides will be able to follow along at the same time as well.

There is an introductory slide right there. And I'm just going to go right to the presentation.

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Slide 4: CML 2012

Just to describe what I hope to talk about in a very short time. The goal today is to provide an update on important issues in the management of CML in 2012.

I was asked to provide more of a timely update rather than just a basic review and so I'm hoping to review both some general information, but also provide some of the newest updates from the recent American Society of Hematology meetings that were in San Diego this past December.

The topics that I hope to cover are listed here. The majority of the time will be spent reviewing current treatment options for CML patients. I also plan to highlight just a few of the newer emerging therapies for CML, and briefly discuss what are some increasingly important quality of life issues in the management and care of patients with CML. At the end I'm going to just briefly touch on the role of bone marrow transplant if we have time, and then touch on what's a very, very important topic-the role of clinical trials in the advancement of CML treatment. And then I do hope we'll have 20 or 30 minutes to take questions as well.

Slide 5: Epidemiology of CML

To start, this next slide is to remind everybody that CML really still is a relatively rare disease. It affects approximately 1 or 2 out of every 100,000 people. The average age is 53, but the incidence certainly increases as patients get older. In the modern era at least half of all patients are actually diagnosed just by routine blood testing, without symptoms. Occasionally patients still do come to medical attention because they're having symptoms, often related to abnormal blood counts, perhaps an enlarged spleen or other medical issues that prompt an evaluation. But the overwhelming majority of patients, when they are diagnosed, are diagnosed earlier in the course of disease with chronic phase.

I'm not going to have time really to review all of the general signs and symptoms associated with CML. I know this information is readily available online and in other sessions as well. I'd like to remind everybody, though, as we move forward, of the natural history of CML because I will use these terms throughout the presentation.

Slide 6: Clinical Course

The next slide that comes up is just reviewing some terminology and the three phases of CML. Most patients are diagnosed in what's referred to as a chronic phase. This is generally a slow-growing stage with very few symptoms. In the era before drugs like Gleevec® and the newer medications, a chronic phase would typically last four to six years, and invariably without more effective treatment would progress through a more aggressive and more symptomatic phase, called an accelerated phase, culminating ultimately in a blast crisis. Blast crisis CML can rapidly be life-threatening with very few effective treatment options at that point. And therefore if we really think about the goals of therapy, a major goal of treating CML is to prevent progression through these more dangerous phases.

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Slide 7: Treatment Options for CML

On this next slide that is coming up, I've listed some of the treatment options for CML available as of January, 2012. Before the year 2000 or 2001, the drugs Hydrea® and interferon were really the mainstay of medical treatment for CML. These are grayed out on the slide in part because I'm not really going to discuss these treatments, as they've largely become historic, at least to the point that their use is limited to some very specific clinical situations. I intend more to focus on the use of imatinib or Gleevec, nilotinib or Tasigna® and dasatinib or Sprycel®. These are the drugs that are referred to as tyrosine kinase inhibitors and I hope to briefly discuss some of the newer similar type of drugs that are currently in development. I may be able to touch just a little bit on the role of bone marrow transplant if we have time, as I mentioned. But what I hope to show you is how the treatment approach and prognosis for CML has changed dramatically with the development of these drugs, from where we were ten years ago.

Slide 8: Gleevec vs. Ifn/AraC

Imatinib was the first and I believe still the best example of what we refer to as targeted therapy for CML.

Imatinib really became the standard of care as initial therapy for newly diagnosed chronic phase CML based on a large and critically important clinical trial. This is the trial that's referred to as the IRIS Study, which many people may be familiar with and certainly have heard that term. This was a clinical trial that randomly treated patients with a new diagnosis of CML with either imatinib or a combination of interferon and a chemotherapy drug, Ara-C. The major findings of this study, that are still talked about today, were released after five years of follow-up and they're highlighted on the slide that's showing now.

Ninety-eight percent of patients had what's referred to as a complete hematologic response, meaning normalization of their blood counts, 87 percent had what's considered a major cytogenetic response, and almost 80 percent of patients had a complete cytogenetic response, meaning disappearance of all the cells containing the Philadelphia chromosome.

After five years, 89 percent of all patients remained alive and the vast majority were without progression of their CML.

In addition to being more effective, it's generally accepted that Gleevec or imatinib was better tolerated than the comparison drugs like interferon. The cytogenetic response is important because it correlates best with the long term efficacy of imatinib. Patients who had complete disappearance of the Philadelphia chromosome after one year of therapy had a 97 percent chance of remaining in remission five years later.

It's also important to note that even patients who didn't have a complete cytogenetic response still had a very high probability of remaining alive and without progression of their CML five years later.

