CML–Expert Information about Diagnosis and Treatment

Michael J. Mauro, MD
October 25, 2011 1:00 PM ET

Slide 1-CML-Expert Information About Diagnosis and Treatment

OPERATOR:
Hello, everyone, and welcome to *CML–Expert Information About Diagnosis and Treatment*, a free telephone webcast education program. It is my pleasure to introduce your moderator, Mabel Maia of The Leukemia & Lymphoma Society.

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

We are proud to offer this important program in collaboration with Alianza Latina of Latin America. We would also like to acknowledge and thank Novartis Oncology and Bristol-Myers Squibb for their support of this program.

Today we are simultaneously interpreting our program into Spanish. If you'll notice I'm speaking a little bit slower today and also Dr. Mauro will be speaking a little bit slower, to allow for simultaneous interpretation.

We have over 1,000 individuals participating from all over the world and because of our simultaneous interpretation, we have large audiences participating from Spain and other Latin American countries. On behalf of LLS, thank you for joining us today.

We are audiotaping and transcribing this program for future posting on the LLS website at www.LLS.org/leukemiaeducation. This provides an opportunity for you to read or listen again to today's program, especially to follow up on terminology or therapies you may have missed.

You should have received or downloaded program materials for today's program. Dr. Mauro has also provided slides and he will explain the information on the slides during his presentation. If you not already accessed the slides, you can view or print them from the LLS website at www.LLS.org/programs.

Following Dr. Mauro's presentation, we will take questions from the telephone, web and also pre-submitted questions from our Spanish audience.

Before we begin, I would like to introduce The Leukemia & Lymphoma Society's President and CEO, John Walter, who will share a few words. Hi John.

JOHN WALTER:
Thank you, Mabel. I'd like to add my welcome to all the patients, caregivers and healthcare professionals on the program today. We are fortunate to have as our presenter Dr. Michael Mauro, one of the nation's leading experts in CML. We appreciate Dr. Mauro's dedication to supporting the mission of The Leukemia & Lymphoma Society through his research, his work with our Oregon chapter of LLS and his care of patients with blood cancers. I would like to thank him for taking the time out of a busy schedule to provide us with the latest information on CML diagnosis and treatment.

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JOHN WALTER:

The Leukemia & Lymphoma Society is committed to bringing you the most up-to-date information about your blood cancer. We know it is important for you to stay current, so that you can work with your healthcare team to determine the best options for the best outcomes. Our vision is that one day the great majority of people who have been diagnosed with a blood cancer will be cured or they will manage their illness with good quality of life.

Since 1954, LLS has aware more than $814 million to fund research specifically targeting blood cancers. We will continue to invest in research for cures and programs and services that improve the quality of life for patients and families.

This program is one step on the road of your journey to managing your life with CML.

Thank you and I'll turn the program back over to Mabel.

Slide 2-Michael J. Mauro, MD

MABEL MAIA:
Thanks, John. I am now pleased to introduce Dr. Michael Mauro, Associate Professor in the Division of Hematology/Medical Oncology, Department of Medicine in the Center for Hematologic Malignancies at the Knight Cancer Institute at Oregon Health and Science University in Portland, Oregon.

Dr. Mauro, we are so privileged to have you with us today and I now turn the program over to you.

DR. MICHAEL MAURO:
Thank you, Mabel, thank you, John. And a very big thank-you to The Leukemia & Lymphoma Society for all the work you've done, your partnership and your invitation to allow me to speak today.

Welcome to the entire audience. Good evening, good morning, good afternoon, wherever you are. Buenos dias, buenos noches, for those of us in the Spanish speaking world.

I'm going to speak to you today about CML therapy. I'll raise several topics, but I'd like to leave ample time for questions at the end because one of my favorite things to do is really to have an open dialogue with my patients about new issues related to CML and how we can best treat this disease.

Slide 3-What Causes CML?
What causes CML? CML is a unique cancer driven by a chromosome translocation or swap in cells in our marrow that divide and repopulate our blood. It's not an inherited disease and there really are few known exposure risks. What makes it most unique is it really has a singular driver, the Philadelphia chromosome. This marker is easy to identify, it's central for the diagnosis and it interestingly is seen in normal individuals with very detailed testing, and low frequencies, so does not cause cancer in all individuals, so it's a common genetic error.

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DR. MICHAEL MAURO:

Slide 4-The Philadelphia Chromosome

This is a visual representation of the Philadelphia chromosome, where we see exchange between chromosomes 9 and 22, creating an abnormal fusion gene called Bcr-Abl on chromosome 22. It's the juxtaposition of the Bcr driver, if you will, next to the oncogene Abl, that triggers the leukemia transformation in progenitor blood cells and really is the sole cause of CML.

