

Understanding CML: *A Conversation With the Experts*



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Welcome

Carson Jacobi Pattillo, MPH

Hello, good evening, and welcome. My name is Carson Jacobi Pattillo, MPH, and I am the Vice President of National Education Programs for *The Leukemia & Lymphoma Society*. We welcome all of those who are onsite at The Governor Hotel in Portland, Oregon, and also those listening via telephone to this evening's program titled **Understanding CML: A Conversation With the Experts**. We have more than 900 people

participating in our interactive program, which we are audiotaping and videotaping for future posting on the LLS's Web site. In late January, we will release the webcast including a written transcript of this program.

Understanding CML: A Conversation With the Experts is a part of *The Leukemia & Lymphoma Society's* patient education series, and we would like to acknowledge Novartis Oncology for their understanding of the importance of support, education and the continued need for up-to-date information for patients and their families. We would also like to thank the Oregon Chapter of *The Leukemia & Lymphoma Society* for helping us to organize this evening's program.

We mailed a packet of information to everyone participating, and for some who registered recently, your packet will arrive shortly. Your packet includes a workbook with information about our speakers, their topics and the program agenda. For those of you on the phone, you can view the speakers' slides online tonight by going to *The Leukemia & Lymphoma Society's* Web site, that's www.lls.org/leukemiaeducation, and clicking the link for the program. You will also find an order form for *The Leukemia & Lymphoma Society's* publications and a blue program evaluation form. For nurses and social workers, this is a continuing education program, and we have included a yellow evaluation form in the packet for you to claim your 2 credits. We encourage you to look through the materials at your leisure if you have not already done so.

Now most of our 900 participants are within the United States, but we do have some callers from France, India, Italy, Singapore, South Africa and Thailand; we welcome all of you.

After our keynote presentations, there will be a panel discussion during which we will answer questions submitted in advance by program registrants. And following, we will open the program for live questions to you, our expert panel, [from] our audience here in Portland, Oregon, [and] from those of you on the phone. We'll take some questions on the phone and

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some from the live audience. As you listen to the presentations, think of any questions you may have for our experts.

Because we have hundreds of people participating via telephone, our panelists may not be able to get to your questions. However, immediately following the program this evening, you can call *The Leukemia & Lymphoma Society's* Information Resource Center (IRC) and speak with a master's level oncology specialist who can answer your questions or help you obtain more information. The Information Resource Center, which we refer to as the IRC, can be reached by calling toll free 1-800-955-4572. That number is on the materials included in your packet. You can reach the IRC Monday through Friday, 9:00 AM to 6:00 PM Eastern Standard Time. Tonight, the IRC is extending its hours until 11:00 PM Eastern Standard Time/8:00 PM Pacific Standard Time.



I now have the distinct pleasure of introducing Dr. Brian Druker, who will provide an overview on new developments in the treatment of newly diagnosed patients. Dr. Druker is the Director of the Oregon Health & Science University (OHSU) Knight Cancer Institute; he is the JELD-WEN Chair of Leukemia Research and is a Howard Hughes Medical Institute investigator at OHSU.

Dr. Druker led the development of Gleevec[®] (imatinib), which has been hailed as the first of a new class of molecularly targeted therapies against cancer, thereby transforming the world of cancer research and treatment. He has received numerous awards, including the Lifetime Achievement Award from *The Leukemia & Lymphoma Society*.

Please join me in welcoming Dr. Druker.

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What's New for Newly Diagnosed Patients

Brian J. Druker, MD

Thank you very much, Carson. Welcome to the audience here and to those of you on the phone. It's a pleasure to be back as part of this program, and it's a pleasure to have you back here in our home of Portland, Oregon. On my first slide, you can see our beautiful tram and new building on our South Waterfront Campus.

What I want to do tonight is talk about what's new for newly diagnosed patients with chronic myelogenous leukemia (CML), but prior to doing that, I want to give you some background about how we monitor CML and what some of the terms mean. For those of you who have listened to these teleconferences previously or who have seen me in my clinic, this is going to be old hat for you, but those of you that are new to the program or are newly diagnosed, I really want to spend just 5 minutes getting us to speak a common language because as you'll hear throughout my comments and throughout Dr. Shah's comments, it's important that we understand what our goals of therapy are, and to understand what the goals of therapy are you kind of need to know a little bit of the insider's doctor's language. So I'll walk you through that relatively slowly and carefully.

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Monitoring Chronic Myelogenous Leukemia (CML)

- Blood counts
- Tests for the presence of the Philadelphia chromosome
 - Cytogenetics – bone marrow – 20 cells
 - FISH – marrow or blood – 200 cells
 - PCR – marrow or blood – 1 million cells

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How do we monitor CML? Clearly, we can monitor blood counts. We can also test for the presence of the abnormal chromosome that marks leukemia cells, the Philadelphia chromosome. We can look for the Philadelphia chromosome either through cytogenetics, it can be done on bone marrow, or we'll look at 20 dividing cells. We can also use FISH (fluorescence in situ hybridization), either on blood or bone marrow, where we look at 200 cells, either dividing or non-dividing, or a polymerase chain reaction (PCR) where we can look for traces of leukemia in as many as a million cells.

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White Blood Count (WBC)

1 trillion	500,000	CML – at diagnosis
	50,000	
# of leukemia cells	5,000 – 10,000	Normal
True 0		

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So, let's talk about this in a slightly different way, and let's think about this in terms of numbers of leukemia cells. The ideal would be not to have any leukemia cells. If you didn't have any leukemia cells, you don't have leukemia, and if we can ever get you to that point, we can say that you're cured. At diagnosis, most people with CML will have a white count of 50,000 to 500,000. A normal white count should be 5,000 to 10,000. That's anywhere between 5 to 50 times the upper limit of normal. In a normal bone marrow, there are 1 trillion

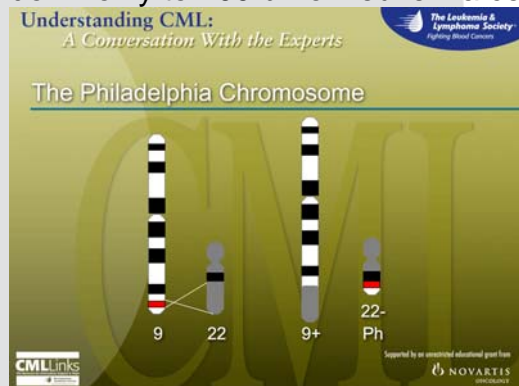
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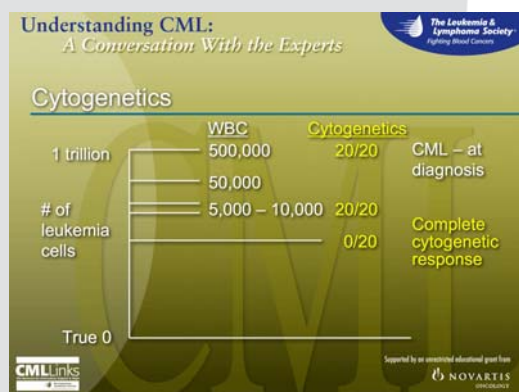
cells. Now that sounds like a big number, but that's how many normal cells are in a normal bone marrow. If the bone marrow's been taken over by leukemia, you have as many as 1 trillion leukemia cells. That may sound like a huge number, but that's how many cells a normal bone marrow has, and now your bone marrow has leukemia.

The first goal of therapy is to get your white count down to normal. If you have a normal white count, we would call that a complete hematologic response. So a complete hematologic response simply means a normal white blood count.

Now the problem with that is that we really don't know how much lower you've gone, how close you are to zero. We've only reduced the number of leukemia cells by maybe 10-fold, perhaps down only to 100 billion leukemia cells. So we've got to do much more sensitive testing, and



this is where cytogenetics comes in. This looks for the abnormal chromosome. This abnormal chromosome, which marks the leukemia cells, comes about because 2 chromosomes, chromosomes 9 and 22, exchange pieces, and you end up with a short chromosome 22, which is called the Philadelphia chromosome, and a longer chromosome 9. It's this short Philadelphia chromosome that we can look for in the bone marrow that marks leukemia cells and is actually what causes leukemia. This is what we look for in cytogenetics. We look for the presence of the Philadelphia chromosome. As I mentioned, we look at 20 cells. Typically, when someone is diagnosed, all 20 of their bone marrow cells will have the Philadelphia chromosome. So it'll be 20 out of 20 Philadelphia chromosome positive.



Now when somebody has a normal white blood count, what if they still were 20 out of 20 Philadelphia chromosome positive? What that tells us is that most of their blood cells are still leukemic despite having a normal white blood count, and our estimates would be that that patient has 100 billion leukemia cells left. Now, the reality is it's better to have a normal white count than a white count of 500,000, but you could still be left with a lot of leukemia cells. So the next goal of therapy would be to try to get somebody down to 0 out of 20 Philadelphia chromosome positive, also called Philadelphia chromosome negative, or a complete cytogenetic response. All those terms mean the same thing. It just means we've gotten you to Philadelphia chromosome negative.

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In reality, we've only looked at 20 cells. A normal bone marrow has a trillion. We've just looked at a drop in the bucket. We've got to get much more sensitive tests if we're going to figure out how well controlled somebody's disease is. Again, however, it's far better to be Philadelphia chromosome negative than Philadelphia chromosome positive. So we need a more sensitive test known as PCR.

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Polymerase Chain Reaction (PCR) Testing

- Detects 1 leukemia cell in 1,000 to 1 million normal cells
- Can be qualitative
 - Present or undetectable
- Or quantitative
 - Gives an estimate of the number of leukemia cells

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PCR testing is, for those of you that follow some of these crime scene dramas, the cops go to the scene of the crime, they scrape a piece of blood and figure out who did it. We can sort of do the same thing with a test tube, a vial of blood. We can look for a trace of leukemia in that vial of blood. So with PCR testing, we can amplify a signal, and we can see 1 leukemia cell in between 1,000

to 1 million normal cells.

Now this PCR testing can be qualitative. It simply gives you a positive or negative. It tells you if this Philadelphia chromosome abnormality, which we'll now call BCR-ABL, is present or not present. We can also do a quantitative test where it gives us an estimate of the number of leukemia cells.

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PCR

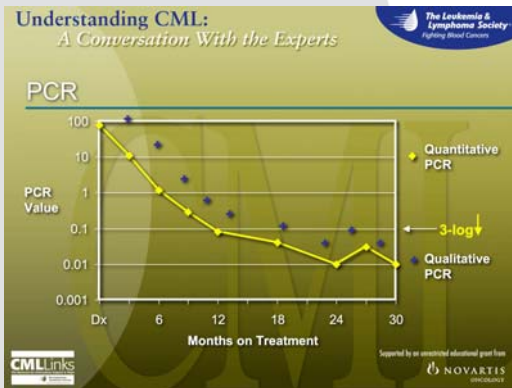
# of leukemia cells	WBC	Cytogenetics	PCR
1 trillion	500,000	20/20	
	50,000		
	Normal	20/20	
		0/20	
1 million			PCR undetectable
True 0			

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So if we put this back on our graph, the reality is that we now can go from 1 trillion cells down to 1 million leukemia cells, but we have to make a couple of points here. First, if you do an equivalence ratio, 1 in 1 million is equivalent to 1 million in 1 trillion. So PCR undetectable could still mean you have 1 million leukemia cells left. It doesn't mean cured, and it also means that we can't do anything more sensitive to look for lower levels of leukemia. So PCR undetectable or PCR negative doesn't mean cured. It just means the lowest level we can identify.

