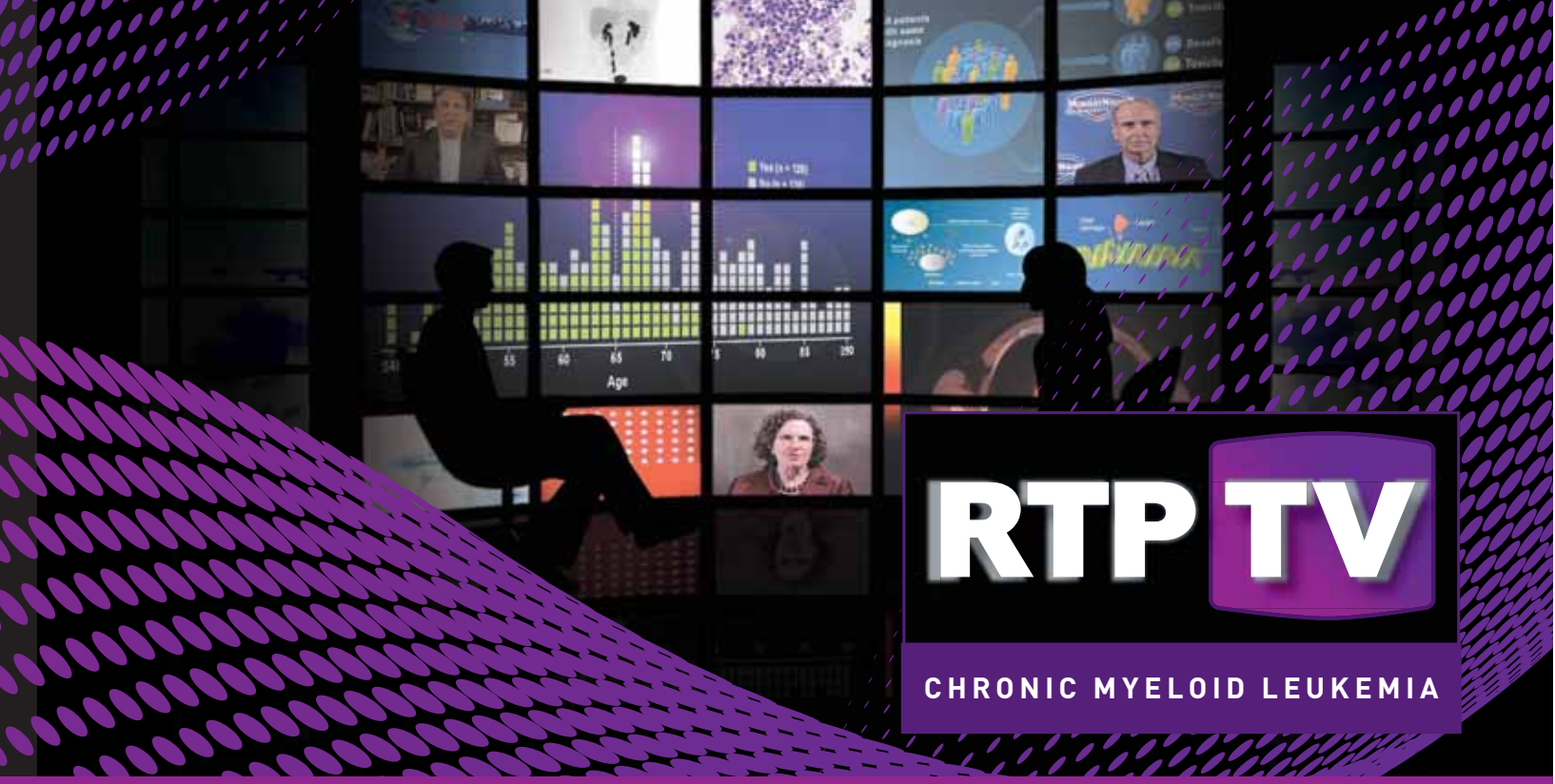

Tuesday, August 2, 2011

Transcript of Webcast

DR LOVE: Welcome to RTP TV. I'm Neil Love. And tonight in our eighth webcast in a row, and our final one, chronic myeloid leukemia, a fascinating topic that seems to be getting more and more interesting every day.