Slide 5-Profiling the CML at Diagnosis

When we are faced with a case of CML there are a number of tests that help us understand how the disease might behave with treatment and how to best manage it. Of course, blood testing often makes the diagnosis. This will drive a search for the Philadelphia chromosome and confirming the presence of the Philadelphia chromosome in conjunction with typical CML features, really makes the diagnosis.

It's important for patients when they're diagnosed to be properly staged. More advanced forms of Philadelphia-positive leukemia, such as accelerated phase or blast phase, are important to know. They may be treated differently and may behave much more aggressively.

Amongst patients in chronic phase something called the Sokal score, developed by Joseph Sokal a number of years ago, helps predict response, particularly to imatinib or Gleevec® and likely helps gauge estimates of response to our newer drugs. This is quite a simple score to calculate, based on a patient's presenting features as listed: their blast percentage in their blood, basophil count, spleen size, platelet count and their age.

For any patient with CML in whom bone marrow transplant is an option, this should be discussed. It is wise to simply define this option, understand the risks involved, to query if a donor might be available for patients. As this is still a curative option, it's rarely performed as a primary treatment for CML, but it clearly remains an option to consider in certain cases of CML, particularly advanced forms of CML.

Slide 6-Response After Diagnosis

I like to describe CML to my patients and others as a marathon, not a sprint. The wonderful news with CML now is it's generally a chronic illness that we can manage quite well with low toxicity and highly efficacious therapy.

We treat CML now based on achievement of landmarks of response over time and therefore patients need to expect certain levels of response over time to be considered responding adequately or to be thinking about changes needed in their therapy and physicians as well need to follow their patients appropriately to optimize their treatment.

Slide 7-Response in CML

I often describe CML as an iceberg turned upside down. When someone presents with CML we see a large volume, we see high blood counts, we see an enlarged spleen, we see a bone marrow that's very heavily involved with abnormal myeloid activity generally. And we look to see the disease volume shrink and have clear landmarks over time that tell us how the disease is responding. Our initial response generally expected

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Slide 7-Response in CML

in the first few months and certainly by three months is for normalization of the blood counts, resolution of an enlarged spleen, and this is called a complete hematologic remission or CHR. Increasing we expect early cytogenetic response and that is reduction in the Philadelphia chromosome level as measured by conventional tests such as a bone marrow karyotype, bone marrow FISH or as an alternative, peripheral blood FISH. By six months we expect patients to have reduction in their Philadelphia chromosome levels to some degree and ideally they should have reduction below 35 percent. This is called a major cytogenetic response or MCYR. By 12 months we generally accept as an additional landmark a complete cytogenetic response, that is patients are expected to or our treatments expected rather, to cause a complete cytogenetic response or CCYR, by that time point.

Increasingly as well with newer therapies such as nilotinib and dasatinib, our focus is on molecular response. Here as the disease continues to remit we see further reduction in the volume of CML as measured by molecular testing, looking at RNA or DNA with the oncogene or driver of CML, Bcr-Abl.

We can often see these levels drop to low levels. One landmark is called a major molecular response or MMR. This is a 3-log reduction in the Bcr-Abl levels from when a patient started treatment until that level. That means CML is shrunk to 1/1000th of its original size. Further reduction is measurable by PCR and in fact often patients have such a good response that Bcr-Abl is no longer detected. This is now called a complete molecular response or CMR. And while it implies a complete elimination or absence of Bcr-Abl, it should probably be interpreted as levels of Bcr-Abl below the level of detection with our current technology.

The meaning of this type of response, while logic would say that this would be where we all want to be, where all patients would want to be, but in the research of CML we're still continuing to define exactly what a complete molecular response means, we're increasing our ability to define it and hopefully over time we'll see more and more patients get to such low levels or absent levels by standard technology with a marker or driver of CML.

Slide 8-What's Considered a Good Response?

As I've just described, what is considered a good response? By three months, just to reiterate, a complete blood response is really expected and more recent guidelines have shown us that patients who have cytogenetic response or bone marrow response, that is reduction in the Philadelphia chromosome levels by conventional testing, such as the karyotype or FISH, this really represents an ideal response and particularly may be what we expect as we treat patients increasingly more often at diagnosis with our newer therapies for CML, particularly nilotinib and dasatinib. This gives us an early opportunity to address delays in achieving cytogenetic response or missed responses. Recent research may show that even a major or complete response may be expected at three months and this remains to be determined. But as you can see, we're setting the bar higher and higher for our therapies.

Again, at six and twelve months we expect the remission to be complete. And that is by bone marrow testing, karyotype and FISH. And again molecular response, the 3-log reduction or major molecular response, really offers further reduction in the CML disease volume and further reduction in risk, with the patients achieving a major molecular response having the lowest likelihood of disease progression.