Slide 9: Imatinib in CP CML

Now this type of information has recently been updated as you can see on the next slide. Every year the data from this original study gets updated. What I'm showing you now is data updated after eight years of follow-up.

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DR. DAVID PORTER:
The important piece of information is that patients in remission after four or five years of therapy have a very low risk of progression in their fifth, sixth, seventh and out to their eighth year of treatment. We know from the initial trials and long-term follow-up, that less than 2 percent of patients have progressed in any given year beyond the third or fourth year.

This slide updates the anticipated outcomes for patients who were treated with imatinib. And you can see there was no patient who progressed between year 5 and 6. Only one patient progressed between year 6 and 7 and one patient between year 7 and 8. After eight years of follow-up, 71 percent of all patients still had a complete cytogenetic response, 92 percent of patients still had not progressed over all that period of time.

Because of these excellent outcomes, which have never been seen before in CML, imatinib has become the accepted standard of care as the best initial therapy for most patients with chronic phase disease. Response rates are higher and longer. The drug is better tolerated than previous standard options such as interferon or other therapies.

It is true, however, that imatinib does not work for everybody. There still are patients who are resistant or progress on therapy and patients who cannot tolerate it because of side effects.

Slide 10: When Gleevec Stops Working

There are a number of options to consider if and when imatinib were to stop working. But the major options are the two newer tyrosine kinase inhibitors now available for clinical use. These are dasatinib or Sprycel and nilotinib or Tasigna. Both drugs may be more potent inhibitors of CML, of BCR-ABL than imatinib, and can be effective when imatinib stops working.

Slide 11: Dasatinib for Imatinib Refractory or Intolerant CML

Dasatinib, shown on this next slide, is a stronger inhibitor of the BCR-ABL protein than imatinib is, and it works even when there are mutations present that make cells resistant to imatinib. When used to treat patients who have failed imatinib, approximately 90 percent of them will have improvement in their blood counts, 59 to 63 percent will have a complete cytogenetic response, again meaning disappearance of all the cells containing the Philadelphia chromosome, again an outcome that may correlate with long-term benefit.

In studies using dasatinib when imatinib was not effective, 80 percent of patients had failed to progress two years later and 90 percent were still alive. So 80 percent of these patients were still in remission at least two years after starting therapy.

Slide 12: Nilotinib in Imatinib-Resistant or -Intolerant Patients with CML in CP

Nilotinib (or Tasigna) is another new tyrosine kinase inhibitor that also binds the BCR-ABL protein stronger than imatinib does and again it can work when BCR-ABL is mutated, making it resistant to imatinib.

Nilotinib has been tested for patients also resistant to imatinib. This slide shows the results of the study treating 321 patients who had failed imatinib. Forty-one percent had a complete cytogenetic response (disappearance of the Philadelphia chromosome), and 88 percent of these patients were still alive two years later. This was a study as of 2007.

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DR. DAVID PORTER:

Slide 13: Nilotinib: Four Year Follow-up

The results of the study were updated with newer information after four years of follow-up at this recent American Society of Hematology meeting in December. And the slide I show you now is the update after longer follow-up of these patients treated with nilotinib. After four years of follow-up, only 3 percent of all these patients had progressed, 78 percent of all the patients remained alive, and with four years of treatment there were no new unusual side effects, implying that the side effects or the toxicity was not cumulative over time. And in fact, between year 2 and year 4, only one patient enrolled on the study died and it was from issues unrelated to CML. I believe it was a patient who unfortunately had lung cancer.

Slide 14: Newer Tyrosine Kinase Inhibitors as Initial Therapy for CML

Since these drugs are so potent in cases where imatinib is ineffective, it was of course logical to test them not only when imatinib fails, but as initial therapy instead of imatinib. Results from some of these clinical trials will be shown on the next few slides.

Slide 15: Dasatinib versus Imatinib

Dasatinib has been compared directly to imatinib in a clinical study involving 519 patients. The abbreviation that I use, CCyR, stands for complete cytogenetic response, that means disappearance of the Philadelphia chromosome-containing cells. And the slide that I show you highlights that more patients treated with dasatinib had a complete cytogenetic response at 12 months of treatment, 77 percent versus 67 percent, as well as a major molecular response, which means that PCR testing, which is high sensitivity testing for CML, shows significantly less CML, and there was less with dasatinib than with imatinib. Fewer patients progressed to the advanced phases of the disease with dasatinib. The side effects or safety profiles were similar between the two drugs and it appeared that dasatinib had a higher and faster complete cytogenetic and molecular remission rate at one year, with no excessive toxicity.