As we've done in our prior webcasts, we're going to really string this whole discussion tonight around faculty cases. We have six cases that we're going to use. If you have any questions you'd like to see the faculty address or any comments, just type it into the lower left part of your screen, and we'll see how many of these we can deal with.

Here's where we're heading. The first two topics are major issues in terms of choice of initial TKI up front, monitoring. And we're also going to talk about side effects and adherence and a couple of other topics.

But first, let me just turn to Susan O'Brien and ask you, I'm kind of curious about the questions that you get from physicians in practice about CML and how they line up with what we have identified as our top three, which are choice of TKI, monitoring, and adherence.

DR O'BRIEN: I think that those are clearly the three most important. We're lucky enough to have a number of very good choices. How do we make the choice between the TKIs? Monitoring has become more complicated over time compared to the old days. And what to do in terms of making sure that the patients are really taking their drug? I think these are *the* most important questions.

DR LOVE: So Neil Shah, in a second we're going to let you briefly present two patients who presented and kind of use that as a focal point to talk about initial therapy and choice of TKI. But again, just taking a step back, as you hear questions from oncologists in practice and see patients, what are some of the areas that you think maybe we should try to clarify tonight?

DR SHAH: Well, I think these are certainly the most common areas. Probably more than 95 percent of the questions surround one of these three areas. The only other thing I would add would be that we sometimes get asked about the appropriate timing for allogeneic small cell transplantation. But that's something that we're deferring more and more because we have a multitude of highly effective oral agents at the present time.

DR LOVE: So in a second, we'll have Neil present his case. And actually, we're going to have the audience respond to it and see what they might do in a patient like this.

I'll also mention that we surveyed 25 community-based oncologists this week, and we're going to bring in their comments and their questions and their perceptions about this disease as we go through tonight.

Neil, can you briefly tell us about this 18-year-old patient?

DR SHAH: Yes. This is a case, if you will, of lightning striking twice to a young man, 18 years old, who had been diagnosed with an atypical form of cystic fibrosis just a couple of years earlier. And so he was getting monitored regularly, blood counts and the like, and had an asymptomatic leukocytosis. And, as usual, was worked up for infections and so on and subsequently referred to my pediatric colleagues, and they diagnosed him as having a BCR-ABL-positive myeloproliferative disorder. And you can see that his presenting features were kind of typical of a patient who has no symptoms, essentially just incidental leukocytosis, mild thrombocytosis was observed as well, and his bone marrow biopsy was consistent with chronic phase CML. And the Philadelphia chromosome was detected in all metaphases and analysis, which is typical for this disease.

You've got a quick glimpse of his peripheral blood. And this is showing you the Philadelphia chromosome in the lower central part. You can see the chromosome translocation between chromosomes 9 and 22, which results in the fusion of the BCR and ABL genes in a pathologic sense.

DR LOVE: Anything else you want to say about him personally, Neil? I mean, 18 years old, just starting college. This is kind of a tough time, or any time is a tough time to contemplate this diagnosis, but any specific impressions you had of him?

DR SHAH: Certainly, he was concerned. I think even more so, his mother was extremely concerned because she had had already this one issue to deal with, with his cystic fibrosis. And now getting told that her son had a form of leukemia on top of that certainly made her, understandably, very anxious. But I think we had a very lengthy conversation that first day about what to expect, if he tolerates therapy well, if he responds well. And this is really giving us a glimpse into the future of where we feel comfortable treating a young individual like this with tyrosine kinase inhibitor therapy as first-line therapy as opposed to taking such a patient to allogeneic stem cell transplantation, like we would have done probably just 10 to 15 years ago.

DR LOVE: In a second, we're going to see how the audience would likely manage this 18-year-old man. While they're voting, Susan, how would you be thinking through this case?