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Slide 9-PCR Testing in CML

PCR testing really is the workhorse of monitoring CML currently. And our current technology can detect one leukemia cell in a thousand in very basic assays, or up to one cell in a million in more sensitive assays. They can be qualitative or quantitative and we really desire the tests that are quantitative, that can give us a number, or really a percent of leukemic genetic material compared to a normal baseline or benchmark.

And it's very important to look for PCR testing that's reported on the international scale. When I talk about a 3-log reduction I'm speaking of a 3-log reduction as measured by the international scale or standardized yardstick by which we measure reduction in Bcr-Abl transcript levels.

Several labs available globally do report Bcr-Abl testing, that is PCR testing on the international scale and efforts continue to try to standardize this across the globe.

Slide 10-PCR Monitoring

So different labs will have different results. There are only a few labs, unfortunately, in the U.S. that use the international scale. And it's important to then use the same labs, so trends can be followed, in the case of a lab that may not be reporting on the international scale. Many patients and physicians ask me how to interpret PCR testing and sometimes it's a challenge because of the different reportings that exist. Again, negative results depend on the quality of the sample and the quality of the lab.

And our treatment has improved and our outcomes have dramatically improved. But some caution is required in the interpretation of a complete molecular response for patients who are PCR negative. The meaning of these levels again isn't clear and logically this is what we desire. But what this means for the long-term outcome of patients with CML is something we're about to define, I hope. So I encourage people and physicians to keep patients on therapy and not to assume that this represents a point where therapy can be stopped.

Slide 11-When Should a Change in Therapy be Considered?

When should a change in therapy be considered? If a patient doesn't show resolution of changes in their blood or a complete blood response by three months, this is a clear sign of what's called primary resistance. In addition, if a patient doesn't show any evidence of cytogenetic response at three months, one ought to consider multiple lines of questioning, is the patient able to take therapy, is there some issue with other medications, or is there potentially also primary cytogenetic resistance and should a change in therapy be instituted? If a patient has no cytogenetic response by six months, this is an even more important warning sign. Many different research efforts have proven this fact. Additionally, if patients still have evidence of the Philadelphia chromosome by conventional tests such as the karyotype or FISH after one year of therapy, cytogenetic resistance is suspected and really a change in therapy may be warranted.

I describe these targets based on our knowledge of the time line of response of imatinib or Gleevec. Our initial treatment choices have expanded in many places in the world, in 2011, with the availability of nilotinib and dasatinib for primary, for front line use. Our expectations are increasing and again the bar is being set higher and higher, so stay tuned for new landmarks of response which may be more meaningful and time points when patients may consider changes in therapy.

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DR. MICHAEL MAURO:

Slide 12-Nilotinib or Dasatinib

Nilotinib or dasatinib are both good options for patients newly diagnosed with chronic phase CML. The early data, from one to two years of follow-up, does clearly suggest a higher rate of response, faster response, both cytogenetic, both chromosome based testing, and molecular or PCR based testing. It additionally offers protection from progression, to accelerated or blast phase, this is one of the most important advances I believe, is the primary treatment of chronic phase CML, is preventing patients from moving on to an advanced form of CML.

The side effect profile is narrower for nilotinib and dasatinib. There are new drug specific side effects that are possible. Physicians and patients alike need to be aware and communicate openly about side effects to avoid toxicity. But in general these drugs are all well tolerated and our newer options are no more toxic in many ways and if there are new toxicities or enhanced toxicities, they're often early and quite manageable.

Slide 13-Is it Safe to Stop Treatment?

I mentioned earlier about the caution with regard to patients stopping therapy. Is it safe to stop treatment in patients who are, quote, PCR undetectable, or those that have a complete molecular response? There are small studies which are quite intriguing, with follow-up now up to a year and beyond and several years in some very small studies. And it does show that some patients, perhaps a 40 percent fraction in two large studies, have not shown evidence of CML proliferation as tested by PCR assays after stopping therapy. It's quite a bit early to assume that this is possible in a broad sense. We still don't have a tool to predict who may or may not relapse. We have concern over the quality of remission regained and when someone loses response and is then retreated. But clearly this is the focus of our efforts. We are aiming for a cure, that is remission that's sustained without treatment in patients with CML and hopefully we'll get there within reach. I think it's quite fair to say that a cure is within reach.

Slide 14-When Should Stem Cell Transplant be the Main Focus of Treatment?