Slide 16: Nilotinib versus Imatinib

Similarly, nilotinib has been compared to imatinib. These results were also published several years ago, but recently updated at the ASH meeting in December. There's now longer follow-up of several years. The slide that I show you is a side by side comparison of two different doses of nilotinib, 300 milligrams twice a day and 400 milligrams twice a day, compared to a standard dose of imatinib, 400 milligrams once a day.

These updated data show a higher molecular response rate, (that's in the top row, MMR), by three years of treatment for nilotinib compared to imatinib. Fewer patients progressed to accelerated phase or blast crisis and in fact no patient progressed after the second year. Remarkably, 98 percent of patients remained without progression two years later. PFS stands for progression-free survival, that means lack of progression.

Probably most importantly, 94 to 97 percent of all patients, regardless of their treatment, remained alive three years later, despite the drug they were taking.

The side effects profiles again were similar. And between 9 and 13 percent of patients had to stop their treatment because of side effects. But this is similar in all treatment groups.

DR. DAVID PORTER:

Slide 17: Nilotinib versus Imatinib: Three Year Follow-up

So to summarize the updated and longer term follow-up using nilotinib compared to imatinib, there was no new safety concerns and no cumulative toxicity. With three years of follow-up there continues to be a higher response to nilotinib over imatinib and an acceptable side effect profile. There was less progression with nilotinib and faster and higher response rates, and importantly, there was no difference in survival with patients taking one drug or the other, at least at this time point. And that's actually a very critical point.

Slide 18: Conclusions

So if we look at using these new drugs as primary therapy, some of the conclusions are shown on this next slide.

One can conclude that nilotinib at either 300 or 400 milligrams twice a day has a higher response rate and less progression compared to imatinib in newly diagnosed chronic phase CML patients. Dasatinib at 100 milligrams a day induced a higher and faster complete cytogenetic and molecular response rate compared to imatinib. And since a complete cytogenetic response may be associated with better long-term outcomes and lack of progression, these may be very effective treatment options. However, it should be highlighted that neither drug has yet shown to result in longer survival, at least at this point in follow-up.

All three drugs have been approved as initial therapy for CML and I believe all three in fact are reasonable options for newly diagnosed patients.

Slide 19: Comparison of Available TKIs

With a number of different choices, how would one decide on the right drug as initial therapy? There are some issues that one may take into account when trying to pick the right drug, as shown here.

There are some different features. Calling your attention primarily to the last row here, both imatinib and dasatinib are given orally just once a day. Nilotinib is a medication that's given twice a day. Imatinib should be taken with food, usually a large glass of water or other beverage. Dasatinib can be taken generally without regard to food. Patients on nilotinib need to avoid food two hours before and one hour after the dose, which for some patients has convenience concerns or issues, but generally can be done.

Slide 20: Toxicity

The next slide reviews some of the potential side effects of these drugs. In fact all three of these medications have similar side effects, but some of the side effects may be more common with one medication compared to another. All of these drugs can cause fluid retention, weight gain, rashes, fatigue, they can lower the blood counts, and cause gastrointestinal side effects, such as nausea, abdominal cramping, diarrhea, even vomiting.

But what I tried to do is highlight that some of these side effects are more common with one drug compared to the others. The most common side effects associated with imatinib tend to be fatigue, muscle cramps and myalgias or muscle aches, fluid retention and edema, meaning swelling, and nausea with occasional vomiting. Imatinib is also more likely to lower the white blood count, referred to as neutropenia, than the other drugs.

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DR. DAVID PORTER:
Dasatinib has a similar list of side effects, but one of the more unique side effects is this drug has been more commonly associated with a small, but significant risk of fluid accumulating around the lungs, that's referred to as pleural effusion. It can be mild or it can be severe. Anyone having trouble breathing with any of these medications should seek medical attention to make sure this is not an issue. When this is mild it can be treated with diuretics or water pills and other conservative measures. The drug can be stopped and even restarted safely in some patients.

With nilotinib, again the side effects are similar, but in addition this drug has been associated more often with problems involving the pancreas, pancreatitis, which is inflammation of the pancreas, and an elevation of certain blood tests, called the lipase and the amylase, which comes from an inflamed pancreas. There was initial concern that the drug could affect the electrical activity of the heart, what people refer to as QT prolongation. This is an uncommon issue and it turns out is really an issue with all three of these medications and therefore these drugs need to be used in caution in patients with heart diseases and on certain medications. Monitoring at the beginning of therapy with an EKG may be needed for some patients as well.

Interestingly, while all these drugs have similar side effects, they may not be cross-reactive. In other words, patients may experience a side effect on one medication, but may not have the same side effect if they switch to a different medication.

Slide 21: Can tyrosine kinase inhibitor therapy be suspended or discontinued?
Now that we've started to discuss how potent these medications can be, a very interesting topic and a major issue in this field, particularly since so many patients are now achieving complete remissions, is whether or not these drugs can be suspended or discontinued.