DR O'BRIEN: I would generally start with a second-generation TKI, and most of the time it's a flip of the coin, to be honest with you. I think here, what I might be thinking about a little bit more, based on the patient's age being only 18, is the adherence to treatment. And given that the dasatinib is once a day and nilotinib is twice a day, as I think we're going to talk about, in this specific case where you're dealing with a teenager I might be looking more towards the once-a-day dosing.

DR LOVE: Neil, maybe you can talk a little bit about what actually happened with this patient.

DR SHAH: Actually, what Susan mentioned did factor into the decision process, but I look at — and we're going to go over the data, I'm sure, in a few minutes — but I look at the two second-generation drugs as being essentially equivalent in previously untreated patients. And so I present the efficacy data essentially that way, and we talk about some of the salient distinguishing features. And amongst them are the once daily, with or without food, for dasatinib versus twice daily on an empty stomach. And an 18-year-old college freshman, I didn't try to steer him myself, but when he heard about that, he thought he'd want to try the once-daily drug. And he did, in fact, start on dasatinib.

DR LOVE: And you can see the audience actually seems a little bit more swayed toward nilotinib, but still, 75 percent of the audience choosing a second-generation TKI. So before we go on to your contrasting case, Neil, current status of this patient?

DR SHAH: The patient has done remarkably well. He's actually had a major molecular response, achieved in a very short period of time after six months. And he is tolerating therapy extremely well and is doing well at school too, all of which are making his mother a lot less anxious and certainly a lot happier.

DR LOVE: Always good to keep the parents and the mom happy. And we are going to talk about monitoring of patients like this, but before we do, just to bring in a human/patient care point of view, your second case, Neil.

DR SHAH: This is somebody at the other end of the career schedule. This is a 59-year-old physician who had worked in the military and was retired. Which is a painful reminder to all of us in practice that, had we gone into the military, we'd probably all be retired at such a young age. But you can see that he

actually presented with more substantial disease burden, a white count approaching 200,000 with five percent blasts, a good number of basophils, some anemia and substantial thrombocytosis.

He again had a marrow consistent with chronic phase CML and the detection of the Philadelphia chromosome in all cells. And this is just a sign of his peripheral blood, actually that had a large number of immature granulocytes, but again nothing to suggest that he had blast phase disease. He had chronic phase disease with just a very high white count.

DR LOVE: So we're going to again ask the audience how they would be thinking this through and then go to Susan. But first, Neil, any comorbidities at all?

DR SHAH: This patient actually had a number of comorbidities. He had been hospitalized about a year earlier for some surgical issues, and he developed ARDS. He had reflux disease, for which he was on proton pump inhibitor therapy. So he had a few other things ongoing, actually.

DR LOVE: So when you assessed him, particularly in terms of cardio, respiratory and pulmonary after the ARDS, at that point, any specific issues or concerns?

DR SHAH: From that perspective, he was doing okay. But with that history, it did factor in a little bit to my choice of therapy, certainly.

DR LOVE: Susan, how would you be thinking through? You can see the audience mainly talking about one of the second-generation agents, a little bit more in terms of nilotinib. But how would you be thinking through this case?

DR O'BRIEN: Well, since he was in the military, I wouldn't be worrying about compliance in this case. But I don't know the full story of the ARDS. That might make me a little anxious in terms of "Did he have any residual lung damage" and if he was one of the minority of patients that were to develop a pleural effusion on dasatinib. So maybe in this case I might be leaning a little bit more towards the nilotinib, depending on what his underlying pulmonary status was.

DR LOVE: Neil, maybe you can follow up in terms of what happened with this man.

DR SHAH: Yes. The other issue that I alluded to is he was on a proton pump inhibitor, and that's known to actually diminish the absorption of dasatinib. So it's not dangerous from a toxicity perspective, but you do worry a little bit that the patient may get a subtherapeutic dose. And so for that, and the reason that Susan mentioned, the twice daily on an empty stomach, for this particular individual, clearly posed no problems whatsoever. He elected to go on nilotinib therapy and has actually also done very well. Has achieved a complete cytogenetic response after six months of therapy and is tolerating the therapy, having some issues with rash and headache, but otherwise is doing reasonably well.