I alluded earlier that stem cell transplantation still represents a treatment option. When should it be the main focus? When someone with CML has moved into an advanced stage, long term remission is much more uncertain. If a patient has chronic phase CML and is difficult to get into remission, they have little or no response despite switching treatment, this is another category where transplantation should be reconsidered. Lastly, there are certain types of resistance known, specific mutations in the Bcr-Abl target, particularly a molecular mutation such as a T315I mutation. There is a novel therapy, a drug called ponatinib, that's quite effective for this mutation and the results are very promising, but that drug is still in the midst of clinical trials. Until it's broadly available, many patients who have such a mutation should be considered for a transplantation.

Slide 15-Conclusions

In order to leave plenty of time for questions I'm going to wrap up. So our conclusions are there are multiple options when chronic phase CML is diagnosed. We now again, perhaps not everywhere, but we're moving towards global access for patients to be able to have nilotinib, dasatinib or imatinib as front line therapies for CML. We're lucky in the United States where all three drugs have been FDA approved for that indication. They have additional indications as well.

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DR. MICHAEL MAURO:

Slide 15-Conclusions

It's important to have dialogue about what's the best fit for each patient based on their medical history, the risk of certain side effects specific to each drug, preferences the physician might have or the patient might have, depending on what they know and hear about the drug.

And it's really quite a blessing to have multiple options for patients with chronic phase CML, so moving between therapies is possible.

It's very critical that we tailor therapy for each patient. We really want to optimize response and avoid toxicity and when there are multiple options, this is much more possible. Intolerance to medication, even the low intensity side effects that are chronic, may be grounds to consider a switch in therapy.

One of the most important things about CML therapy is taking therapy consistently and our current recommendations are that it's taken indefinitely. So taking therapy that's difficult and causes chronic toxicity, may be impossible for patients over the long term. If we manage side effects we're going to increase the likelihood of perfect or near perfect adherence. And recent studies have shown dramatic differences in the response of patients who have very high compliance or adherence to their prescription versus those that unfortunately have side effects or other issues that make it tempting or necessary for them to stop treatment.

I want to thank you for your attention, your efforts to call in and log in for this call today. I'm so glad to have you all here and I'm going to open up the lines for questions and anything is fair game and I'll continue to speak slowly so we can get the answers translated well. Thank you.

Slide 16-Question and Answer Session

MABEL MAIA:

Thank you so much, Dr. Mauro, for such an informative presentation.

Like Dr. Mauro said, it is now time for the question and answer portion of our program. If you're hearing this program in English, the operator will explain how to queue yourself for questions. I have pre-submitted questions from our Spanish language audience and I will alternate with each of the live questions. So if you are hearing this program in Spanish, please disregard the following instructions stated by our operator.

Operator, please give the instructions to our English telephone and webcast audience.

OPERATOR:

If you're hearing this conference in English, to participate in the call by asking a question, please dial star-1 on your keypad. If you are joining us by the web, simply click on Ask a Question, type your question and then hit Submit. We will take questions in the order they are received. We can only take one question per person. Once your question has been voiced the operator will transfer you back into the audience line. Again, to ask a question, please dial star-1 on your keypad or click on Ask a Question, type your question and then hit Submit.

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MABEL MAIA:
Thank you, Operator. We are going to take our first question from the web and Kimberly writes, "It seems that many patients, including myself, have experienced a variety of difficult side effects on Tasigna®, Sprycel® and Gleevec. What is the latest research on patients in major molecular remission who have come off of meds and continued to monitor their Bcr-Abl?"

DR. MICHAEL MAURO:
That's an excellent question. I alluded to it briefly, but let me explain a bit more. There were two fairly large studies in Australia and France for patients who had not a major molecular response, but a complete molecular response or, in fact, PCR that was undetectable in very good laboratories such as those in France and Australia. Such patients are in the minority, but were eligible for trials, so their treatment was stopped. What we found was in both studies that if relapse occurred it occurred generally within the first few months, that is about six months after stopping treatment. Things that predicted for better likelihood of not relapsing or showing disease regrowth were duration of prior therapy, particularly duration of imatinib therapy. Also patients with higher risk disease, higher so-called risk, had lower chances of success staying in remission off-treatment. The number of patients who were able to stay in sustained remission without treatment was approximately 40 percent in both studies. So we learned a lot, what predicted for the ability to stop or not and what the likelihood was. Again, many things are missing. First is a tool to be able to predict which patients might relapse and which ones have lower risk, would hopefully not. It may come with further research into the profile of leukemia and genetic patterns we see at diagnosis or potentially prior to stopping therapy.

We also need more time to follow patients who are retreated and go back into remission to ensure that the quality of the remission they regain is the same as the quality of the remission they risked when they stopped treatment. However, this is very exciting and I agree that for many patients with chronic toxicities from all three drugs, stopping therapy is an option that presents itself, but needs to be taken quite carefully and a patient needs to be monitored very closely if this is decided upon. It really should be done within a context of a clinical trial, but I can understand the potential motive and necessity of it in certain cases.