Slide 22:Impact of Dose Reductions/Interruptions
I want to begin to show you what happens when patients stop or discontinue some of these medications. At the ASH meeting in December information was presented regarding the impact of decreasing the dose or interrupting treatment on patients who were being treated either with dasatinib or imatinib.

Fifty-two percent of patients on dasatinib and 36 percent of patients on imatinib had a dose reduction or interruption at some point in their treatment for various reasons. On average these drugs were stopped for approximately two weeks and there was no difference in their overall cytogenetic response rate, suggesting that there was no significant impact, at least when holding therapy temporarily for toxicity or side effects, at least for short periods of time.

Slide 23: Discontinuation of Imatinib
The next slide shows information from a study referred to as the STIM Study, for Stop Imatinib. This information was published a couple of years ago, but recently updated this December at ASH. It involved 100 patients who had been on imatinib, who had a complete molecular response ongoing for more than two years. They had their medication stopped. After an average 30 months of follow-up, 39 of the 100 patients did not have a recurrence.

DR. DAVID PORTER:
However, 61 of the 100 patients had at least a molecular recurrence when tested by PCR, most within seven months of stopping treatment. Fifty-six of these 61 patients who seemed to recur achieved a complete response again when they were restarted on imatinib. Patients who had been on imatinib for more than five years before stopping were less likely to progress. Interestingly, by stopping imatinib in 100 patients, the study estimated that it saved approximately 4 million Euros, an interesting fact to consider in today's healthcare and economic climate certainly.

Slide 24: Can tyrosine kinase inhibitor therapy be suspended or discontinued?

There's additional information that I'm not going to have time to review in detail, but going back to my initial question, can tyrosine kinase inhibitor therapy be suspended or discontinued, it appears that over half of all patients will have their CML progress at least at low levels, though it's important to note that it may remain very treatable even when it progresses. My advice right now is that patients in remission not stop their therapy unless it's in the context of a carefully monitored clinical trial and certainly not without the knowledge of their treating physician.

Slide 25: Newer Tyrosine Kinase Inhibitor Therapy for CML

It's also important to note that a number of other drugs are being tested and developed for CML. Some are even more potent inhibitors of BCR-ABL. Some are designed to work against BCR-ABL that's resistant to the currently available drugs.

There are numerous agents in clinical trials around the country and around the world and I just wanted to highlight a couple for you.

Slide 26: Bosutinib vs. Imatinib in Newly Diagnosed CML

One drug that's fairly far along in clinical development is highlighted on this next slide, called bosutinib. These are results of a study comparing bosutinib to imatinib, again presented at the hematology meetings this past year. As you can see, there are similar numbers of complete cytogenetic responses, though perhaps more major molecular responses ("deeper responses") with bosutinib,. There's similar progression-free and overall survival. This suggests that this is another very potent drug that may be useful in the treatment of CML in the future.

Slide 27: Other Novel Agents or Trials

Another drug that's in development is a drug called ponatinib. This is particularly important since there are some patients with CML that don't respond to the available tyrosine kinase inhibitors. There is one particular mutation referred to as the T315I mutation. And while that's an unusual finding, it predicts that neither imatinib, dasatinib or nilotinib will work. There are new drugs being tested to target this mutation and this drug ponatinib is one of them that's fairly far along in testing.

This drug was studied in 403 patients who had failed either dasatinib or nilotinib and the the results are shown on this slide. The side effects are similar to the other tyrosine kinase inhibitors. Just looking at patients who had the T315I mutation, 48 percent of these patients went on to have a complete cytogenetic response.

DR. DAVID PORTER:
This is a major addition to drug therapy, particularly for patients with this mutation.

Slide 28: Long-Term Issues in Managing CML as a Chronic Disease
I want to switch just a little bit to talk about long-term issues managing CML as a chronic disease. With a number of different effective drugs, CML for most patients has become a chronic issue and that brings up a number of long-term problems in managing CML chronically.

Slide 29: Quality of Life for Patients with CML
Most patients now live many years and we have to consider important quality of life issues in caring for people. These may be related to emotional aspects of living with a chronic illness, the need for long-term and often expensive treatment, and management of potentially chronic long-term side effects from this treatment.

Slide 30: Quality of Life on Long-Term Imatinib
This has actually been studied in important detail. I'm showing you the results of a study involving 448 patients who were on imatinib for CML between three and nine years. All patients had had a complete cytogenetic response and they were asked a series of 36 questions about eight different issues, having to deal with physical function, role limitations because of symptoms, body pain, health perceptions, vitality, social functioning, their role limitations because of emotional issues and mental health, and their answers were compared to a general population of patients without CML.