The second point is that about 80% of patients treated with imatinib will be between Philadelphia chromosome negative or complete cytogenetic response and PCR undetectable. Most people will be there. The only way we can monitor patients in this range, where the majority of people are, is through PCR testing.

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So let's look at this graph, looking at PCR values, and here I've taken what's now known, on the left-hand side, something called the International Scale where newly diagnosed patients arbitrarily would have a value of 100, and I've done 10-fold reductions, and you can see on the very far right we have a 3-log reduction. That just means 1,000-fold reduction in the number of leukemia cells, and that has some prognostic importance.

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PCR Monitoring

- Quantitative monitoring is preferred
- Different labs will have different results
 - Standardization is necessary and is being worked on
 - Until then – use the same lab so trends can be followed
- Negative results depend on the quality of the sample and the quality of the lab

We can make a couple of other points. First, I've shown this on a quantitative scale, meaning the quantitative PCR that gives us a number. If we did a qualitative PCR that just said present or absent, all of these values would be positive. You couldn't tell the difference between a newly diagnosed patient who would have a value of 100 and a very, very well-controlled patient, who would have a value of 1, which would likely be a complete cytogenetic response, 0.1 or even lower. So the reality is this quantitative PCR gives us a far better insight into how well controlled people's leukemia is.

Second, clearly quantitative monitoring is preferred. It gives us an indication of where people are. The problem, though, is that different labs will give you different results. If you come to my hospital in Oregon or Dr. Neil Shah's hospital in San Francisco, we'll give you different results. We are working on standardization so that you can go anywhere in the world and have the same testing done and the same results done, but unfortunately we don't yet have a standardized test. Until then, my recommendation is that you send your samples to the same lab so that you can follow a trend. For those of you who are interested, Novartis has set up a program called the CML Alliance™ and they currently use 2 labs. If you're currently not being done at one of these labs, I would urge you to think about working with your physician through the CML Alliance, to have your testing done routinely at a standardized testing laboratory.

A third point about monitoring is that negative results also depend on the quality of the lab and the quality of the sample. The sensitivities vary from lab to lab, from 1 in 1,000 to 1 in 1 million, and so negative at 1 in 1,000 is not as good as negative at 1 in 1 million. Different labs, again, will have different results.

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What's Considered a Good Response?

- 3-log reduction in PCR at any time
– 0.5% risk of relapse that declines over time
- Complete cytogenetic response
– 2% risk of relapse per year that declines to 0.5% per year after 4 years
- Stable complete cytogenetic response = 3-log reduction

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What do I consider a good response? There's a 3-log reduction. Any time you get it, it is a great place to be. Six months, 1 year, 2 years, that's a great place to be. The risk of relapse is a half percent per year, and it decreases over time. So at a half percent per year, that means that at 10 years, 5% of people in that category would relapse. With a complete cytogenetic response to Philadelphia chromosome negative, there is a 2% risk of relapse per year, and by year 4 of maintaining that response, it declines to a half percent per year. So my view is that a stable complete cytogenetic response is equal to this 3-log reduction.

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When Should a Change in Therapy Be Considered?

- Lack of a complete hematologic response after 3 months of imatinib
- Greater than 95% Ph+ after 6 months of imatinib
- Greater than 35% Ph+ after 1 year of imatinib

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What about when a change in therapy should be considered? Certainly somebody who doesn't get their blood count to normal in 3 months, I would certainly consider switching therapy. I would also consider switching therapy for somebody who's greater than 95% Philadelphia chromosome positive after 6 months or 35% positive after 1 year of imatinib therapy. During the discussion, Dr. Shah and I can talk a little bit about when to get a complete cytogenetic response, when to get this 3-log, and there's currently a fair bit of individual variation between physicians about what to do with those patients.

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**Dose of Imatinib
400 mg Versus 800 mg**

- Randomized study showed no difference in responses
- Trend to faster responses in patients who could maintain higher dose therapy
- Drug levels may be predictive of 3-log reductions
- More toxicity with higher dose therapy

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What about the dose of imatinib? At the recent American Society of Hematology (ASH) meeting, there were 2 random studies that looked at 400 mg versus 800 mg and showed no differences in response. There was, however, a trend for fast responses in patients who could maintain higher dose therapy, and there was also a suggestion that people with high drug levels of imatinib may be more likely to get this 3-log reduction but at the expense of having more toxicity. The point here is that early on when people did nonrandomized studies, they just looked at 800 mg and compared historical data on

400 mg, but 800 mg looked a lot better. When you did a head-to-head comparison with identical comparison groups, no significant difference was seen. It points out the importance of doing these randomized controlled studies to guide therapy.

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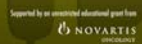
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Should Imatinib Drug Levels Be Monitored?

- Definitely worth checking in patients with less than optimal responses and undue toxicity
- May be worth adjusting dose in newly diagnosed patients
 - More data needed



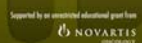
Should we be monitoring drug levels? Certainly, in patients with less than optimal responses and severe toxicity, we absolutely would recommend monitoring drug levels, and as we look at the emergence of this new data about higher drug levels resulting in better responses, we're seriously considering that newly diagnosed patients should have a spot drug-level check. We might be able to adjust their therapy, but also, I think we still need some more data.

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Nilotinib or Dasatinib for Newly Diagnosed Patients

- Early data suggests higher rates and faster responses
- Similar to early data that examined 800 mg of imatinib
- Need to wait for results of randomized studies



The 2 new drugs that Dr. Shah will talk about that are showing significant activity in relapsed patients have now been tried in newly diagnosed patients. Once again, the early data suggests higher response rates and faster responses. This early data looks similar and maybe even a little bit better than when imatinib at 800 mg was examined in this group of patients. It's my view that we wouldn't change therapy until we do a head-to-head comparison looking at imatinib versus one of these 2 new drugs, but clearly we need to do these studies, and if these drugs are better, we need to change our

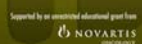
treatment recommendations based on these randomized studies.

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Is It Safe to Stop Imatinib in PCR Undetectable Patients?

- Small studies
- Follow-up averages less than 2 years
- Some patients (50% or less) have not had their PCR become positive
- Too early to know if this is safe



What about stopping imatinib? Many patients are undetectable by PCR. There were 2 studies reported at the ASH meeting that were very small, with follow-up averaging around 6 months, and for a few patients, a couple of years. What was interesting is that a few patients, maybe 5% or 10%, haven't had their PCRs become positive. In reality, there are very few patients who are past 1 year on these studies. Many of the patients who haven't relapsed had previously received interferon but, in fact, there were some patients who had only received imatinib. Their PCRs were negative for a

couple of years, and they haven't relapsed. It's absolutely intriguing to think that there may be a small subset of patients for whom we could stop imatinib, but we clearly need way more follow-up and more patients on these types of studies.

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Could the Dose of Imatinib Be Reduced Over Time?

Who

- Patients with at least a 3-log reduction in PCR maintained for at least 2 years
- Patients with a complete cytogenetic response maintained for at least 4 years
- Patients for whom imatinib is affecting quality of life

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What about lowering the dose of imatinib? Certainly, I would consider lowering the dose for patients who have had a least a 3-log reduction, have a very low risk of relapse, and maintain this for a couple of years. I would also consider lowering the dose for people with a complete cytogenetic response who have maintained that for at least 4 years, when I know their risk of relapse is extremely low, and for anyone for whom imatinib is affecting the quality of their life.

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Could the Dose of Imatinib Be Reduced Over Time? (cont)

How

- Needs careful review of doses required to obtain response
- Drug levels should be monitored and should not be reduced below 500 ng/mL
- PCR needs to be monitored every 3 months – minimum
- We have lowered doses gradually

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How would I do this? First of all, I'd look to see what doses did it take to get them to their response. If they needed 800 mg to get to a complete cytogenetic response, I'm not going to be eager to lower their dose. If we started them on 800 mg, and they got a very rapid response, I might actually think about lowering them. I would absolutely recommend levels and not reducing below a drug level of 500 ng/mL. That's typically achieved with imatinib doses of 300 mg to 400 mg per day. I would be monitoring PCR very closely every 3 months, sometimes even more often, and we typically

have lowered the doses very gradually, not making rapid changes. If the PCR goes back up, we can again increase the dose.

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Conclusions

- Gleevec at 400 mg/d is the standard therapy for patients with CML
 - Randomized studies ongoing comparing imatinib to nilotinib or dasatinib for newly diagnosed patients
- Need to identify which patients are least likely to respond or at highest risk for relapse
 - ? Drug level monitoring
 - Other tests in development

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What conclusions should we take away from this? In our practice, imatinib at 400 mg per day is still the standard of therapy. There are ongoing randomized studies that are comparing imatinib to nilotinib (Tasigna[®]) for newly diagnosed patients who eagerly await the results of those studies, and we hope within another year or 2, we'll have those results. We clearly need to do a better job of identifying which patients are least likely to respond or are at the highest risk of relapse. These might be patients for whom more intense drug level

monitoring would be in order. In addition, we have other tests in development that may help us identify which patients should be treated with some of the new drugs or higher dose therapies.

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Future Directions

- Unlikely that current drugs will cure CML
 - Early studies of stopping imatinib are inconclusive
 - Need further research into methods to eradicate remaining CML cells

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What about the future? Although I mentioned some intriguing results about stopping imatinib, it's my view that these are inconclusive, and it's my current view that the current drugs are unlikely to cure CML as a single agent, and we absolutely need more research into methods into eradicating remaining CML cells. With that, I'd like to thank you for your attention, and I'll look forward to some of your questions.

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Introduction to Dr. Shah

Carson Jacobi Pattillo, MPH

Thank you very much, Dr. Druker. We will hear again from Dr. Druker during the panel discussion.



It is now my pleasure to introduce Dr. Neil Shah, who will review evolving therapies for the treatment of relapsed or refractory patients with CML.

Dr. Shah is an assistant professor in the Division of Hematology/Oncology in the Department of Medicine at the University of California, San Francisco School of Medicine in California.

He published the first preclinical studies of dasatinib (Sprycel[®]) in 2004, and was closely involved with the clinical development of this agent for the treatment of imatinib-resistant and imatinib-intolerant CML. He is working to further improve the success of targeted therapy for CML and other malignancies.

Please join me in welcoming Dr. Shah.

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What's New for Relapsed/Refractory Patients

Neil P. Shah, MD, PhD

Thank you, and thanks for that wonderful presentation, Dr. Druker. My goal here is to talk about the flip-side of the coin, specifically, what to do in patients who are not responding adequately to imatinib or those who have lost a response, and I think we should also consider the options for patients who are having difficulty tolerating imatinib.

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Imatinib as the Medical Standard of Care for Chronic-Phase (CP) CML Patients

- Imatinib at a dose of 400 mg daily is generally well-tolerated, and should be considered first-line treatment
- The majority of imatinib-treated chronic-phase CML patients achieve deep responses that are most often durable
- Patients who are tolerating and responding deeply to imatinib appear to have a lower risk of relapse after the third year of treatment
- More patients are becoming PCR-undetectable over time
- Imatinib is clearly improving overall survival in chronic-phase CML patients

Half-full?