In these studies patients were followed monthly with sensitive Bcr-Abl testing and I would recommend that as a minimum in addition to very close follow-up with someone knowledgeable about CML, to manage such a situation.

MABEL MAIA:
Thank you, Kimberly, for submitting your question. We will take our next question from the telephone audience, please.

OPERATOR:
Our next question comes from Valerie in Texas.

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VALERIE:
I would like to know, I take Gleevec and I've been taking it for four to five years probably now, but I still get sick off of it sometimes. I always take it on a full stomach, but maybe depending on what I'm eating, I don't know. But I get sick within the first 30 minutes sometimes. Do you know why?

DR. MICHAEL MAURO:
Valerie, thank you for your question. You raise an important example of when chronic toxicity or chronic side effects may be needing medical attention. Of course, there are very basic questions to ask about such a side effect. Are there other medical problems or conditions that need to be treated such as acid reflux or even ulcer disease? Gleevec can be hard on the stomach and is recommended to be taken on a full stomach, as you're doing. That being said, even if no other problems exist, patients can get nauseous and get sick with their treatment.

If all other issues are ruled out and maximal supportive care, that would be potentially the inclusion of an anti-nausea medication, judicious use of acid blockade medications, if the symptom persists this might be an example of a situation where a change in therapy should be considered.

Our newer agents, nilotinib and dasatinib, have less GI toxicity than imatinib does to a degree. And either of them could be considered and they might be a good fit to relieve the toxicity and to allow or to facilitate chronic therapy without chronic toxicity.

MABEL MAIA:
Thank you, Valerie, for your question. Our next question is from the Spanish audience and it comes from Flore, "I was diagnosed two years ago and I started on 400 milligrams of Gleevec, but it was a slow response, so now I am on Tasigna and having optimal response. What is the life expectancy with these characteristics?"

DR. MICHAEL MAURO:
Thank you for that question as well. Our understanding of the long term natural history of CML is really being written as we speak. If we look at patients who have less than ideal response to imatinib, who then moved to nilotinib, there is very good likelihood for those patients to achieve a rapid cytogenetic response or as this caller or this participant has described an optimal response. Achieving early response likely increases the odds of long-term stable response. The exact details or the exact odds might be hard to describe, but for the majority of patients, the overwhelming majority, 80 plus percent range of patients who achieve early cytogenetic response to second treatment are likely to continue to have major or complete cytogenetic response over time. If the response deepens to a major molecular response or level below that, I would suspect that the chances are even greater. We even have difficulty describing to patients who respond optimally to their first treatment, such as imatinib, what their long term prospects or outcomes are. But I'm happy to say that for many patients we would expect that they may have a normal life span. For younger patients we expect decades of response when the disease seems to be in deep remission and several years have passed and the relapse risk is quite low.

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MABEL MAIA:
Thank you, Flore, for submitting your question. We'll take our next question and it comes from the web from Amanda, "For patients diagnosed with CML in their early 30s, is there a recommendation to have a bone marrow transplant before 50, even if they have CMR?"

DR. MICHAEL MAURO:
This is a great audience, very good questions. That wonderful question really represents some of our dilemma with the uncertainty about the future. For younger patients in whom a stem cell or bone marrow transplant is often quite feasible and even when donors are available, it seems quite natural to think that that should ultimately be part of the treatment. Given the uncertainty of very long term stable remission, for example, someone in their 30s, the good news is transplant technology, transplant risks continue to improve and that procedure will become safer and safer over time. Our ability to better use stem cell transplantation has made huge strides and I think will continue. So if someone is diagnosed with CML at a young age, if they respond well to one of the non-transplant therapies, imatinib, dasatinib, nilotinib or even our drugs that will come in the future, it may be that their risk of transplant will not change in the short term and the disease will tell us what we need to do. I often tell my patients that if someone has a very rapid cytogenetic and then complete molecular response, I often advise them to explore their transplant options and to know what they are because that defines what you expect from your non-transplant therapy. And then to watch carefully over time. The risk of transplant does change with age and development of other medical problems, so as we approach the later 40s and early 50s, transplant may become a more risky endeavor. But if a patient is diagnosed now in their 30s I think it's reasonable to consider continuing on non-transplant therapy in the setting of an ideal response because if several years have passed and remission was seamless and ongoing, it seems that the likelihood of relapse is quite small and maybe zero.

MABEL MAIA:
Thank you, Amanda, for your question. We will take our next question from the telephone audience, please.

OPERATOR:
Our next question comes from Jason in Colorado.