Slide 31: Quality of Life on Long-Term Imatinib
Based on their answers to these questions, a so-called quality of life score was developed for these patients. The quality of life score was worse for CML patients compared to the general population overall. And in particular in the age group of patients 18 to 39, there were worse scores for social functioning and physical functioning. The scores were worse for patients 40 to 59, specifically in issues dealing with limitations because of symptoms, role limitations because of emotional issues and other general health perceptions. Importantly, for patients over 60 the quality of life scores were very similar to the general population. Women seemed to have lower quality of life scores than men. And men's scores were similar to the control population as well.

Slide 32: Percentage of CML Patients Reporting the Symptom by Level of Severity
This next slide is somewhat busy, but just shows you what patients reported as the symptoms most affecting their quality of life. The black top of each bar shows the symptoms that were considered "quite a bit or very much affecting their quality of life". Fatigue, muscle cramps, muscle pain and edema were the major symptoms.

I'm sure there are people on the phone here who can certainly identify with that.

Slide 33: Bone Marrow Transplant for CML
I'm really not going to talk much about bone marrow transplant for CML. We used to talk about this as the only known cure and the question has certainly come up of whether or not CML indeed needs to be cured.

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DR. DAVID PORTER:
Bone marrow transplant can cure over 50 percent of patients, but is associated with very high risks. Because of the newer effective therapies, very few transplants for CML are done in the modern era.

Slide 34: Making Continued Progress in CML Therapy

I hope that at this point it's obvious that there has been tremendous progress in the past decade in our approach to CML management. It's critical, however, that we continue to make progress in CML therapy, so how do we do that?

Slide 35: Importance of Clinical Trials for CML

I do want to highlight the importance of clinical trials for CML. The IRIS Study, that I mentioned at the very beginning of my presentation, compared Gleevec to interferon. To this day it is still one of the best and most important clinical trials ever conducted for CML. It dramatically changed our treatment approach, and this field continues to evolve rapidly because of it.

In fact, it's important to remember that most clinical trials are not testing a good therapy compared to an unknown or bad therapy. Most are generally using a good therapy and trying to make it better.

There's even good medical and scientific evidence that patients who participate in clinical trials get excellent, if not better, clinical care, sometimes because of the very detailed planned monitoring of the trial.

There are numerous resources to find access to clinical trials. Information can be found on various websites that I list here, through organizations including The Leukemia & Lymphoma Society. There's a website called clinicaltrials.gov, which lists just about every trial in the United States and many international studies. Other websites include Oncolink, sponsored by the University of Pennsylvania. The American Cancer Society. Good old-fashioned Google. And many other resources as well.

Your physician certainly should be able to point you in the right direction to access relevant clinical trials.

Slide 36: Survivorship

And finally, as CML is becoming more of a chronic disease, in the last minute I just want to highlight some important issues of what we refer to as "survivorship".

Slide 37: Photo

I realize that this diagnosis and these treatment options can be very, very overwhelming. Many patients initially feel like the patient shown on this next slide; perhaps scared and overwhelmed and just wanting to scream at times.

Slide 38: Living with Chronic Leukemia

When living with chronic leukemia, however, it's important to remember that adjusting to this diagnosis may take time, but it is possible and it does happen, and one needs to be patient.

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DR. DAVID PORTER:
Take an active role in your care, learn about CML, talk with and use your caregivers, other patients, family, friends. Understand both the indications and the goals for your treatment. And that includes both the initial short-term and the overall long-term goals.

Slide 39: Resources
Use your available resources. There are many and I only list a few on this slide, which is number 39. There are some wonderful support groups available for CML patients. There are a number organized by the LLS that do wonderful things for patients. There are other support groups as well. The LLS as well as others offer numerous educational programs, such as this one. Their First Connection program is a wonderful resource to take advantage of. There's an opportunity for financial assistance when needed. Other organizations such as Gilda's Club and the Wellness Community or American Cancer Society and many others have important resources that one should be able to access as well.

Slide 40: Conclusions
So with that I hope I've described to you how treatment options for CML have changed dramatically in the last decade. As of January 26, 2012, there are three very effective and appropriate initial therapies for CML. Imatinib, dasatinib and nilotinib are all reasonable, excellent initial treatment options.

I hope I've also shown you how intensive scientific research, rational drug development, and more importantly, the participation of hundreds, if not thousands of patients in these critically important clinical trials have led to these incredible breakthroughs that I'm able to share with you. Changes not just in the management, but in the outcome and prognosis for patients with CML have been rather dramatic and rapid. Many of these exciting new developments are improving on already very effective treatment.

So for patients with these new treatment options, these therapies have turned a disease that was once uniformly fatal without a bone marrow transplant, into a chronic condition that seems to be managed successfully in most people with drug therapy for many years in so many people.