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As Dr. Druker just mentioned, I think we all still must consider imatinib the standard of care for newly diagnosed chronic-phase CML patients, and a dose of 400 mg remains the proper starting dose as of this time. The majority of patients with chronic-phase disease do achieve quite deep responses. So, the number of patients who achieve a complete cytogenetic response (that Dr. Druker defined for you) after 12 months of imatinib, is somewhere between 65% and 70% of patients who begin imatinib 400 mg daily. By 18 months, somewhere close to 75% of patients reach have a

complete cytogenetic response. The take home message is that, for the majority of patients, imatinib is effective at achieving a deep level of remission that I think most experts would be satisfied with, but keep in mind that means after 18 months, 25% of patients are clearly not doing as well as we would like them to do.

Patients who are tolerating imatinib and have a deep response have a lower risk of having a “loss of response event” after the first 3 years on imatinib, and that, of course, gives us some optimism that the long-term outlook for these patients may be actually improving as time goes on. It appears thus far that the majority of patients who are not going to do well on imatinib can be identified within the first 3 years.

Another issue that I think is really quite intriguing is the fact that after about 12 months, only somewhere between 5% or maybe as many as 10% of patients are undetectable by the PCR test for BCR-ABL, the gene that drives CML. What is rather intriguing is some studies done in Australia and studies performed on IRIS (International Randomized IFN versus ST1571) Study patients have found that somewhere between year 3 and year 4, the percentage of patients who are having deeper molecular remissions is actually increasing. It appears that there's a gradual decline in disease burden in a substantially higher proportion of patients well beyond the first 12 months. Once patients get to where their disease is undetectable by the PCR test, it is no longer possible to quantify the disease. It is tempting to speculate that the disease burden is actually continuing to decline below the level we can detect, but there's no way of knowing this at the present time. We won't know whether or not anybody is possible cured for

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several years because that would be our estimate for how long it may take to go from having 1 cell to having the disease be clearly detectable.

Most important, imatinib is clearly improving overall survival in chronic-phase patients. We know somewhere around 5% of patients have succumbed due to their disease after 5 to 7 years, which is far less than what we would have had predicted prior to the imatinib era. Dr. Druker deserves a tremendous amount of credit for pioneering this form of therapy for this disease.



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Imatinib as the Medical Standard of Care for CP CML Patients (cont)

- A substantial number of patients develop resistance to imatinib, and few meaningful treatment options existed for most of these patients until recently
- A small number of patients are highly intolerant of imatinib, many patients deal with unpleasant side effects on a daily basis
- Imatinib does not appear to be curative; most patients will likely require long-term treatment
- Approximately 25% of patients meet definitions of imatinib resistance within 18 months of initiating therapy
 - Importance of adequate disease monitoring (especially within the first 3 years) to identify chronic-phase CML patients most likely to benefit from alternative treatment strategies

Half-empty?

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There is a substantial proportion of patients who lose response to imatinib. Because we can identify these patients and those at highest risk for losing response through some very important disease monitoring techniques, we've changed our definitions of what constitutes resistance. There's a good proportion of patients who do develop a loss of response or who are considered resistant after 18 months. There is a small percentage of patients who are highly intolerant of imatinib—on the order of somewhere between maybe 2% and 4% of patients—in whom the risk of continuing

therapy is too great, because there's perhaps a really bad skin rash or there are liver damage. These imatinib-intolerant patients had no other effective therapeutic options before the second line treatments that I'm going to discuss became available, because in most cases these patients were not candidates for allogeneic stem cell transplantation.

Despite the fact that there's only a small percentage of patients who are highly intolerant of imatinib, I think it's important to realize that given the current recommendation that patients continue therapy indefinitely, we need to be a little bit more mindful of some of the less severe side effects that people have to deal with on a day-to-day basis. And, to me, some of the good news about having several agents available for this disease is that the management is becoming in some ways more like the treatment of high blood pressure, where the most important thing is to control the disease. To achieve that, you would like to preserve a good quality of life for patients, and having multiple agents for the treatment of high blood pressure, we can sometimes go from one to the other and find one that works best for a particular patient.

The same thing holds true now with these second-generation kinase inhibitors that I'm going to talk about. There are some patients who have more side effects on the second-line agents, and there are some patients who actually have fewer. It's very important to keep this issue in mind. As Dr. Druker mentioned, most patients will require long-term treatment with imatinib. We do not think it's wise at the present time to discontinue the drug in responding patients

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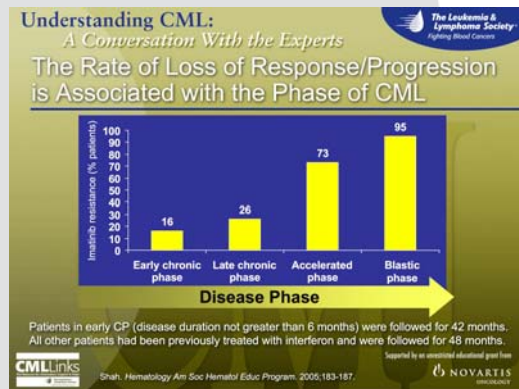
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outside the context of a clinical trial. As I mentioned earlier, approximately 25% of patients by 18 months after starting imatinib will be expected to have met a definition of imatinib resistance. In most cases, the only way that these patients can be properly identified is if their physician is monitoring the disease properly, and unfortunately that's not always the case. I suspect we'll get to explore that issue in the panel discussion or in the questions that may come after that.



An important point regarding the rate of loss of response and progression to imatinib is that the phase of the disease in which a patient is diagnosed is very important in determining the likelihood that a patient will perhaps lose a response and progress. Towards the left, you can see that the patients who have the lowest risk of losing a response or progressing are patients who begin imatinib in what we call “early” chronic-phase disease. These are patients in whom imatinib is started very shortly after the diagnosis is made. The first large group of patients to

receive imatinib were actually “late” chronic-phase patients who were resistant or intolerant to interferon therapy. It's important to realize that these patients had their disease for some period of time before they started imatinib, and what you can see here is that the rate of relapse and progression was quite a bit higher in this group of patients than in early chronic-phase patients.

Another thing that's not shown here is that the rate of initially achieving a deep response—a complete cytogenetic response—in this group of patients is actually lower than in the patients who started imatinib earlier. The survival of these patients was a bit lower than patients who start imatinib earlier. Beware that this is not a randomized study. Every effective therapy that we've had for this disease does its greatest amount of good the earlier it is offered to patients, and imatinib appears no different in this regard. You can see in the more advanced phases, the accelerated phase and the blast phase, unfortunately, loss of response and progression are far too common.

Understanding CML:
A Conversation With the Experts

Failure to Respond Adequately to Imatinib (complete cytogenetic response by 12–18 months) Appears to Be Related to the Level of Kinase Inhibition Achieved in Some Patients

- Possible Mechanisms
 - Inadequate plasma levels of imatinib
 - Low expression of drug pumps (eg, OCT1) that actively pump imatinib into cells

Some patients may have too few normal blood stem cells, which could prevent them from achieving a complete cytogenetic response

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How are we defining imatinib resistance? As I mentioned earlier, an inability to achieve a complete cytogenetic response by somewhere between 12 and 18 months, but no later than 18 months, is widely accepted. There's some data, that has not been clearly demonstrated yet in studies, that suggests the likelihood of achieving a very deep response may be higher by achieving a greater degree of BCR-ABL inhibition, either through a higher dose of imatinib or a higher imatinib plasma trough level,

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or alternatively through a more potent inhibitor. There have been some studies that have shown a correlation between the likelihood of achieving a complete cytogenetic response and the imatinib plasma levels. Other studies have suggested that certain drug pumps, which are actively transporting imatinib into cells may be important and if patients have a low level of one of these drug pumps, they are less likely to achieve a deep response. And it remains likely that there are some patients who may not have enough normal hematopoietic stem cells to repopulate their bone marrow, once we get rid of the cells that have the Philadelphia chromosome. There may be some patients in whom it may be very, very difficult to ever achieve a deep cytogenetic response.

Understanding CML:
A Conversation With the Experts

Loss of Response to Imatinib is Most Often Due to Loss of Molecular Target Inhibition

- Mechanisms
 - Outgrowth of one or more clones harboring an imatinib-resistant BCR-ABL kinase domain mutation (most common)
 - Overproduction of BCR-ABL via genomic amplification

“Second-generation” BCR-ABL kinase inhibitors are effective against most imatinib-resistant mutations, and are more potent than imatinib in the laboratory

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We actually understand a fair amount about why patients may lose an established response to imatinib. In most cases, the resistant cells have found a way around the presence of imatinib, and this is typically achieved through the selection of cells that have mutations where imatinib binds to its target that prevent imatinib from binding. So these cells can survive and grow despite the fact that a good concentration of imatinib is present in the plasma and presumably in the cells. There are also some cases where resistance arises through a different mechanism, which is to over-produce BCR-ABL. The increased amount of BCR-ABL in the cells enables the cells to outcompete the imatinib. Importantly, the second-generation kinase inhibitors are both more potent than imatinib, and they have activity against almost all of the resistant mutations that have been characterized. Both have been shown to be problematic in patients.

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Dasatinib and Nilotinib are FDA-Approved Second-Generation BCR-ABL Kinase Inhibitors

- Effective in patients with imatinib-resistant or imatinib-intolerant chronic-phase CML
- FDA approved for all phases of CML and Ph+ ALL (dasatinib) and chronic and accelerated phases of CML (nilotinib)
 - Advanced phase responses are not highly durable
- Generally well-tolerated, but some patients are intolerant; very little “cross-intolerance”

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Dasatinib and nilotinib are the 2 drugs that are FDA (Food and Drug Administration) approved for the treatment of imatinib resistance and imatinib intolerance. These drugs are both approved for chronic-phase and accelerated-phase CML. Dasatinib is also approved for blast-phase CML and Philadelphia chromosome-associated acute lymphoblastic leukemia, which is another disease that’s driven by BCR-ABL, the target of all these drugs. As with imatinib, the responses that have been observed with these newer more potent drugs are most impressive in patients who are in the chronic phase. Unfortunately, most patients in the advanced phase have a short response duration.

Both of these drugs are generally well tolerated, but some patients do have problems tolerating one or both of them. There appears to be very little “cross intolerance,” meaning that if a patient has for example, a bad skin rash on one of these drugs, it appears very unlikely that

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Understanding CML:
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Dasatinib and Nilotinib are FDA-Approved Second-Generation BCR-ABL Kinase Inhibitors (cont)

- Loss of response to these drugs has been observed
- As with imatinib, it is unlikely that cures will be achieved in a substantial number of patients treated with dasatinib or nilotinib
- Problematic imatinib-resistant mutations:
 - Dasatinib: T315I, F317L
 - Nilotinib: T315I, Y253H, E255K, E255V, F359C, F359V

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they will have that same problem on a second-line drug. Therefore, the fact that there are numerous choices is excellent news for all patients with CML.

Understanding CML:
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Dasatinib in Early Chronic Phase (ECP) CML Best Response (N=44†)

Response	No. (%)
CHR	44/44 (100)
Cytogenetic Response* CCyR	40/40 (100)
Molecular Response* MMR	21/40 (44)
CMR	2/40 (5)

† 1 patient discontinued therapy after 3 doses
* Patients with at least 3 months follow-up

Borthakur et al, ASCO 2008 #7013

Loss of response to these agents has been observed. These drugs are not foolproof. There are some mutations that can cause resistance with these drugs, as with imatinib, it is unlikely that these drugs are curing anybody with the limited experience to date. The mutations that are imatinib resistant that pose particular problems for each of these drugs are listed here. I would like to point out that the T315I mutation has been particularly problematic because it is cross-resistant to all of our approved drugs, but there are some investigational agents that I'll talk about in a moment that may have some activity against this mutation.