DR LOVE: So we want to bring in, also as part of this discussion, before we get into some of the key data, what we learned from these 25 oncologists in practice. I should mention, these are all docs who'd worked with us on education programs, presenting cases, et cetera. I would say probably, maybe, a little bit better informed than the average oncologist — busier, successful docs, but certainly very high-end, if you want to use that word, oncologists. There are 25 of them. We surveyed them in the last week. We asked them how many cases do you have of CML in your practice. On average, it's about nine. So we have more than 200 cases. Almost all of these patients are on TKIs. And from their assessment — and we'll talk a little bit about this later — about 15 percent, from their point of view — they thought were having problems with adherence.

Here, you can see the breakdown of which TKIs they were receiving. And, of course, a lot of these patients — we don't know right now, because we didn't ask that — were probably treated, at least started on treatment in the presecond-generation age, but two thirds of them were on imatinib. When we asked these docs, "Right now, what do you consider to be your primary TKI up front?" you can see that 85 percent of them said either nilotinib, dasatinib or a coin flip. And we actually gave both of you the survey, and both of you answered "a coin flip" also. And we'll pursue that as we go through some of these data.

But let's talk first a little bit about monitoring of these patients. Susan, you have the interesting pleasure of being the head of the NCCN Committee. And Neil, you're on the committee, so you had a chance to really think through how to communicate these things.

I want to start out with Susan, and just basically give us a broad description of how you approach this. And while we're doing that, we're going to ask the audience this question: We want you to assume that you have a patient, like one of Neil's patients who's been started on a TKI, who's now out at three years in major molecular response. Tolerating treatment well, not having any adherence problems that

you could assess. And our question is — and also, in CCYR, in general, at this point in time: How often would you be ordering a quantitative PCR? And while they're voting, Susan, maybe you can just provide a capsule viewpoint of how you approach monitoring and maybe some of the misconceptions you see out there.

DR O'BRIEN I think the gold standard is still complete cytogenetic response. And that may change over time with longer follow-up. But right now, patients who achieve that response have an excellent long-term outcome.

I think the important thing about PCR monitoring is that you can't really just look at the specific value and always know what to do. The key is, is it going up or is it going down? I think a rule of thumb is, if it's going down, good. If it's stable, that's okay. If it's going up, by itself that doesn't make you declare the patient a failure. What it does is make you then look to see if they're losing their response on a cytogenetic basis. And so the key is that the PCR is something that guides you, potentially to change your therapy only when you've backed up that rise in the PCR with an actual cytogenetic analysis, and not necessarily changing, based on the PCR by itself. I think that's a very important point.

DR LOVE: Neil, maybe you can talk a little bit about the usual patient who gets a TKI, like your two patients, and the milestone or the first 18 months of what you normally see. And then comment on the issue of, again, you get out three years, like this poll question, and you can actually see the audience is kind of split about whether every three or six months. But any comments, Neil, about the first critical 18 months?

DR SHAH: I think what we've learned, pretty convincingly, from the imatinib era is that, at least on imatinib — if patients who may be in the minority, but there is a substantial proportion who will not do well on imatinib and will lose response — the majority of that action occurs within the first three years. And that puts the onus, I think, on us, the treating physicians, to really make sure that during the first three years they're being adequately monitored. And the NCCN guidelines are available online. Certainly, bone marrow assessments every six months are recommended until achievement of a complete cytogenetic response is obtained. And then, also, simultaneous with that is quarterly quantitative PCR. So that can be done on the peripheral blood. It's an easy thing to do. And I certainly do it quarterly.

I think if you get out to three years and beyond, and a patient has a very stable response and you think the patient is very adherent with therapy and reliable, I think you can make an argument that going to every six months is justifiable, simply because in that depth of response the overall majority's responses are very stable.

DR LOVE: Susan, I was interested in our poll of oncologists. We asked them, "What's your comfort level, in terms of ordering and interpreting CML assays?" And again, I can tell you that a lot of these were very prominent oncologists, and about half of them admitted to having some level of confusion. I'm curious, Susan, where do you think the confusion is?