And as I mentioned earlier, treatment of CML is no longer looked at as one major battle or a sprint to some difficult finish line, but as we describe it here, it's more of a long distance run and requires a great deal of stamina, yet with a finish line really in sight.

And I think with that philosophical closing, I can end my presentation and would be happy to take questions.

Slide 41: Question and Answer Session
MABEL MAIA:
Thank you so much, Dr. Porter, for your clear and informative presentation. Like Dr. Porter said, it is now time for the question and answer portion of our program. For everyone's benefit, please keep your questions general, without any personal details, so Dr. Porter can provide an answer general in nature.

MABEL MAIA:
Our first question comes from the Web. It's from Jeffrey. "If a patient is currently on Gleevec and having no side effects and has reached an MMR, is there any reason to switch to Tasigna or Sprycel at this point?"

DR. DAVID PORTER:
Jeffrey, that's an excellent question. I get asked that all the time. I personally don't think there's any reason. As I mentioned to you, the data currently shows that Tasigna and Sprycel may have higher response rates, but if one's already had an excellent response on imatinib switching may not be necessary. And there's no data as of yet that switching affects long-term outcome or overall survival. So when a drug is working so well, I don't see the utility in switching to something that may not be needed and would continue something that is currently working.

MABEL MAIA:
Great, thank you, Jeffrey, for your question. Operator, we're going to take a question from the telephone audience.

Operator:
Our next question comes from Terry in Utah.

TERRY:
Hi, I was just wondering if you've already reached the MMR, how often should you be seeing your doctor and how often do you have the BCR-ABL test done?

DR. DAVID PORTER:
The issue of monitoring, Terry, is a really important issue and this is an excellent question. Most recommendations are to have molecular testing (PCR testing) done anywhere between every three to six months, once you've achieved the MMR or major molecular response. There's a little bit of controversy whether it needs to be every three months or whether every six months is sufficient. But if it's done at least at that frequency I think that that would be adequate.

MABEL MAIA:
Terry, thank you for calling in. Our next question comes from the Web and it comes from Michael. "I am two weeks out from a bone marrow transplant. This is due to cumulative effects of chemotherapy over time. What studies are being done to understand toxicity over time, when moving from Gleevec to Sprycel to Tasigna?"

DR. DAVID PORTER:
So, Michael, good luck to you, being so soon out after a bone marrow transplant. There are a lot of studies being done to monitor patients after drug therapy. One of the advantages of clinical trials is that you have the ability to monitor outcomes over longer periods of time. It's not just during the initial treatment phases. We are learning about cumulative side effects for patients who may have been on one drug and then entered a clinical trial on a second drug and maybe even a third drug.

DR. DAVID PORTER:
A lot of that data takes a long time to collect and be presented. But I think just about every trial now using some of these new drugs monitors for toxicity, monitors for cumulative side effects, and we do learn more and more all the time.

MABEL MAIA:
Thank you, Michael, for submitting that question. Operator, we'll take our next question from the telephone audience.

OPERATOR:
Our next question comes from David in Indiana.

DAVID:
I was on Gleevec for eight years and then switched to Sprycel because I lost my complete molecular response. On Sprycel I had heart rhythm problems. Then I had problems with pleural effusion. My question is, and now I've been taken off of any treatment at all, how likely is it that the pleural effusion was actually caused by the Sprycel?

DR. DAVID PORTER:
So very, very hard to say, David. It sounds like you've had a hard time with these medications. If you're still on the phone, do you know how Sprycel worked for you?

DAVID:
The last two checks I was in complete molecular response.

DR. DAVID PORTER:
Fantastic. I think that's the best news. Sprycel, and in fact all of these drugs, have been associated with pleural effusions. Without, of course, knowing more about you medically and what other reasons you may have had for a pleural effusion, I think it's very hard for me to say. But it is a drug that has been associated with causing this fluid buildup around the lungs and even in people with other predispositions to develop pleural effusions, when on these drugs, and that does develop, we're obviously very, very cautious about using them and only use them with very, very careful monitoring. When that type of side effect happens with one drug, we will often change to an alternative; perhaps nilotinib instead of dasatinib, etc. So hard to answer very specifically, but it is one of the side effects of that drug.

MABEL MAIA:
David, thank you for your question. Our next question comes from Teresa. "Is there any research being done on younger patients with CML and the effects of treatment on fertility? I was diagnosed at age 26 and was first on Gleevec and now switched to Sprycel. Wondering if there's any information out there regarding these issues?" And also, Dr. Porter, if you can just touch upon and address fertility concerns for men taking Gleevec.