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Nilotinib in ECP CML Best Response (N=47)

Response	No. (%)
CHR	38/38 (100)
Cytogenetic Response* CCyR	39/39 (100)
Molecular Response* MMR†	15/42 (36)
CMR	6/42 (14)

* Patients with at least 3 months follow-up
† Not including CMR

Cortes et al, ASCO 2008 #7016

Dr. Druker mentioned that dasatinib and nilotinib are being tested in studies of patients who have not had previous imatinib. Here is a small single-arm study from Houston. What has been impressive is that the complete cytogenetic response rate with dasatinib or with nilotinib approaches 100%. So it appears that almost all patients are capable of achieving a complete cytogenetic response with these agents, but please bear in mind that these are only 2 small studies.

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Second-Generation BCR-ABL Kinase Inhibitors

FDA-approved

- Dasatinib (BMS-354825)
- Nilotinib (AMN107)

Investigational

- Bosutinib (SKI-606)
- INNO-406 (NS-187)

- Capable of inhibiting most imatinib-resistant mutations
 - T315I is highly resistant to all of these drugs
- More potent than imatinib in laboratory studies

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There are now ongoing randomized studies, we may know within the next 1 to 2 years whether these agents are more effective or not and whether they are as well tolerated or not as 400 mg of imatinib.

In addition, there are some investigational, second-generation agents that don't really add too much to the armamentarium. They may have different side effect profiles, so patients who may have intolerance to all 3 of the approved drugs may be able to tolerate one of these other agents, but all of them fail to effectively deal with the T315I mutation.

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Investigational "Third-Generation"
ABL Kinase Inhibitors

Currently in clinical trials

- PHA-739358 - phase II
- XL228 - phase I
- AP24534 - phase I

Not yet in clinical trials

- TG101223
- SGX 70393

No longer being clinically developed

- MK-0457 (VX-680)

- These agents have activity against the T315I mutation in the laboratory. MK-0457, PHA-739358 and XL228 have shown early signs of clinical activity.

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There are investigational third-generation agents that are designed to effectively deal with the T315I mutation. I have listed a few here. At this moment, one that I'm most excited about is the third one listed here from a company called Ariad [Pharmaceutical, Inc.] [AP24534]. Dr. Druker's lab had presented some laboratory data on this compound at the recent ASH meeting. Essentially, this drug appears to have activity against a large number of mutations, including the T315I mutation, and it does not appear to suppress the growth of cells that don't have BCR-ABL in the laboratory, but it's still only in early clinical trial development, and we'll learn more as time goes on.

Understanding CML:
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Targeted Kinase Inhibitors and CML:
Future Directions

- The increased potency and clinical activity of second-generation agents in the imatinib-resistant and imatinib-intolerant setting raise questions about how to best manage CML in the future.
 - Imatinib followed by dasatinib or nilotinib?
 - Dasatinib or nilotinib in newly diagnosed patients?
 - Combinations or sequences of kinase inhibitors?
- Incorporation of mutation detection into treatment decisions is becoming standard
- The availability of multiple ABL kinase inhibitors may further delay bone marrow transplantation

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There was an agent that is no longer being clinically developed called MK-0457 but, again, these agents all have activity in the laboratory, and at least all 3 of the ones that are currently in clinical trials do have some level of activity that has been demonstrated in clinical trials.

As far as the future, it's hoped that the increased potency and clinical activity of these second-line therapies will perhaps help us push the envelope in terms of achieving deeper and more durable responses in a larger proportion of patients than what we've been able to achieve with imatinib. There are questions that will come up: What's the optimal sequence of these agents? Should we perhaps start with the second-line agents and reserve imatinib for later? This will likely be addressed in the coming years.

Mutation detection is extremely important in patients who are not responding well to imatinib as it can help physicians choose which second-line therapy will be optimal for a particular patient or if a patient may not be well-served by either second-line therapy.

Understanding CML:
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Targeted Kinase Inhibitors and CML:
Future Directions (cont)

- PHA-739358 and XL228 appear to have some clinical activity in CML cases harboring the T315I mutation
 - Intravenous medications
 - Response rates not high
- Effective long-term treatment strategies for advanced phase CML and the T315I mutation are needed
- Strategies to eliminate minimal residual disease would be ideal

Participation of CML patients in clinical trials is required to develop better therapies

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It is predicted that bone marrow transplantation will be further and further delayed because of these second-line agents, but it would be nice to know how long we should wait for a response to second-line agents before we decide to pursue bone marrow transplantation in patients who have that option.

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Some investigational agents have been shown to have some activity against the T315I mutation. The ones that have shown the most activity so far are intravenous medications. The response rates have not been very impressive. We do need effective long-term strategies to treat this particular mutation, and as Dr. Druker mentioned, strategies to eliminate the last few remaining CML cells in patients who are responding deeply would obviously be ideal. I just want to put a plug in for the continued participation of CML patients in clinical trials, because we can sometimes become complacent when we have drugs that can achieve deep remissions in the majority of patients, but we know that there is still, of course, a lot of important work to do.

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Panel Discussion

Moderated by: Carson Jacobi Pattillo, MPH

Thank you very much, Dr. Shah.

We will now begin the Panel Discussion for this program. Questions have been submitted during the registration process. The first question that we have for the panel discussion is, "If I am in complete cytogenetic response but not a major molecular response with imatinib, should I be worried? Should I increase my dose of imatinib or should I switch to another drug?"



Brian J. Druker, MD

Before we get to that question, in my introduction, I forgot to say something critically important. When we project the average survival of patients with CML to be an average of 30 years, that means that if a person is diagnosed at age 60, we're projecting that person should live until the age of 90. That's saying we think they may die of something else, not their CML, and that's a great place to be.

Despite that, we have to be sure that CML isn't the major problem. So dealing with questions like "Am I in complete cytogenetic response without major molecular response?" is something that we need to address, and the reality is there's no simple answer. Early on in my slides, I said that a stable complete cytogenetic response is equal to a major molecular response, but that may be very different for somebody who's 70 years old, tolerating imatinib therapy well, and really has no other treatment options, as opposed to a 25-year-old with whom we're trying to decide between bone marrow transplant and nontransplant therapy or maybe much more aggressive therapy.

In general, I've not been pushing people to get to this 3-log reduction. I'm perfectly happy when people are at a complete cytogenetic response, but it is individualized, and I'd be interested in your opinion, Dr. Shah, because I know there's a fair bit of variance on this question.

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Neil P. Shah, MD, PhD

Yes, there is indeed a fair amount of controversy. It's clear that the complete cytogenetic response by 12 or 18 months at the latest is a goal that we should try to achieve in every patient.

Now, above and beyond that, the amount of benefit that this 3-log reduction, or major molecular response," as it is referred to, adds to patients who have a complete cytogenetic response but don't achieve a 3-log reduction is really rather small. Nonetheless, there is a slightly lower likelihood of transforming to accelerated-phase or blast-phase CML, and that is something that we don't have good therapies for at the present time that will lead to durable remissions in the absence of a transplant. I would agree with you in as much as if I have a younger patient who possibly has a transplant option, I will try to push for a 3-log reduction. I won't recommend transplantation should he or she fail to achieve a major molecular response, as long as they have a complete cytogenetic response. But, of course, the important aspect in all of this is disease monitoring because almost all patients who will lose a response from this level of remission will do so in a very gradual, step-wise manner, and if we're performing the quantitative PCR test every 3 months, we have an opportunity to identify loss of response early, before it progresses to where it may be more difficult to treat.

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Panel Discussion

How do you suggest managing the side effects of imatinib (ie, muscle cramps, stomach upset, diarrhea, fatigue)?

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Carson Jacobi Pattillo, MPH

The next panel question is, "How do you suggest managing the side effects of imatinib (ie, muscle cramps, stomach upset, diarrhea, fatigue)?" You talked about quality of life.

Brian J. Druker, MD

I'm going to thank Carolyn Blasdel, who has been my research nurse for 10 years, since patient number 2 on imatinib. She has more experience at managing these side effects, and she put together a little cheat sheet for me on how she manages these. For muscle cramps, sometimes imatinib can cause low calcium, low phosphorus, and/or low magnesium. We check for that and we replace them. We try to make sure that people are well hydrated. We often will use calcium supplements, typically calcium citrate at 5 mg to 600 mg per day, and occasionally people try tonic water if they like it. If it's persistent, we check for any of these side effects, and we check blood levels of imatinib.

For stomach upset, we suggest people take their imatinib with their largest meal of the day. If that doesn't work, we'd split the dose. Oftentimes, there can be some stomach irritation, so we try some medications like Pepcid[®] (famotidine) or, if that's not working, some Nexium[®] (esomeprazole). If people are having heartburn, we do things like elevate the head of the bed,

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and occasionally, stomach upset can be another way of saying nausea. So occasionally, we try an antinausea [drug] like Compazine[®] (prochlorperazine) or Zofran[®] (ondansetron).

For diarrhea, we found that Imodium[®] (loperamide) is the most effective. Sometimes Metamucil[®] (psyllium fiber) can work. Sometimes acidophilus supplementation can work, and obviously, if it's persistent, we'd be checking drugs and looking for other causes.

For fatigue, again, we're looking for anemia, whether that could be supplemented with some of the red blood cell stimulating medicines. We absolutely want to make sure we're checking for thyroid function, B₁₂ or folate deficiency or iron deficiency that might be a cause of their anemia. And then, of course, we also want to screen for depression, for which fatigue can be a symptom. So we really try to do a comprehensive analysis of what can be underlying the symptoms. If the symptoms persist, and we've checked imatinib levels, then we would certainly be think to switching to other drugs because of what Dr. Shah mentioned about lack of cross intolerance.

Neil P. Shah, MD, PhD

I have, I guess, a little bit of a different take on this. I mean, certainly, before the second-line agents were available, I would do everything I could to support patients through this because there weren't any other effective options. Whether the second-line agents are as good as imatinib or better, we don't yet know the answer. Knowing how these drugs work makes me optimistic that they're every bit as good as imatinib, and so I actually use a very low threshold when considering switching patients to one of these second-line agents, particularly in light of some of that provocative data I showed you that reveal that the second-line agents in newly diagnosed patients are achieving deep, deep remissions. That again leads me to think that these agents are probably every bit as effective as imatinib and perhaps more so. And one thing that we've learned from both these second-line agents is that while the drugs have activity in patients who have been treated with imatinib for some period time they appear to have greater activity much earlier in the disease course.

I don't have data to prove this, but I look at these agents as the most active agents that we currently have. Therefore, at the first sign of what I consider to be significant intolerance to imatinib, I'll always involve the patient in making this decision; it's not for me to say that some mild or moderate nausea or even facial edema is not severe enough to be described as unacceptable. I have a 42-year-old patient who has had a beautiful response to imatinib but is very, very distressed about facial edema, and she's tried diuretics and so on, and we don't feel comfortable advising her to go down on her dose of imatinib nor can we say that it's okay to go off of imatinib periodically. So, we had to consider switching the patient for what many would say is a cosmetic intolerance. Given that we have multiple agents, I'm certainly more proactive today in switching patients.

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Another place in which we differ is in the value of imatinib plasma level testing. I almost never check that because the test would have been of far greater use if there were no other therapies available. The main benefit of that test has been shown when it's checked on day 29 after starting imatinib; patients who have a low plasma level have somewhere around a 60% chance of achieving a completely cytogenetic response after 1 year versus patients who have a higher trough level, who have a 70% chance.