DR O'BRIEN: I think that, to be fair to people in practice, they're getting a little bit of a mixed message from the academic community. There are some people who are very focused on major molecular response and other people who've said, as I've just said, as long as you have a complete cytogenetic response and the PCR is not rising, you're fine. And so there is, I think, a little bit of a mixed message about what is the endpoint that you want to get to. And then, there's also the issue of what defines a major molecular response, because most of the standard labs don't do the correction for the International Scale. And so that's another issue that makes it a little bit confusing for somebody who's not in an academic center, to be able to interpret the PCR.

So I think there are aspects of the monitoring that can make it confusing. And I think, again, one of the important things to remember is that if it's going up, you don't want to just necessarily act on one PCR. You need to see the trend over time, and then that should trigger you to look at the cytogenetics.

DR LOVE: And we're not going to go through, piece by piece, the exact recommendations out there. As we always do with our webcast, I'm going to send out an email in about a week announcing the rebroadcast of this. If you want to look at it again or recommend it to one of your colleagues, you can take a closer look at these. We also have the ELM criteria. But I want to get more of a conceptual portrait from the two of you about these assays. But first, Neil, do you agree with Susan's thought that you don't change therapy unless you go back and redo the cytogenetics, get another bone marrow?

DR SHAH: If there is a convincing rise. Some have said a fivefold increase is convincing in their particular assay. I think in general practice, 10-fold, but you want to confirm it. And, of course, you want to make sure

that the patient's been adherent, because nothing will make a PCR test go up like a patient who stops taking their medication.

If you also, simultaneously with that, detect a mutation that you know to confer a clinical resistance to that medication, I think irrespective of getting another bone marrow assessment, I think it could be justifiable to switch such a patient. But switching somebody just for a two- or three-fold increase or some mutation that may not represent a true drug-resistant mutation, I agree that that's not warranted.

One thing I would say, just to speak to something that Susan mentioned, is there has been a lot of, maybe if you want to call it mixed messages coming from the thought leaders in this field.

This is also an area that's undergoing evolution because these recommendations have been established with relatively short follow-up. You might say, well, if you have a 60-year-old and you're pretty happy with having a complete cytogenetic response or maybe even only a major cytogenetic response. But if you have somebody who's 18, like the first patient we discussed, and they have what you hope will be 50, 60 years of life ahead of them, I think that in such a case, the data that's evolving is suggestive that the deeper the response, in general, the better patients will do. And this will likely continue to evolve as we get longer follow-up with patients on TKIs. And all of these have been essentially established in the imatinib era. And what the second-generation drug milestones are going to be is still in the process of being established because the follow-up is really very short with those agents in the front-line setting.

DR LOVE: It's really amazing, when you talk to investigators like the two of you, there's just so much information. It almost becomes like a Talmudic discussion. I can really see the challenge. Oncologists are taking care of renal cell, lung cancer, and everything else, trying to keep up with everything.

We tried to pick out a few of the key points that maybe people could take away. And also, looking at some of the practice surveys that have been done — ours as well as one that Mike Mauro reported at the ASCO meeting just last month. But maybe, Susan, if you want to comment a little bit on this issue of disease burden and these key tests that we're talking about.

DR O'BRIEN: I think that this is a nice schematic to show the depth of response that you have and that you can measure with each of the different tests. And the point is that once you get a complete cytogenetic response, which happens in the vast majority of patients, that's not a way to monitor anymore. And that's why we've moved to the RT-PCR. The issue is that we don't have very well-defined endpoints, like we do for cytogenetics, to say if you don't have this molecular response at this point in time, we should change. And the reason we don't have that yet is because, again, with the follow-up that we have, mainly on imatinib, as Neil said, the molecular response doesn't appear to be quite as relevant as the complete cytogenetic response.

I do think the other point Neil made that's very important, and I agree with him, is that all bets may be off when we go to using the second-generation TKI first. Some of these guidelines are almost certainly going to change. If these are better drugs with quicker responses, then the endpoints that we're going to look at in terms of declaring somebody a failure or deciding to change therapy are probably going to be quite different.