JASON:
My son was diagnosed with CML when he was 4 and he's now 7 and he's had a great response. He's been on Gleevec this whole time. However, in the last six months or so we were noticing that his kidneys and liver are having issues, which they think is related to Gleevec, and they're considering switching him to one of the other drugs, either dasatinib or nilotinib, to see if that drug will continue to keep him in remission and be easier on his organs. Have you seen any of that in your studies where people do great on one drug, however, it starts to affect different organs.

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DR. MICHAEL MAURO:
Thank you for that question. And first thing to say is best of luck to such a young gentleman with CML, fighting CML. Yes, we do see both liver and less often renal or kidney toxicity from all of our therapies and again this represents a situation where the tolerance of the drug needs to be strongly critiqued and a switch to another drug should be thought as a definite option. The newer agents are less well studied in the pediatric population, but there is data and I believe their likelihood of remission should be the same or better than with imatinib. So if a switch to a novel agent would relieve that toxicity, I would be quite hopeful. There may be more uncertainty with regards to the long term toxicity risk or the long term safety. Again there's a little less data in younger individuals, but I think for the sake of avoiding what may be chronic and debilitating or damaging toxicity to the liver and kidneys from therapy, no matter how good it is, a switch would make sense to me.

MABEL MAIA:
Thank you, Jason, for your question. Our next question comes from our Spanish audience from Nidia, " I would like to know how accurate are the results of a cytogenetic bone marrow study?"

DR. MICHAEL MAURO:
Thank you, Nidia, that is asking about a test considered the gold standard or the benchmark for early response in CML. A cytogenetic study from the bone marrow tells us, generally a 20 cell sample, how many cells have the Philadelphia chromosome detected visually. That is we can see chromosomes 9 and 22 are altered. This, although it's only a 20 cell test, has enhanced specificity and sensitivity for the leukemia population because CML cells grow and divide in cultures outside the body more easily. So even though it's a small sample, it has been proven through multiple decades in research to be a very good surrogate or indicator of reduction in CML disease.

Another way to do a cytogenetic test is to use a fluorescent probe in test called FISH, which I've mentioned several times, but not described. This uses a larger number of cells, often 200 or more, and this also has enhanced specificity for the leukemia cells, can be done on the blood or the bone marrow. While this is an additional tool, it hasn't been supported to be used as the primary way to follow a patient into remission. Simultaneous samples of a patient, from the blood and the marrow, may be equal, but there's a fairly broad error bar, if you will, or difference we can see. And I often have seen patients whose cytogenetic or bone marrow chromosome testing is better or worse than their blood FISH testing. So I still recommend bone marrow chromosome testing for the early assessment of response in chronic phase CML. And all of our research has used that benchmark as a way to gauge early response. I know it's uncomfortable to have the bone marrow, but the good news is many patients have rapid response and perhaps one or two or a limited number of bone marrows are really all that's necessary to show what the stage of CML is and then an early and then a complete cytogenetic remission.

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MABEL MAIA:
Thank you, Nidia, for that question. We will take our next question from the web and it comes from Pam, "Can a shingles vaccine be given to a CML patient who has already had shingles episodes?"

DR. MICHAEL MAURO:
We may have to dial in an infectious disease expert for that question. But I'm asked about vaccinations in CML patients regularly. My overall impression is that patients with CML in response or remission who have near normal or normal blood counts should be able to receive the vaccinations that a non-CML patient can receive and that they should mount a good response, essentially derive benefit from the vaccine and they should not have excess risk of side effects or potentially risks associated with vaccines when sometimes the actual illness or something like the illness can be associated with the vaccine. The question about shingles vaccine in a patient who's already had herpes simplex virus or varicella zoster virus, is a different question. I think that's very specific to each patient.

MABEL MAIA:
Thank you, Pam, for submitting your question. We will take our next question from the telephone audience, please.

OPERATOR:
Our next question comes from Mark in Illinois.

MARK:
My daughter was diagnosed many years ago with ALL that included the Philadelphia chromosome. And she's had a long medical history since that time. She was diagnosed in late 1996 and then relapsed after a course of chemotherapy and then had a bone marrow transplant and then was in remission for four to five years after that and then had a very unusual relapse that was not related to her blood counts. She had extramedullary tumors that were discovered. And so tested positive for ALL Ph-positive. So I guess I have a two part question. One is she's currently doing well and on Gleevec and I guess the first part of my question is, is the information that you are discussing about CML, would it apply primarily to ALL patients with Ph-positive, because I know there is a sizable population of patients in that group. And also in terms of the future, she's been on Gleevec for about five years now since her most recent relapse and should she be considering any other of the later generation of kinase inhibitors or should she just, as long as things are going well, just continue what she's doing now with Gleevec?