So, yes, response rates are a little bit worse if patients have low trough levels, but the difference is not dramatic and I don't really know whether people have correlated trough levels with toxicity, and since there are these second-line agents that are more potent, my bias has been to switch patients much earlier on.

Carson Jacobi Pattillo, MPH

So it's important for patients to be knowledgeable about their options, and to always have an open dialogue with their treatment physician and team to move forward for the best thing for them.



The third question that's come through is, "What should I do if my white blood cell or platelet count is low? Should treatment be held, the dose lowered, or should I switch to a different drug?"

Neil P. Shah, MD, PhD

In terms of intolerance to imatinib, one exception for the second-line agents has to do with what we call hematologic intolerance, meaning patients who take imatinib and have a problem with their blood counts

being persistently low. While low blood counts should be expected within the first few months after starting one of these drugs that targets CML cells, and while we want and expect the blood counts to come down initially, we would not like to see them go down or stay too low. And what is essential at preventing that from happening is something that we can't predict by looking at any patients through any test, and that is their hematopoietic reserve, which refers to the supply of normal bone marrow stem cells. And if a patient has a good reserve, these cells should continue to divide and multiply, and if a patient has low counts initially on imatinib, those will, after a period of time, typically recover. We don't want the counts to go down and stay down for too long because there are risks of infection, risks of bleeding, and so on.

The minimum dose of imatinib that we believe to be effective is 300 mg once a day. Below this dose, we are not adequately hitting the target, but, of course, interruptions are sometimes necessary. If there are patients who require repeated interruptions on imatinib, which, from what we can tell, is probably not as potent at hitting the target as some of the newer drugs

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then, in my opinion, it's highly likely, and in my clinical experience, it's also highly likely that if you switch them to treatment with a second-generation drug, they will encounter the same problem. These patients may need to have periodic interruptions for a prolonged period of time. There are a few patients I've treated that can't tolerate higher doses than 300 mg of imatinib on a daily basis, but those patients are exceedingly rare, and then transfusions and the like can be used.

Brian J. Druker, MD

I would agree entirely that if patients have low blood counts with therapy, it's their disease, not the drug, and by switching to a different drug, you're just going to have the same problem. My view is that if somebody has low blood counts, they need more aggressive therapy, not less aggressive therapy because they have more advanced disease. We typically will try to do everything we can to keep people on therapy using white blood cell stimulating medication. There currently is now an FDA-approved platelet stimulating medication. I have no experience with that yet, but I'm sure that we'll learn about that in patients with low platelet counts next year. So these are patients who I think actually need more aggressive treatments. Switching drugs really isn't going to help very much. It's the lack, as Dr. Shah said, of normal blood cells in the bone marrow that's the problem, not the lack of effectiveness of therapy.



Carson Jacobi Pattillo, MPH

Our last panel question is, "My doctor will not test me using PCR; he only uses FISH. What arguments can I use to convince him to test using PCR? I show no BCR-ABL using FISH."

Brian J. Druker, MD

Dr. Shah and I previewed this question, and we kidded a little bit. How do you tactfully say maybe you should think about switching doctors? The reality is that patients need to be their own advocates. The reality is that many doctors in the community are outstanding physicians, but they're not CML experts, and CML is a relatively uncommon disease. And, again, the doctors in the community are very smart, competent, well trained, but there's a difference between what they're going to know about CML if you're the only CML patient in their practice, and what someone like Dr. Shah or I know about managing the disease.

In our clinics, we're very adept at seeing patients every 6 months, once a year, working with local referring physicians, trying to improve the level and the quality of the care. If the physicians in the community aren't willing to improve the quality of their care, we're set up to take care of patients with CML, as are many experts around the country, but I do encourage patients to take control and take charge of their illness. You're the one with the largest stake in

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this disease. Your doctor is going to try to do the very best, but the very best depends on the level of expertise.

Neil P. Shah, MD, PhD

The only way that this would be justifiable is if this patient is in the part of the world that doesn't have access to a PCR test. Then this would be all we would have. Not all PCR tests, as Dr. Druker mentioned, are created equally, and there are so many of them out there, and I don't want to get into recommending one test versus another, but I certainly tell my chronic-phase CML patients this is one of the most important tests we can do. We can determine their level of response better with this test than with any other test. We can detect relapsing disease early. This is an essential test that patients absolutely must have.

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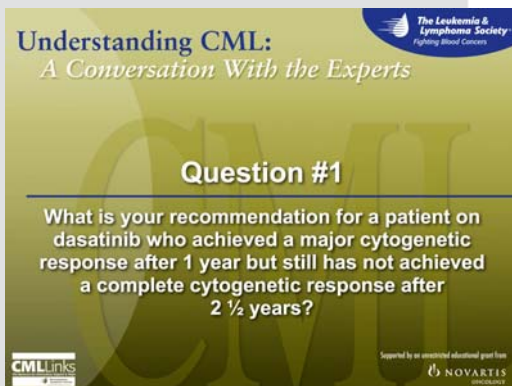
Question and Answer Session

Moderated by: Carson Jacobi Pattillo, MPH

Thank you very much for the discussion. It is now time for the interactive part of our program, the question and answer session. Before the operator gives instructions to the telephone audience to queue themselves for questions, I'd like to remind all of you that we have hundreds of people on the telephone, and we also have guests here in our audience in Portland. We will take questions from the telephone audience and from our

Portland audience. For those of you here in Portland, please raise your hand, and someone will bring a microphone to you. For everyone to benefit, please try to keep your questions general in nature and Dr. Druker and Dr. Shah will provide an answer general in nature. For those of you on the telephone, your microphone will be muted after you ask your question so our experts can respond. If you have a specific question for one of the guest speakers, please address the speaker, so we will know to whom the question is directed.

We will take our first question from the Portland audience.



Question 1

Thank you. What is your recommendation for a patient on dasatinib who achieved a major cytogenetic response after 1 year but still had not achieved a complete cytogenetic response after 2 ½ years?

Neil P. Shah, MD, PhD

One thing that we absolutely need to do with these newer treatments, as I've alluded to briefly, is determine what constitutes resistance. Everyone can easily spot resistance when there is a loss of an established response, but does the failure to achieve a complete cytogenetic response after 18 months on dasatinib or nilotinib mean that a patient is less likely to do as well as somebody who does achieve that level of response? The only data that we have to date comes from a single institution, the MD Anderson study, which looked at both dasatinib and nilotinib and found that patients achieving a major cytogenetic response after 12 months correlated to a better clinical outcome. They did not look after 18 months, but bear in mind the follow-up times with these new agents is still quite limited. It may be some period of time before we get more information. I would, obviously, want to watch a patient who fell into that category very, very carefully. If they had a transplant option, I am generally making the assumption that the same guidelines that we're using should be, until further notice,

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employed with the second-line agents. I don't think one could be faulted for seriously looking at a transplant option.

Another thing to consider is to do a mutation test because the patient may have a mutation that's causing the problem. Certain mutations respond preferentially to dasatinib or nilotinib. So I would approach it that way, especially if there were no transplant option.

Carson Jacobi Pattillo, MPH

Thank you for that question. We'll take our next question from the Portland audience.

The slide features a green background with the title 'Understanding CML: A Conversation With the Experts' at the top left. The Leukemia & Lymphoma Society logo is in the top right. The main text reads 'Question #2' followed by 'How often should I have blood tests upon starting imatinib?'. Logos for CMLinks and Novartis are at the bottom.

Question 2

Dr. Druker, how often should I have blood tests upon starting imatinib? The hematologist is suggesting, or planning on, every 5 weeks.

Brian J. Druker, MD

The question is about how often to check blood counts immediately after starting kinase inhibitor therapy. Generally, we'd look about every other week, monitoring blood counts, and if they start to get low we might even go to once a week. If they're pretty stable after the first

couple of months, we'd try to lengthen that out to every 4 weeks. By the time somebody gets to a complete cytogenetic response, we'd lengthen that out to every 6 weeks or even longer. But early on, there's a pretty high risk of the blood counts going quite low, so we really do recommend monitoring about every other week as you're getting started and then lengthen the interval depending on the clinical situation.

Carson Jacobi Pattillo, MPH

We have another question live here in Portland.

The slide features a green background with the title 'Understanding CML: A Conversation With the Experts' at the top left. The Leukemia & Lymphoma Society logo is in the top right. The main text reads 'Question #3' followed by 'Is it necessary to continue with expensive testing if PCR testing has shown no sign of CML?'. Logos for CMLinks and Novartis are at the bottom.

Question 3

Thank you, Dr. Druker, for developing the drug [imatinib], which continues to keep me alive. I was diagnosed in 2002 and have been in remission for over 6 years. My question is regarding the need for bone marrow biopsy. Historically, my oncologist has ordered this test every 1 to 1 ½ years. My PCR tests for the last 3 years have shown no sign of CML. Is it necessary to continue with this expensive test?

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Brian J. Druker, MD

Thanks for the question. I'll be interested to hear Dr. Shah's opinion on this as well. After 5 years, well after complete cytogenetic response, I rarely am getting marrows anymore, and certainly after 5 years, I'm not doing them at all. There's just no point. You're monitoring a 1,000-fold lower by the PCR testing than you ever could by the bone marrow cytogenetics. I just don't see any point in doing it. The risk of relapse has gone down. The PCR is way more sensitive, and you could do it off of blood so I just don't see any point.

What I have done in people who are in a complete cytogenetic response in the first 5 years, I typically would do a bone marrow at about the 3-year anniversary and about the 5-year anniversary, because there have been some abnormalities that we might pick up in other cells, and if that happens, then I might do marrows routinely, but if the marrows are normal, I just don't see much of a point in doing them anymore.

Neil P. Shah, MD, PhD

I generally agree. I probably don't even do the 3- and 5-year marrows. The reason is because the only way I would act upon an abnormal chromosome in another cell that doesn't have the Philadelphia chromosome is if the patient had some meaningful evidence of another abnormality, meaning if the patient has a suddenly lower platelet count or a new anemia that isn't explained by an obvious cause. Then, I would do a bone marrow biopsy at that time, but I'm not in the habit of doing bone marrow biopsies once patients achieve a complete cytogenetic response once on a bone marrow biopsy.

Carson Jacobi Pattillo, MPH

Thank you. We will take another question from our Portland audience.

Words of Encouragement From a Participant

For our listening audience, I would like to give you hope. I was diagnosed in 1999. I started treatment with Dr. Druker in 2000, and in February, I will be a 9-year survivor. I just want everyone to have hope. My quality of life is fantastic, and I just wanted to give hope to the audience. (APPLAUSE)

Carson Jacobi Pattillo, MPH

We will take our next question from the telephone audience.

Question 4/Jerry

Hi, Dr. Druker. Thank you so much for taking my call. I'm 5 years out on my CML, and I am having trouble, as you explained earlier, getting definitive lab results. I'm

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wondering how can I send my lab to you so I can get a conclusive, definitive answer.

Brian J. Druker, MD

Again, I would look at the website for CML Alliance. It's www.cmlalliance.com, and there are a couple of labs that are doing the PCR monitoring, and very high-quality PCR monitoring, through the CML Alliance. There's lots of testing out there. It's not very well standardized, there are lots of variation and these are a couple laboratories that really are trying to do better. Over time, these tests will get standardized, but until then, I think this is a good alternative.