DR LOVE: So the issue of assays is something we talk about all the time in so many different tumors: EML4-ALK in lung cancer, obviously, ER and HER2 in breast cancer, et cetera. And I try to keep my eye out for things that really are important and that catch attention. And one of the things that you both mentioned was this issue of the International Scale, and Mike Mauro's study found that about half of oncologists were not aware of it.

Susan, can you just briefly explain what this is and what it means?

DR O'BRIEN: Yes. It means that each laboratory's results are a little bit different. And as you know, a three-log reduction is what we're generally talking about for a major molecular response.

In one lab, a three-log reduction may come out to be 0.01, in another lab it may come out to be 0.02. And so what the labs generally do is report what's a major molecular response based on standardization. And that's what you'll get from most academic labs. And that gives you a way to interpret the number that you have rather than just saying, which we do, admittedly, when we talk about it for simplicity, that while a three-log reduction or less than 0.01 is generally a major molecular response, there can be quite a bit of variation from lab to lab.

I think an important thing to remember for people who are using commercial labs where they don't quite know what the standardization is, is at least the one thing that you can do is always use the

same lab over and over, because at least if you see changes where the PCR is going up or down and it's coming from the same lab, you can believe it's going up or down. If you get one value in one lab and one value in another, what might look like an increase in the PCR may not be an increase at all. So, at least it's important to stick with the same lab.

DR LOVE: So, Neil, what about the International Scale specifically? I'm looking at an assay that came from a community-based setting. And they're actually saying here, "Quantitative comparison with the International Scale." So at least I see that. Is that what you're looking for in the report, some mention of the International Scale?

DR SHAH: Yes. The International Scale was initially established by assessing 30 untreated chronic-phase patients and averaging their results. Obviously, that was a finite resource that is now long gone, but in the wake of that, there have been attempts by a number of people to standardize the tests that are available. And unfortunately, not everybody has yet come on board.

But this issue of major molecular response was actually defined based upon a three-log reduction from that initial baseline of 30 untreated patients. And so we now have the International Scale to supplant that, if you will, and so a three-log reduction is believed to be equivalent to that major molecular response in the IRIS study. And that has been associated in various analyses with more favorable outcomes.

And so, yes, there are PCR tests that are commercially available that do report on an International Scale. And I would certainly say to any physician that has the opportunity to access such a commercial test to do so, because I think it takes a lot of the guesswork out of it, which is what it's designed to do.

DR LOVE: So, Susan, you had pointed out to me this poster that Mike Mauro presented at ASCO, a survey of more than 500 US-based oncologists, I guess fairly recently, although they didn't have the date on there. You can see in our survey, which we did last week, it seems like a higher fraction of docs were talking about second-generation agents up front.

But the other thing they asked about was what do they consider to be the primary goal of treatment. And you can see that the commonest answer was MMR or CMR, Susan. What do you consider the primary goal of treatment?

DR O'BRIEN: I consider the primary goal a complete cytogenetic response. Would I like to see a complete molecular response? Yes, of course I would. But as long as I have a complete cytogenetic response and I don't have a rising PCR, I am pretty happy with that response, because we know that they can be maintained for many, many years.

One of the issues in terms of looking at major molecular response and some of the data that you see suggesting that people who get one do better than people that don't, is that when they're looking at major molecular response, yes versus no, the "no" is often including people who don't have a complete cytogenetic response. It's everybody else, and that's the problem with that type of analysis.

Usually when you look at the analysis and then take the people who don't have a major molecular and look at the people who have a complete cytogenetic response versus those that don't, that's where you see the big difference in the outcome. So you can't just look at it simplistically as major molecular response, yes-no, because the "no" includes groups that we would clearly call failure based on not achieving a complete cytogenetic response.

DR LOVE: On this series, of course, we set it up to be right after ASCO, hoping there might be some data that we could talk about. I'm going to ask you both about some data that was presented at ASCO. Here is the initial IRIS study and the follow-up that really revolutionized the field. I think most people are familiar with the two papers last year in the *New England Journal* looking at nilotinib and dasatinib, but then, Neil, at ASCO there were two follow-up reports looking at these studies with a 24-month follow-up.