DR. DAVID PORTER:
This is aery, critical and important question, Teresa. There is a lot of interest in this topic. Of course, research is difficult. These drugs are not recommended for women who are trying to get pregnant and certainly who are pregnant. The research mainly comes from observations of people who got pregnant somewhat inadvertently on these drugs. There is a fair amount of data that's known. The largest amount of data involves 180 women, who had been on imatinib during pregnancy, most unexpectedly, of course. There is information on outcomes from the pregnancies on 125 patients. Half of those deliveries were normal; in other words there were normal infants born in half of those deliveries. About 14 percent of those pregnancies ended in a spontaneous abortion. While that sounds high, it's important to note that there is about a 10 to 15 percent spontaneous abortion rate in the normal population, so it didn't seem to be any higher. Twelve infants were born with abnormalities at birth. And there were a number of recurrent deformities, a lot of them involving bone abnormalities and skull formation. And while it can't be proven, there was a suggestion that these were recurrent abnormalities, raising concern that they could have been related to imatinib.

Therefore there is a real concern for pregnancy on imatinib and that concern is justified by looking at these outcomes.

If a woman does become pregnant, most people recommend immediate discontinuation of imatinib. And then there are several options. One could consider continuing the pregnancy, but with very, very close monitoring. In any case there has to be some very, very detailed counseling in that situation.

There are alternative therapies. Interferon, which used to be the mainstay of treatment for CML, can be given to women who are pregnant, generally safely.

There does not seem to be significant issue with taking imatinib for the male partner, for the father of the pregnancy. There's been no suggestion that that results in any fetal malformations. Nevertheless, most people recommend appropriate contraception and intensive counseling. Many male patients will have their drug interrupted during a period of time when they and their partner are trying to conceive, so that there is no concern for interference with imatinib.

So thank you for a very good question.

MABEL MAIA:
Thank you, Teresa, for your question. Operator, we're going to take our next question from the telephone audience.

OPERATOR:
Our next question comes from Rosalyn in Georgia.

ROSALYN:
Question, I have a lot of dark spots on my hand and my face and I was going to use a bleaching cream or something. But my oncologist says this is a side effect of Gleevec. I'm wondering if it would help to use any of this other stuff.

DR. DAVID PORTER:
Rashes are very common with Gleevec and in fact with all these drugs. Often the rashes are diffuse, but they can be in some small areas. My personal feeling is anybody who develops dark spots, whether or not it seems to be related to Gleevec and started shortly after treatment, should have a dermatologist look at them. And any skin spots, particularly dark ones, should be evaluated by a dermatologist. I'm not sure what kind of bleaching cream you're referring to, but I would let a specialist look at that and make a comment on the most appropriate creams.

MABEL MAIA:
Great, thank you, Rosalyn, for your question. Our next question is from the Web and it comes from Stephanie. "What information do you have on treatment for children with CML? My 8 year old son was diagnosed this past November with CML and is currently on Gleevec and is responding well. However, my concern is there is no information on long-term effects of Gleevec in children. What are your thoughts?"

DR. DAVID PORTER:
I think you hit it right on the head, there isn't a lot of information about long-term effects beyond the 10 or 11 years that Gleevec has been available. And the other issue, of course, is that we have no idea how long Gleevec is likely to be effective. When we're talking to someone who may be 60 or 70 years old and can tell them that we think this drug is likely to work for 20 or 30 years or even longer, that sounds quite exciting. For someone who's diagnosed at 8 years old, that's certainly nowhere near as exciting.

There is a lot of work being done in children who are taking Gleevec or taking imatinib and these other drugs. The side effects are being monitored and recorded very carefully. As of yet there doesn't seem to be any unique issues in children in terms of development that I'm aware of, but in terms of taking it for 10 or 15 or 20 years, I think we just don't know yet, though I do know that that information is being collected and hopefully we'll learn more and more over the coming years.

MABEL MAIA:
Stephanie, thank you for submitting your question. Operator, we'll take our next question from the telephone audience.

OPERATOR:
Our next question comes from Christy in Missouri.

CHRISTY:
My question was basically the same that was already asked about women that become pregnant while on Gleevec and what the standard treatment is or recommendations from a physician's standpoint, when that happens.

DR. DAVID PORTER:
The initial recommendations, if somebody is on Gleevec and becomes pregnant, is to stop the drug. I think the next decision is whether or not the CML needs to be immediately treated. So for instance, somebody may become pregnant and they're in a complete remission on Gleevec. It's very possible that they do not need treatment for their CML. They can interrupt therapy and make a decision about what to do next. For somebody who does seem to require therapy for their CML while pregnant, interferon seems to be a safe option. It's been given to patients who have been pregnant, with no suggestion that it results in fetal abnormalities.