Carson Jacobi Pattillo, MPH

Thank you for the question. We'll take another from our telephone audience.

Question 5/Sharon

Good evening. I have been on imatinib for 6 years with success, and my insurance provider is threatening to not cover the cost of imatinib after my renewal period in January. I don't know if I'm going to win that battle or not, so in preparation I've tried to investigate alternatives. Assistance programs to cover the cost of imatinib are not viable in my case, and I wondered if you know anything

about the clinical trial at Johns Hopkins by Dr. Douglas Smith on the vaccines and if you think that would be a good alternative for me if I am without imatinib.

Neil P. Shah, MD, PhD

I don't have any bright ideas on how you may get access to imatinib if you're not getting any help from the patient assistance program. I want to make sure that you are aware of that program. With respect to a clinical trial, I would not have a lot of enthusiasm in your case. It's amazing what this class of drugs has been able to accomplish, and if you are responding well, I haven't been made aware of anything anywhere near as promising as this class of drugs. I think the vaccine strategy is provocative, but vaccine strategies have been around for a number of years. I think that if they really were effective in a large proportion of patients, we would have already known that by now.

Brian J. Druker, MD

I would just add that typically in a vaccine strategy, you would add the vaccine to imatinib or dasatinib or another agent as opposed to replacing [that agent]. It's sad to think that patients can't afford medications. We need a solution to that problem, and that's obviously off the topic of this discussion, but it's really just a sad commentary. Certainly, we would encourage you to look at the Novartis Patient Assistance Program and other pharmaceutical assistance programs that are available so you can stay on a drug or medication that's saving your life.

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Carson Jacobi Pattillo, MPH

I'd like to add that I am sorry that you're going through that struggle with your insurance company. As Dr. Druker said, some of the pharmaceutical companies do have assistance programs, and *The Leukemia & Lymphoma Society* does have a co-pay assistance program, and we are currently accepting patients who have CML and can help with treatment-related costs.

I would also like to mention that we have some international participants today, and an organization that we partner with is the MAX Foundation, and if you're in need of information about access to treatment in your respective countries, I'd encourage you to contact the MAX Foundation. Their Web address is www.maxfoundation.org.

We'll take our next question from the telephone audience please.

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Question #6

In the appropriate patient after trials of imatinib and second-generation medications, is transplant the only true cure? When would you consider that?

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Question 6/Vincent

Thanks for the excellent information you've provided so far. I am a newly diagnosed patient and also a fairly well-informed pharmacist just diagnosed 3 weeks ago. What I'm curious about is stem cell or bone marrow transplant, in the appropriate patient after the adequate trials of imatinib and second-generation medications. Is that the only true cure, and when would you end up considering that?

Neil P. Shah, MD, PhD

We have, of course, longer follow-up and longer experience with transplantation for this disease. We do know a few things about transplantation which gives us all a bit of pause. One is that there is treatment-related mortality associated with the procedure that even under the best of circumstances in a low-risk patient with a good match may be as high as 15%. So that's a 15% chance of dying, not due to the disease, but due to the treatment within 1 to 2 years. And what I had mentioned earlier and what Dr. Druker has published is that the results with imatinib look far superior to that after 5 years and now 7 years. It may be a long, long time before 15% of imatinib-treated patients will succumb to their disease or to toxicity, and so the potential long-term payoff of transplantation may not be evident for years and years down the road.

Having said that, another concern about transplantation is that there are late relapses that occur 15 years to 20 years down the road, and even though we used to think people who were 5 years to 10 years down the road without evidence of relapsed disease were cured, we're finding out that that's not necessarily the case. So I would reserve transplantation in chronic-

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phase patients for those who had resistance to both imatinib and at least 1 second-line kinase inhibitor, or those who had imatinib resistance and had convincing evidence of this highly drug resistant T315I mutation.

Carson Jacobi Pattillo, MPH

Thank you, Vincent, for the question. We'll take another question from the telephone audience.



Question 7/Trey

Thanks for your excellent work in the field. What is the latest information about causes of drug resistance, and are either of you concerned about using lower levels of imatinib, say, down to the 200-mg dosage, if someone's PCR is undetectable after 2 to 3 years?

Neil P. Shah, MD, PhD

Most of what we know about drug resistance I tried to put into my presentation. In terms of patients who don't achieve an initially desired response, to some extent that may reflect the potency of the agent that is being used. Assuming in this case, Trey, that you do have this deep remission, the concern I would have would be that we know that patients who lose their response frequently do so because of mutations that can cause resistance. The thing about these mutations is that there are a large number of different mutations that have been shown to be capable of causing resistance to the imatinib in patients, and they is a degree of relative resistance among them. So there are some mutations that are highly resistant to even the highest doses of drug a patient can take, but then there are others that are only moderately resistant. And my concern with lowering the dosage, if you're not having any side effects, is that you would be opening the door for maybe one of these resistance conferring mutations.

If you are having side effects, despite the fact that you're having this level of response, if that's not something that can be adequately controlled with acceptable, supportive measures, medications or some of the things Dr. Druker mentioned earlier, then I would be in favor of just giving a trial for a second-line agent. I think that imatinib will always be there for you to go back to. I don't think you will have any irreversible side effects or toxicity on the newer agent. So that's how I would approach it.

Brian J. Druker, MD

My general view here is you either treat or you don't treat, and if you're going to treat, you should stay on effective doses. If people are having problems and thinking that they might want to lower the dose, that's when I would use drug level monitoring as opposed to a fixed dose, and I know that if we go below a dose or a drug level of about 500 ng/mL that that would,

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in my mind, would be an unacceptably low drug level. It would open the doors, as Dr. Shah said, to resistance.

Generally people on 300 mg or 400 mg will be at that drug level so we don't need to monitor because we know that that's what they're going to achieve, but if they're having toxicity, or if we're thinking about lowering the dose, I would never go below 300 mg without checking a drug level and making sure that we're in that safe range. Otherwise, I'd just as soon take people off, as opposed to selecting for resistance, exposing them to lower than acceptable drug levels.

Carson Jacobi Pattillo, MPH

Thank you, Trey, for the question. We'll take our next question from our Portland audience.



Question 8

I also had a question about bone marrow transplant. Knowing that there's such a large mortality rate with bone marrow transplant, when would you recommend bone marrow transplant? For instance, in the case of a patient with hematologic intolerance. I mean do you wait for 18 months? If they don't achieve complete cytogenetic response, would you recommend a bone marrow transplant for a young patient? How do you decide?

Neil P. Shah, MD, PhD

I think any chronic-phase patient should go on imatinib first, but if they do have an issue with failure to achieve either any cytogenetic response after 6 months, or a major cytogenetic response after 12 months or a complete cytogenetic response after 18 months, then by definition they have failed imatinib.

You brought up a very interesting and important potential cause of resistance, and that may be a patient who just doesn't have bone marrow reserve. So a patient who continues to have low blood counts and just cannot tolerate the drug from this perspective, these patients are very unlikely to have any more success with a second-line agent, and if they're young, and if they have a good transplant option, I think it is reasonable under those circumstances.

The other case, as I mentioned, would be anybody who has this T315I mutation, and people don't typically have that in a detectable form prior to therapy so it's only if they're imatinib resistant or resistant to imatinib and another drug that they typically have this mutation.

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Another group of patients to consider are those patients who have more advanced-phase disease—accelerated-phase or blast-phase disease—when they’re diagnosed. We still recommend going on a kinase inhibitor first to try to achieve a remission. Once that remission is achieved, we recommend transplantation simply because the rate of relapse is so high.

There is one last thing to say about transplant that I had neglected to mention earlier that limits our enthusiasm about transplantation relates to the proportion of people who are cured but have complications of graft-versus-host disease, and so the quality of life in many of these patients is, unfortunately, not great, but nonetheless, the situations I described earlier is where one needs to think very seriously about transplantation.

Carson Jacobi Pattillo, MPH

Thank you for the question. We’ll take our next question from the telephone audience.

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Question #9

What level of imatinib in the blood is acceptable? When should we consider decreasing the dose?

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Question 9/Rita

This question is for Dr. Druker. Dr. Druker, I would like you to discuss a little bit about what your goal targeted level of imatinib should be in the blood, acceptable in the blood. My 18-year-old son has been on imatinib for 5 ½ years, PCR negative for 4 years. He was started at a children’s hospital in Pittsburgh at 800 mg a day, and he remains on that. I just got the results back about a few days ago on the blood level testing, and his imatinib level was 23,365 ng/mL, and the metabolite was 339 ng/mL.

Since he is so young, and he is on a higher dose, and he has mild to moderate side effects from the imatinib but nothing that’s not manageable, would we want to consider dropping the dose because of his age and because of a 23,365 ng/mL level in the blood?

Brian J. Druker, MD

Thank you, Rita. A couple of things, as I mentioned during my talk, this is somebody who falls exactly within my criteria for lowering dose. Great response, started on high-dose therapy, and anything, a drug level, anything over 1,000 ng/mL, I consider acceptable. The reality is, this is somebody who’s got a great response, low risk of relapse, and it’s actually gone down over time, I’d be thinking about lowering the dose. I’d probably first get on to 600 mg, monitor PCR for 6 months and if the PCR stays undetectable, then I might even begin to back it down to 500 mg for 6 months and then to 400 mg and leave them at 400 mg for, presumably the rest of their lives, until we figure out whether there’s something to add to imatinib to result in a cure or whether we get some long-term, follow-up data that it would be safe to discontinue the medication. But this is exactly the patient that I was referring to earlier that I would be very

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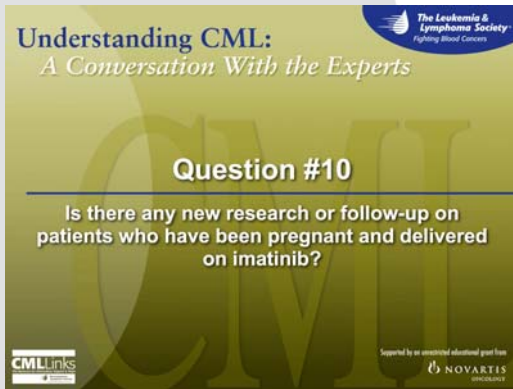


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comfortable beginning to lower the dose based not only on the great response but also the drug levels.

Carson Jacobi Pattillo, MPH

Before we get to the next question from our telephone audience, I wanted to talk about the issue of pregnancy while on imatinib. Is there any new research or any follow-up on patients who have been pregnant and delivered on imatinib? We frequently get that question.

Brian J. Druker, MD

There continues to be more and more experience, as you'd expect over time. There have been a couple of recent publications that question how safe it is for women to conceive while on imatinib therapy. It appears that it's likely safe, but again, it's very small numbers. It looks like some patients can stop their imatinib when they're PCR negative and stay PCR negative for 6 months or more. That means if a woman conceived on imatinib and stopped therapy, she might be able to make it through pregnancy.

Is that a recommended course of action? Is that something that we should consider standard? That is a very difficult and lengthy discussion between patient and physician. The patient's desire to maintain good health and have a family, those are competing options. There's not great data that says that it's safe. There's not great data that says that you can't do it.

Having said that, I've taken probably a dozen women through pregnancy. Generally, I would counsel women that I'd like them to have a deep remission before they considered it. Once they conceive, I'd have them stop therapy and stay off therapy during pregnancy. Erin Zammett, who is well-known to *The Leukemia & Lymphoma Society*, has written a book about doing this. There are examples of women who had done this successfully, but it requires very intense discussions. Dr. Shah, have you had much experience with this?