And I'll just show some of the data and ask you, Neil, to comment on it. First was the issue of MMR in the DASISION trial, looking at nilotinib. Any comments on that?

DR SHAH: Yes. So, this was from the ENESTnd study looking at the cumulative incidence of major molecular response in patients randomized to receive either nilotinib or imatinib. And what I think is encouraging is not only is there a notable difference at 12 months, but that gap between nilotinib and imatinib is maintained at 24 months. And so, again, we can debate whether complete cytogenetic response or major molecular response is a better endpoint, but it's certainly suggesting that deeper responses

are occurring faster in these patients and in a higher proportion of patients on, in this case, nilotinib, relative to imatinib.

DR LOVE: So, Susan, again, in this ENESTnd study — sorry I didn't get that one right — any comments about the data they just presented at ASCO looking at accelerated-phase blast crisis?

DR O'BRIEN: We know that the trial has shown, in the short-term follow-up, a reduced transformation rate. And that's a very important clinical endpoint, because if patients transform to accelerated or blast phase, we know that this is associated with a bad outcome. So this is very clinically relevant.

I think that these differences may become minimized over time. And I say that because we know that with imatinib, the highest rate of progression to accelerated blast crisis is generally in the first two or three years, and then it drops off very dramatically.

But nevertheless, this is a very clinically relevant endpoint, although we're talking about a small minority of the patients compared to the total population.

DR LOVE: And, Neil, here are the comparable data, again presented at ASCO, looking at the DASISION trial that you've been so involved with. Maybe you can comment on this.

DR SHAH: Yes, very similar to what you observed earlier with the molecular response data from the previous study, again, differences, notable differences in favor of the second-generation drug, in this case dasatinib, at 12 months, that are persisting at 24 months. So, again, deeper remissions are occurring in a higher proportion of patients, and they're occurring faster with the second-generation drug.

And this is showing you that this issue of transformation, there's also a hint here that the transformation is less in patients who are treated with dasatinib relative to imatinib. So one important thing to just put out there is there can be a tendency to compare these two studies, because they both compared patients to imatinib, but of course they're not randomized with respect to each other.

And the other thing is this issue of transformation. While it's gotten justifiable attention, it's not a trivial thing to decide when to censor patients for development of transformation. And there were differences in these studies in terms of how they defined transformation, how long they followed patients before censoring them. And so the numbers of patients are generally kind of small, and small differences one way or another can cause patients to be counted or not counted as transformation. So I agree with Susan that I certainly hope to see a more accurate picture of this with 36 to 48 months of follow-up, because we know that the majority of action happens with imatinib during that time period, and we'll be able to compare the second-generation drugs a little bit more appropriately, I think, at that time.

DR LOVE: So, again, Susan, looking at randomized trials, we also have the Intergroup study that was updated at ASCO, also looking at dasatinib. Anything that you want to say in terms of that, Susan?

DR O'BRIEN: Only to say that the data look almost identical to the DASISION trial. And so that's very comforting that another randomized trial by a large group found almost identical outcome in terms of comparing dasatinib to imatinib.

DR LOVE: Before we go on to our next topic and a couple of Susan's cases to get into this issue of side effects and adherence, I want to give you a few questions that we're getting from the audience. These are really great questions. Neil, let's start out with you. Here's the question: "I've been treating a patient with CML for 10 years with imatinib. She remains stable with continued cytogenetic response. She asked about switching to nilotinib or dasatinib. Any reason to do this?"

DR SHAH: Assuming this is a complete cytogenetic response, I would say if this is a patient who is tolerating imatinib just fine without any concerning side effects, I would say there's probably not a compelling reason to switch such a patient.

If this is a younger patient who wants to achieve a deeper molecular response, with the assumption that that will translate to a better long-term outcome, I could see switching such a patient to a second-generation drug for that reason.

The good news is, of course, you're not burning any bridges. You always have the ability to go back to imatinib, and you know the side-effect profile that the patient already has on imatinib.

DR LOVE: Susan, this person didn't mention what the qPCR was. What are your thoughts about Neil's response?