DR. MICHAEL MAURO:
Thank you for that question. I'm so happy to hear that she's doing well, despite the number of battles she's fought.

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DR. MICHAEL MAURO:
So to answer your first question about Philadelphia positive ALL or acute lymphoblastic leukemia, this is really a different disease, but it is driven by the Philadelphia chromosome and thus is amenable to use of kinase inhibitors such as Gleevec, Sprycel or Tasigna. The problem with ALL is, like acute leukemias in general, it's more unstable and can, as your daughter unfortunately experienced, relapse in unusual ways such as in the central nervous system or in extramedullary sites outside of the blood or marrow.

Kinase inhibitors clearly play a role in this disease and have shown to add benefit to chemotherapy and they probably have hopefully helped get her in remission. Since she relapsed I suspect there may be have been other therapies with Gleevec given and this is quite a difficult question to answer, meaning what should she do now. If she has no evidence of her disease, should she stay on Gleevec, should she switch to a novel drug? I would obviously talk at length with her doctors about what evidence is there of any remaining ALL, is there any evidence of the Bcr-Abl, the marker for the leukemic cells which have the Philadelphia chromosome? Is there any evidence of any extramedullary sites of disease? I would assume no.

In such a patient it's likely that the transplant, which I believe you said she had, took back over and something called graft-versus-leukemia effect, where the transplanted immune system has controlled the leukemia once again after kinase inhibitors or kinase inhibitors and chemotherapy have helped shrink an unusual relapse or an atypical relapse, which would be an extramedullary relapse.

If there's no side effects, I often will keep such patients on treatment for a prolonged period of time. The longer a patient goes without relapse after ALL, the lower likelihood there is that the disease will relapse. If there's any question of disease relapse I would definitely think about a second generation compound such as dasatinib or nilotinib, as ALL is much more likely to develop mutations and may become resistant to imatinib.

MABEL MAIA:
Thank you, Mark, for your question. We will take our next question from the web and it comes from Neron, "Can a young man on Gleevec be a father to a normal child?"

DR. MICHAEL MAURO:
Another excellent question. Early on in the course of Gleevec research we did have concerns about certain targets that may be affected by exposure to Gleevec, such as the KIT, and initial animal studies raised some concerns about the male factor and fertility. Subsequently our limited amount of knowledge and research into men who have fathered children on Gleevec has really shown no clear pattern of increased risk of birth defects or complications of pregnancy. I always recommend if a man is on therapy, if he fathers a child, that that pregnancy be considered a higher risk pregnancy and that the couple makes available to themselves the best prenatal testing to assess the child for any kind of abnormalities, birth defects, genetic changes. But I wouldn't say no, I would say yes, that a man on therapy can father children. If there's any question about fertility certainly men can be tested for fertility to see if there are any effects of Gleevec on spermatogenesis or sperm production and the ability to engender a pregnancy.

Michael J. Mauro, MD
October 25, 2011 1:00 PM ET

MABEL MAIA:
Thank you, Neron, for submitting your question. We will take our next question from the telephone audience, please.

OPERATOR:
Our next question comes from Regina in Indiana.

REGINA:
I have a question. I started out on Gleevec, became intolerant to it, changed to Sprycel, went into pleural effusion and cardiac effusion, went to Tasigna, had an allergic reaction to it. I'm back on Gleevec now with lots of side effects, but I'm wondering is there something new that's coming out that maybe can help me.

DR. MICHAEL MAURO:
I'm sorry to hear about the trouble you've had and I've seen many patients with the same story. Yes, there is. I'm happy to say that there is a third generation or newer group of medications under development. There is a drug that's quite far along called ponatinib or its research name was AP24534. This is a drug that was designed for patients who had selective resistance to Gleevec and a second agent and the clinical trial results, the initial study, the Phase I trial, are quite mature and quite encouraging. The overwhelming majority of patients in chronic phase achieve and sustain remission. The side effect profile is different. There are some side effects that overlap with Tasigna and perhaps with Gleevec and Sprycel and I would encourage you or you and your doctor to keep close eye on your response and your toxicity, to try to think about the dose and the drug that might be the best fit that is manageable. And stay tuned as ponatinib is likely to be available to patients in 2012. Although it will be indicated for patients who are resistant to imatinib and a second agent, for those that are intolerant this will represent a nice alternative.

MABEL MAIA:
Thank you, Regina, for calling in and asking your question. We are going to take our next question from the web. It comes from Kim, "If a patient switches from one CML drug to another, how much time should lapse between the two? When switching from Tasigna to Sprycel, I waited over 24 hours as recommended by the pharmacist, but ended up in the hospital after the first dose with severe headache and vomiting. Was this most likely a drug reaction to the Sprycel or a result of taking the two drugs too close together?"