Neil P. Shah, MD, PhD

It doesn't appear to be clearly toxic. There have been a large proportion of healthy children born, but what people want to know is can we say with confidence that it is safe? We cannot say that at the present time, so we cannot safely recommend that patients continue it.

Brian J. Druker, MD

Do you have any experience with dasatinib?

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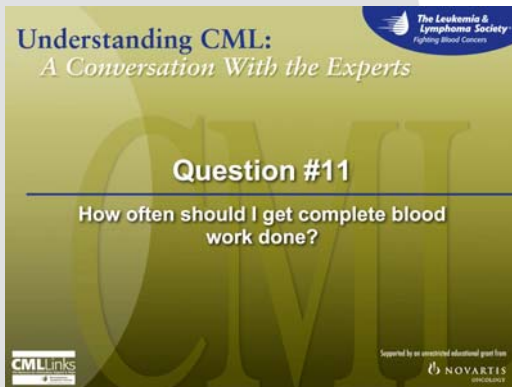
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Neil P. Shah, MD, PhD

With dasatinib, there was a poster at the most recent ASH meeting, which described that there were some healthy children born, but it was just a small number. I don't recall if there were birth defects in any children exposed in utero. I don't have personal experience with patients being pregnant while taking dasatinib.



Carson Jacobi Pattillo, MPH

Thank you. We'll take another question from the telephone audience.

Question 11/Susan

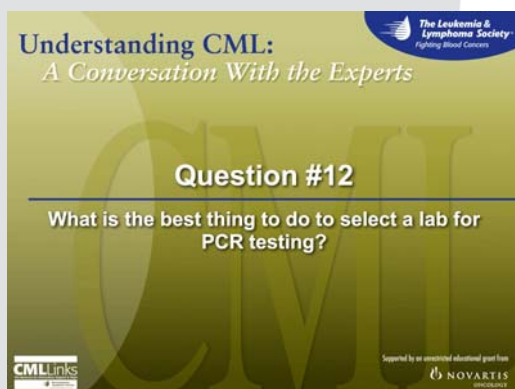
Hi, doctors. I started imatinib in July, so at this point would you recommend that I'm getting complete blood work done? I have 3 months until my next appointment, and I thought it was kind of long. I'm curious.

Neil P. Shah, MD, PhD

We know that if you're talking about a complete blood count, if things have been looking stable and your blood counts are all normal now after 3 months, I think it's okay to get that test every 3 months. If your blood counts are low right now, then you need to have continued monitoring more carefully. It's difficult to answer that without knowing how things have been.

Carson Jacobi Pattillo, MPH

Susan, thank you for the question. We'll take another question from the telephone audience.



Question 12/Brian

Dr. Druker, I was hoping that you would clarify 2 points that you made regarding PCRs. You had first made the point about the importance of sticking with the same lab to sort of establish and follow a trend, but then you've also made the point a couple times now that it's valuable to try to go to one of these standardized labs. I'm wondering where that leaves a person who has sort of 2 years' worth of PCRs at a non-standardized lab and a downward trend to 3 or 3.5 logs. We tried, a few months back, to go to a standardized lab and got a result that was so dissimilar to what we were used to. We didn't hardly know what to make of it. It seemed that not only had we lost the major molecular response but that we had lost even more than that. It was troubling to accept that number and say, "Well, now we're going to start following that and just kind of go along for 3, 6 or 9 months and set up a whole new trend" and try to feel confident during that time. I'm wondering what to do once you've had a trend going

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and whether when you're sort of at this point fully embroiled in it, and what is the best thing to do in terms of labs with the PCRs, whether to just stay where you are.

Brian J. Druker, MD

Thank you. The reality is, if you're satisfied with the lab that you're working with and the results that are coming out, stick with the same lab. You don't want to go from one lab to another lab to another lab. You're comparing apples and oranges and bananas. You have no clue what you're doing. You can switch labs any time and then continue to be followed, but you don't want to be going from lab to lab. If you're looking at an average survival of 30 years, if you've gone 2 years then switched to another lab for the next 28 years, you still get very good trending, but what you don't want to be doing is switching labs each time that the test is done because then you have no idea if the test goes up, was it because you switched labs, or was it because you have early signs of relapse.

Neil P. Shah, MD, PhD

One thing that I recommend to patients in this situation is that one time they have blood samples sent both places so they can have at least a snapshot of what a value at the new lab corresponds to with respect to the old lab.



Carson Jacobi Pattillo, MPH

Let's take another question please from the telephone audience.

Question 13/Shelly

I wanted to ask about the fact that people have a life expectancy of 30 years. I'm 27 years old, so I'm hoping for a longer expectancy with CML. Could you address that? And does imatinib impact fertility as far as making it harder for a woman to conceive?

Brian J. Druker, MD

I said 30 years average life expectancy. That's if we didn't do any more research and if we didn't have drugs like dasatinib or nilotinib around. The reality is that we've got a long time before that 30-year clock is up to have significant new advances in how to eradicate this disease. For somebody who's in their 20s, by the time you're in your 50s, the advancements that we'll make will be significant, and we'll be able to project even longer than that.

On the second issue, there is currently no evidence that any of these drugs affect fertility.

Carson Jacobi Pattillo, MPH

Shelly, thank you for the question. We'll take another question from the telephone audience.

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Question #14

Can imatinib cause heart failure?

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Question 14/Sandra

I saw a report that said imatinib can cause heart failure. Is that true?

Brian J. Druker, MD

Two years ago, there was a report that suggested that imatinib was associated with heart failure. The follow-up studies that have looked at that very, very carefully have failed to confirm any evidence of imatinib resulting in heart failure above and beyond what would be seen in the general population.

Carson Jacobi Pattillo, MPH

We'll take another question, please, from our Portland audience.

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Question #15

As more patients are taking imatinib for longer periods of time, are there any particular side effects that show up from longer-term use?

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Question 15

As more of us are taking imatinib for longer periods of time, are there any particular side effects that show up from longer-term use of imatinib?

Brian J. Druker, MD

We have not seen late side effects showing up, and I appreciate that because as I was thinking about the answer to the last question, I realized that I don't want to downplay the concerns about long-term toxicity. If these are drugs that people have to take for life, we need to make sure that we continue to monitor very, very closely not only with imatinib, but dasatinib, and nilotinib and any other drugs that we use for the potential for long-term side effects. But the good news is that thus far with longer studies, as long as 10 years now with imatinib, we aren't seeing late side effects.

Carson Jacobi Pattillo, MPH

Thank you for the question. We'll take our next question from the telephone audience.

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Question #16

My husband has water retention with imatinib. Besides taking water pills, what can a patient do to alleviate water retention?

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Question 16/Carol

I thank the doctors for doing all of the studies that they have up to this point. My husband has water retention with imatinib, and I didn't know, besides taking any water pills, is there anything that can alleviate this?

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Neil P. Shah, MD, PhD

When we did the first study with dasatinib, I remember we had a patient who was in his 70s who we put on the drug, and we became very concerned because after 30 days, he had lost 30 lbs, and we thought something very concerning was going on with this patient, but his wife said that that was his [normal] weight and his appearance before he started imatinib. There are some patients who accumulate a fair amount of fluid, and before we had the second-line agents, of course, we would try restricting salt intake and using diuretics. The newer agents are associated with a pretty low frequency of generalized fluid retention. Every drug has its own side effects, and I'm not trying to say the newer agents are any safer or better tolerated than imatinib, but if it's really problematic, you may consider one of the newer agents and hopefully the degree of water retention will be less.

Carson Jacobi Pattillo, MPH

Thank you for the question. Let's take another question from the telephone audience.



Question 17/Lou

I'm calling about our son, who is 20 years old. He has CML. He was diagnosed a little over a year ago. He also suffers from celiac disease, and he's away at college, and he seems to get sick quite often whether it's throat viruses, a cold or the flu. I want to know if that's just a side effect from having CML with a suppressed immune system?

Brian J Druker, MD

In general, we don't associate frequent infections either with CML or with therapy with the exception if the white blood count is quite low. But generally, with either imatinib, or even with dasatinib or nilotinib, we've generally not seen a higher frequency of infections than we would in the general population.

Carson Jacobi Pattillo, MPH

Let's take another question from our telephone audience.

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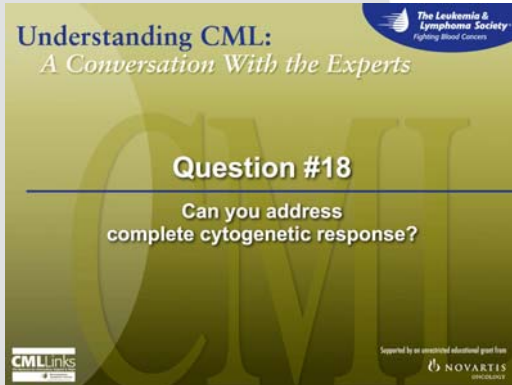


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Question 18/Sue

I'm calling for my mother. She has had CML for almost 2 years, and she's had only 1 bone marrow biopsy when she was an inpatient at the time she was diagnosed. From that time on they only gave her blood work. They told me that she has a complete hematologic response, but her white blood count needs to be in the normal range. Her platelet count is really low, around 70%, and her red blood count seems to be below normal range. I'm pretty concerned about her, but the doctor said that she seems to be doing fine.

Her blood cell counts seem to be within normal range right now. I mean up until a month ago, until she got an infection. They took her off imatinib because her platelet counts went down, they went down from 104 to 69,000, and so they held her imatinib while she was in the hospital as an inpatient. They only treated her infection and her pain, and then they released her after that, and then she got blood work 2 days later, and we find out that her white blood count went up like 3 times, from 4.5 to 12.8, so I'm concerned.

Carson Jacobi Pattillo, MPH

We'll have one of the doctors address the issue of complete cytogenetic response.

Neil P. Shah, MD, PhD

It sounds like her blood counts were relatively stable for a period of time, and then there was this acute infection, and some of her counts changed during that time. That's not unusual. That's nothing to be concerned about, but it is important to know what level of response she has on imatinib beyond just a complete hematologic response. So if a bone marrow biopsy is not going to be done, a good PCR test in some cases can give you similar information. It's very important that she have adequate disease monitoring.

Brian J. Druker, MD

There's another issue here. I frequently get consults on for patients who have quote, "low blood counts," and their treatment has been held, and I'll look at the blood counts, and I wouldn't make any changes based on the blood count. I don't care about the white blood count. I care about the neutrophil count, and if an absolute neutrophil count is less than 1.0 or 1,000, I would either use a white cell stimulating medication or hold therapy, or if the platelet count were less than 50,000, I would hold therapy. Anything more than that, these are people who have leukemia, if their white count or their platelet count is a little bit low, that's a good thing. They're responding to therapy. If it gets too low, then I want to intervene, but I don't want to intervene when it's just a little bit low because that could result in inadequate response to therapy.

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Carson Jacobi Pattillo, MPH

Thank you, Sue, for asking that question on behalf of your mother. We will take our next question from the telephone audience.



Question 19/Jacqueline

Can you tell me when exactly does a clinical trial start: after the FDA has approved a drug or before the FDA approves a drug?

Carson Jacobi Pattillo, MPH

This may be an understanding of the different phases of trials.