The decision about the pregnancy really is a decision that the patient and their physician and their gynecologist, usually someone trained in high risk obstetrics, will make together. Some of these decisions depend on patient preferences, how early in the pregnancy it was identified, how long they've been on Gleevec. So I think stopping the drug, considering whether or not CML needs to be treated, and then meeting with your oncologist and somebody familiar with these issues from an obstetrics standpoint is really critical for appropriate counseling and decisions.

MABEL MAIA:
Thank you, Christy, for your question. Our next question comes from the Web and it comes from Niron. "I'd like to request a status report on CML vaccine that would eliminate continuing everyday dosage."

DR. DAVID PORTER:
Great question and great issue. I can't give you much of a status report. There is a lot of interest in still trying to find a cure for CML, taking it from what has been tremendous progress and success and turning it into a long-term chronic disease, but really treating it and making it go away and stay away. There have been a number of clinical trials done, trying to develop a vaccine that will essentially stimulate a patient's own immune system, to try and kill off the CML cells. The studies that have been done show that that is possible, that one can give a vaccine, you can induce a patient's own immune cells to recognize and target CML, but the responses to date have been quite modest. They haven't been sufficient to eradicate CMLn.

There are new techniques being developed all the time to better stimulate the immune system or to modify somebody's own immune system, to make them kill leukemia cells in a much more potent manner. As yet, those studies haven't been carried out to target CML, but once they become successful in other diseases and other leukemias, it's certainly only a matter of time until the right target is developed, where one can apply those type of techniques to CML. We're not there yet, but there are a lot of people working on that very aggressively.

MABEL MAIA:
Great, thank you, Niron, for your submitting your question. Operator, we'll take our next question from the telephone audience.

OPERATOR:
Our next question comes from Jerry in Florida.

JERRY:
Yes, I was diagnosed about four years ago and started on Gleevec, 400 milligrams. Had severe muscle cramps and couldn't tolerate the cramps. We tried 200 milligrams and I've done very, very well with side effects and my blood work all remains great. Should we consider going to one of the newer drugs or continue with the 200 milligrams and monitor the blood work?

DR. DAVID PORTER:
Excellent question, Jerry, and I'm glad the dose reduction worked for you and made a big difference. In general, dose reductions today are considered suboptimal. Two hundred milligrams a day for most patients is considered a suboptimal dose. But that said, different people respond differently to different doses. I think it depends on what you mean by the blood work is good. If on 200 milligrams a day that is sustaining a complete molecular remission, and certainly a complete cytogenetic remission, I would answer the same way I did one of the first callers, and that is when you have something that is effective, the way that you want it to be effective, I wouldn't necessarily make changes.

On the other hand, if at 200 milligrams a day, which may be a suboptimal dose, isn't resulting in a maximal response, that perhaps the blood counts are excellent, but there still may be cells with the Philadelphia chromosome, or if you haven't reached a major molecular response, which may be an important milestone, there may be some consideration now to changing over to one of the newer drugs.

I think four years ago physicians were much more hesitant to change to the newer drugs without better information. Now that they're available with newer information, many people are more liberal in switching over. And so it depends on what kind of response the 200 milligrams a day is sustaining.

MABEL MAIA:
Thank you, Jerry, for calling in. Our next question comes from Linda from the Web. "In general what percentage of patients need to be switched from Gleevec to Sprycel or Tasigna for side effects?"

DR. DAVID PORTER:
About 15 percent initially, Linda. That's a really good question. And it depends on when you look at that number, but it's somewhere between about 15 and 30 percent of the patients over longer periods of time. From the initial studies done, starting maybe ten years ago through the mid-2000s, it was about 15 percent of all patients. If you look at the studies on all three of the tyrosine kinase inhibitors, a similar proportion of patients have side effects on one as they do the other. And somewhere between about 10 and 15 percent of patients have to stop their drug. Again today with the availability of so many choices, people are a little bit more liberal in switching from one to the other, whereas perhaps five years ago we would tolerate a little bit more intensity of side effects. Today there may not be that need. But a very, very good and important issue.

Slide 42: LLS CML Resources
MABEL MAIA:
Great. Thank you, Linda, and thank you all for your questions. Actually our program has come to a close. And I would like to thank Dr. Porter. We are so grateful he has donated his time with us today.

David L. Porter, MD
January 26, 2012

MABEL MAIA:
We hope many of your questions were answered and that the information provided will assist you and your family in your next steps.

If we were not able to get to your questions or we can provide additional information and support, please call an LLS Information Specialist toll-free at 1-800-955-4572. Or you can also reach us by email at infocenter@lls.org.

On behalf of The Leukemia & Lymphoma Society, Dr. Porter and I would like to thank you for sharing this time with us. Good-bye and we wish you well.

END