Dr. Michael Mauro:
That's an excellent question, Kim. I suspect that somewhat better advice could have been given. If someone has chronic phase CML and is stable and is switching treatment, I often suggest that they have several days without medication in between to allow the drug to leave the body, to have several half-lives worth of time. I generally recommend four to six days, depending on the drug, at a minimum of three or four days.

Michael J. Mauro, MD
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DR. MICHAEL MAURO:
It's possible that Sprycel, which can cause headache as the other drugs can as well, could have simply been the cause. But I have had patients experience what I thought was overlapping toxicities, having one drug in their system and a second drug introduced. Unfortunately, the kinase inhibitors, Gleevec, Sprycel and Tasigna, have never been studied in any degree in combination. So it's safest to leave several days time in between to allow the drug to wash out. Of course, under the close watch of a physician or physician and pharmacist to make sure that that's the right thing to do.

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

Operator:
Our next question comes from Julius in New Jersey.

JULIUS:
Hi, how are you? Thank you for taking my call. I was just wondering why does Novartis charge so much for their drug? It's very hard for me to take or finance Gleevec. I don't understand why Novartis doesn't lower their cost.

Dr. Michael Mauro:
A very reasonable question. It's quite a complicated number of things that go into how a medication is priced and how much it costs once it's been approved. And I wouldn't pretend to know the answer to that. I'm an academic physician in clinical research. What I can say is being on that side of the fence and being an advocate for my patients, I know that many patients are in the same boat. While the companies have their charges and their justifications for that, they also are quite knowledgeable that many patients have co-pays that are quite great and insurmountable or there are situations where someone may not be able to have access to treatment. And for CML being a somewhat lesser or a less common disease, although it's much more prevalent than it ever was, there are very robust patient assistance programs, that patients can access through all the manufacturers to potentially have drug given at reduced or no cost. There's funding, there's co-pay assistance, none at the moment, but there has been and hopefully will be co-pay assistance programs through charitable organizations such as the LLS. There are many different things that can be explored and while we can't perhaps change the pricing of the drug and move mountains in that regard, we certainly can work around it quite nicely and I would encourage anyone with this question, and there may be many of you out there, to push, to be your own advocate, to ask your physician, your social worker, your pharmacist, your sales representative for access and information to ways to help defray or manage the cost of these therapies because that should not be a reason for patients to not be able to be treated with CML.

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MABEL MAIA:
Thank you, Julius, for your question. And you can also reach out to our Information Resource Center at 800-955-4572 for further information.

Our next question comes from the web and it comes from Angela, "Dr. Mauro, thank you so much for your time today and giving me the latest information about treatment of CML. Can you address the latest with regards to the development of a CML immunization? Thank you so much."

DR. MICHAEL MAURO:
Very good question, Angela. We know that the immune system can participate in CML remission. This is why stem cell transplantation works and is an option. Many different approaches have been tried and we have seen mature research on vaccines for CML, where elements of the CML are introduced to trigger an immune response. Some of the challenges have been that these are often studied in patients who are going into or who are in remission. Some of the limitations have been that it would not work in everyone or that they are active, and that they require continual boosting or ongoing therapy with them. It would be quite reasonable if it was highly active and simply required boosting and the vaccine would work broadly. I think the research continues. But at this time we have a few lead vaccines which have shown a potential and may in the future be added to our treatment armamentarium. The other thing to say is a drug called interferon, which was used prior to Gleevec, still has a role in this disease. We continue to try to define it as best as possible. And this drug, which is an immunomodulatory and probably an immunostimulatory drug, does boost responses to Gleevec, when given in combination. And may boost responses when given in combination with other drugs such as nilotinib. And clinical trials have started in this arena.

Slide 17-LLS Resources
MABEL MAIA:
Thank you so much, Angela, for your question, and actually thank you all for your questions. Our program has come to a close. Please help me thank Dr. Mauro. We are so grateful he has donated his time with us today.

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 today, please call The Leukemia & Lymphoma Society's Information Specialists toll-free at 800-955-4572 or you can also reach us by email at infocenter@lls.org. Our Information Resource Center is open and our Specialists are available to assist you.

I would also like to mention our partnership and our friends at the Max Foundation. Because we have several international participants, the Max Foundation helps patients who live internationally and living with CML and their families, in any region of the world who need support services. You can contact the Max Foundation at www.TheMaxFoundation.org.

Michael J. Mauro, MD
October 25, 2011 1:00 PM ET

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

OPERATOR:
Thank you. This does conclude today's webcast. We thank you for your participation. You may now disconnect and have a great day.

END