Brian J. Druker, MD

You have to run clinical trials to get FDA approval of drugs. Period. After a drug is FDA approved, many clinical trials will continue to determine the best use of a drug, whether it's as good as or better than currently available therapies, how it's optimally used and whether it should be used in combination with other FDA-approved drugs or investigational trials. Clinical trials continue after FDA approval, and as Dr. Shah mentioned, we shouldn't get complacent about stopping our clinical trials because we still want to do better, we still have room for improvement and the only way to improve is through the enrollment of patients on clinical trials, so we can learn as much as possible about how to use our drugs.

Carson Jacobi Pattillo, MPH

It's also important to remember that no one at a clinical trial is ever given a placebo. There's just standard therapy and other therapies being tested.

Brian J. Druker, MD

Yes, that is correct.

Neil P. Shah, MD, PhD

If they are given a placebo, it is because there is no effective therapy anyway, no known effective therapy.

Carson Jacobi Pattillo, MPH

That's a myth that we hear frequently. We'll take our next question from the live audience here in Portland.

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Question 20

Dr. Shah, Dr. Druker, first of all I would like to thank you so very much for your years of dedicated research and service to patients. Thank you also for being here tonight and for so graciously answering our questions. You've addressed female fertility and pregnancy, but what about young men on imatinib? How safe is it for them to become fathers?

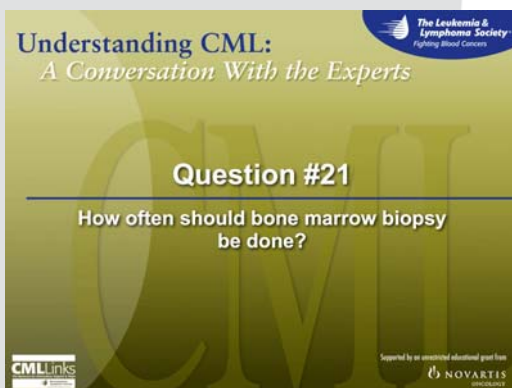
Neil P. Shah, MD, PhD

This has been analyzed in a very small number of cases, and it appears that all the reported children who were born to men who were taking imatinib have been normal, healthy children, but the numbers that have been reported, I believe, may be still in single digits or may be close to a dozen. It appears to be generally safe, but again, we don't know with any great degree of confidence.

Thank you for acknowledging our efforts. I just want to acknowledge the patients who participate in the clinical trials, the study coordinators, and the other people who work with us. I don't know if our wives are listening, but my wife certainly has sacrificed an inordinate amount for me to be able to do what I do.

Carson Jacobi Pattillo, MPH

Thank you for that question. We'll take our next question please from the telephone audience.



Question 21/Shirley

I have had CML for almost 2 years, and my question is, I've only had 1 bone marrow done, and that was just to diagnose me, and I never had another bone marrow since then. I was wondering if I should have another one done.

Brian J. Druker, MD

Generally, I like to judge response based on complete cytogenetic response. It's possible that with a high-quality standardized PCR test, you can get a pretty accurate idea of whether you have a complete cytogenetic response or not, but I haven't yet in my own practice made a complete switch over from cytogenetics to PCR even though I hope to some day to be able to do that. Currently my general algorithm is to do bone marrows every 6 months until I reach a complete cytogenetic response, and then the patients and I will kind of discuss whether we need to do more after that, but I haven't completely given up on doing marrows.

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Neil P. Shah, MD, PhD

Some patients are very reluctant to have a second bone marrow biopsy, if they had a bad experience with the first one. I understand that, especially if they had a bad experience with the first one. In several studies a 2-log reduction in PCR level—and assuming it's reputable PCR test that is performed—seems to be about equivalent to a complete cytogenetic response. It can give you the information. The test hasn't been validated the same way that bone marrow cytogenetics have, and I always have that discussion with patients. If they are fine accepting a little bit of risk of the unknown because we are using a test that hasn't been validated to the extent that the bone marrow assessments have, I'm not going to push them too hard to have a bone marrow aspiration. If they haven't had a 2-log reduction, then I think they really do need to have that bone marrow aspiration.

Carson Jacobi Pattillo, MPH

Shirley, thank you for the question. Let's take another question from the telephone audience.

Question 22/Linda

Thank you for taking my call. I have an 8-year-old son who was diagnosed with CML in September, and I'm being told that bone marrow transplant is the standard procedure for a cure. Is that really the standard procedure for someone this young, or should we continue on imatinib until further research is done?

Neil P. Shah, MD, PhD

Linda, let me just first say that I'm sorry to hear that you're dealing with an 8 year old with this diagnosis. It's very uncommon in that age range, as I'm sure you've been told. When we were initially addressing this question, we still did try to consider transplant as the favorable route for patients who were even younger adults. I think that's changed because we've had more than 5 years of follow-up with imatinib, and we don't feel like patients will lose anything by going on a trial of imatinib.

Having said that, there are a lot of unanswered questions about imatinib in young children who are still growing. I have a patient whose family is convinced that this patient's growth has been stunted because he is on imatinib. We don't know the answer to that. Of course, transplantation itself is associated with its own significant side effects, and although we think of it as curative, as I alluded to earlier, there are patients who are relapsing 15 to 20 years down the road. In somebody who is 8 years old, the likelihood of them being truly cured by transplant, I think that that needs to be very carefully weighed with the likelihood of doing well on imatinib versus perhaps not doing well due to the transplant-related toxicity.

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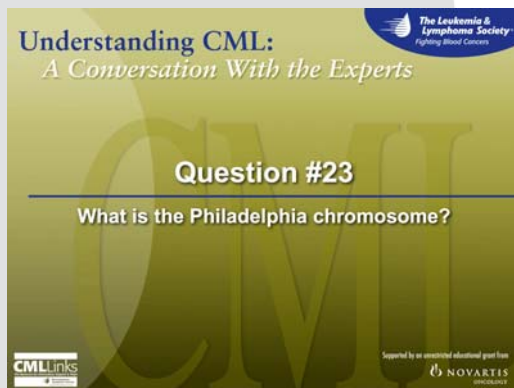
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Brian J. Druker, MD

Linda, I am also quite comfortable starting with imatinib as a test if your son is doing well at 6 months to 1 year. The risk of relapse is so low that I am perfectly comfortable continuing with imatinib therapy. If you have less than optimal response, I would move very quickly toward a bone marrow transplant as opposed to trying to go through a second or third trial of a kinase inhibitor for somebody who's younger. So that's currently been what I've done.

Carson Jacobi Pattillo, MPH

Thank you, Linda, for the question. Let's take another question from the telephone audience.



Question 23/Fran

I just want to thank you for this informative panel and would like to know, if someone is diagnosed with CML, and they do not have the Philadelphia chromosome, what does that mean?

Brian J. Druker, MD

As long as you've got what's called BCR-ABL, then it's absolutely the same as having the Philadelphia chromosome except you can't be monitored by cytogenetics. You have to be monitored either by FISH or by PCR technologies, but the results of imatinib or dasatinib or nilotinib therapy are absolutely identical. If you turn out to have a disease that looks like CML, but you don't have BCR-ABL, then in fact it's not CML. It's a different disease. It's a relative of CML. It's not likely to respond to imatinib or some of these other kinase-inhibitor therapies. It's a completely different disease entity. It needs a different therapy.

Neil P. Shah, MD, PhD

There are some very rare incidences of these cases. Either BCR or ABL can be involved with another partner. If it's a partner that's related to ABL, there is a possibility that you may respond to imatinib, but again, these cases are very unusual, but they clearly exist.

Carson Jacobi Pattillo, MPH

Fran, thank you for the question. Let's take the next question from the telephone audience.

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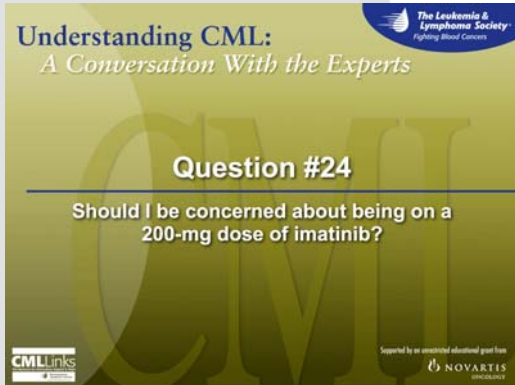


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Question 24/Kathleen

I wanted to tell you that I'm going through 200 mg of imatinib right now, and I was a little concerned after listening to [an earlier] response. When I first started on the imatinib I was on 400 mg, and my white blood cell count was going down below 1.0, and it continued to do that. Every time I was taken off the medicine, I would be off for 5 to 7 weeks, and so my complete blood count kept dropping, my platelets were low, and I was anemic. I've responded well to the 200 mg. I haven't had my BCR-ABL count back yet, but I've been on the 200 mg

since September, and after listening to this broadcast, I was concerned about being on 200 mg.

Brian J. Druker, MD

Kathleen, each patient is going to have to be considered individually. If your blood counts are low, I would actually tend to be a little bit more aggressive with therapy, trying to treat with other medications. I would check a blood level to see if perhaps the blood levels really are significantly higher than I would anticipate for standard dosing, and whether it would be appropriate to use 200 mg. I generally would not like to use that low of a dose without something telling me that it's appropriate being on that dose, because what I really want to do is maximize or optimize your treatment over time, and having you on too low of a dose might compromise therapy.

Again, I would want to have some level of comfort that 200 mg could be safe for you, and in some patients it is. There's a lot of variability in the drug levels from patient to patient. Some patients on 400 mg will look like they're being treated with 800 mg. Some people on 400 mg will look like they're only treated with 200 mg. Each person interacts individually with a medication, and you're somebody that I think needs a fair bit of expertise in managing your leukemia to get an optimal response.

Neil P. Shah, MD, PhD

I would hope that you would be tried on a higher dose again, assuming your counts are in a normal range, because there can be a period of time where the normal hematopoietic cells are recovering and building in numbers. What I have seen, that I want to caution you about, is physicians who are convinced that a patient can tolerate no more than 200 mg because they've had your type of experience, and then 2 years later their white count is 50,000, and the physician is convinced that it is not an option to increase the dose to more than 200 mg because the counts will come crashing down again. I agree with everything Dr. Druker mentioned.

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Closing Remarks

Carson Jacobi Pattillo, MPH

Kathleen, thank you for the question, and I thank you all for your questions. Thank you, Dr. Druker and Dr. Shah, for such insightful presentations. On behalf of *The Leukemia & Lymphoma Society* and everyone here in Portland and on the phone, we thank you for all the work you do every day in supporting patients and their families touched by leukemia. We appreciate that you donated your time to us this evening. I'd also like to thank

everyone here in the Portland audience and on the telephone for spending these 2 hours with us. If your questions were not answered, you can call *The Leukemia & Lymphoma Society's* Information Resource Center; we are extending our hours, as I mentioned previously, until 11:00 PM Eastern Standard Time/8:00 PM Pacific Standard Time. You can find that number in your materials in your packet, but I will mention it once more: 1-800-955-4572.

I encourage all of you to complete and return your evaluation form in your meeting packet. Your feedback helps to shape future programs, determine topics and make the programs as meaningful as possible for you. For those of you in the Portland audience, we will collect the evaluations as you leave. For those of you on the phone, please fill out your evaluation form and mail it in the provided envelope. If you are a nurse or social worker, you can obtain your 2 continuing education credit hours for this program by completing and returning your yellow evaluation form.



Once again, the phone number for the IRC, Information Resource Center, is (800) 955-4572.

On behalf of *The Leukemia & Lymphoma Society* and our guest experts this evening, thank you for joining us. Good-bye, and we wish you well.