DR O'BRIEN: I understand what he's saying. My answer would simply be, "You don't mess with success."

DR LOVE: Yes, that's the thought that was going through my mind, but I can see the other rationale.

Neil, here's another one: How do you explain a qPCR of 0.5 percent and a bone marrow cytogenetics of two over 20 metaphases positive for T922?

DR SHAH: There can be discrepancies between PCR, FISH, metaphase analysis. I think that metaphase is what we probably have the most experience interpreting. One thing that can happen with PCR tests — again, if this is a send-out test to a commercial laboratory — the subject or the thing that's being reported on, is being measured in the PCR test, is something that can degrade over time. And if it wasn't appropriately stored or processed in a timely fashion, you can get an artifactually low — I'm assuming this is a low PCR level — a lower PCR level than would be expected for two out of 20 Philadelphia chromosome-positive metaphases. But I would be concerned.

If this is a patient who's been on for a year or 18 months and has been compliant, has been adherent, I'd be concerned that this patient is not meeting the complete cytogenetic response milestone.

DR LOVE: Before I go to Susan for her thoughts on this, can you just elaborate a little bit more, Neil, about this issue you mentioned of storage of the specimen?

DR SHAH: The PCR test is designed to quantify the amount of BCR-ABL transcript within cells. For reasons that are completely unclear to me, there is one commercial vendor out there that does this test on plasma. And because they can offer the test for less, I think many people who are in charge of making decisions about which test to order will order this particular plasma-based test. But it's very difficult for me, scientifically, to think of what is being meaningfully measured in the plasma. So I would encourage people to stick with cell-based assays.

Nonetheless, RNA is, by its nature, very labile. There are enzymes that degrade RNA in cells. And so as these cells maybe start to die within the test tube, before the RNA is extracted, the level of RNA can drop simply for that reason. And you can have somebody with what appears to be a very low transcript level as a result.

DR LOVE: I want to move into the issue of side effects and adherence. And, Susan, you have two cases that I think get this out on the table. Before you start going through them, Susan, agree-disagree: There's no other situation in oncology — there is no other situation in contemporary medicine — where adherence is more critical than CML. Agree or disagree, Susan?

DR O'BRIEN: Agree.

DR LOVE: Maybe you're a little bit biased, but I'd like somebody in the audience to suggest a situation that's more critical than this one. But we'll get into why in a second.

Susan, why don't you talk a little bit about your 58-year-old woman?

DR O'BRIEN: This is a patient of mine who has actually had CML for 20 years and was originally treated with Hydrea, homoharringtonine, which is now omacetaxine in clinical trials, and interferon, and finally she got on a commercial supply in September 2001 with imatinib 400. And she tolerated it reasonably well and had a good response but then lost her cytogenetic response later. And because of that, at that time nilotinib in 2005, which wasn't yet commercially available, we did have available on a trial, and so she was entered on this trial where she received 600 BID. And because there was a lot of cardiac monitoring and all sorts of monitoring that we probably wouldn't even do in real life, she, at one point in time, had a slightly elevated troponin. Now, this is a woman who has very severe diabetes, also, and diabetic retinopathy.

I would have left her on the nilotinib, to be honest with you, but because of all of the attention with QTc prolongations and the possibility of cardiac side effects, the patient had to come off study, which she did, and then went on dasatinib and had several problems with pleural effusions, such that we had to come down on the dose, but actually, right now, she is being maintained on 20 milligrams, so a markedly reduced dose of dasatinib. And she continues with a complete molecular remission even at that reduced dose of only 20 milligrams a day. So, a woman who's gone through many treatments and, after 20 years, happily has a very good response.

DR LOVE: Neil, before we start dissecting out some of the side effects and toxicity data, just taking a step back, in terms of the decision about initial TKI, suppose somebody were to say to you, "Well, how about imatinib? Why wouldn't I want to use it in this situation?," what argument would you use to persuade them towards your point of view of, as you said, a coin flip between the other two?

DR SHAH: Well, it must be stated that imatinib was a game-changer. And with eight years of follow-up, more than half of the patients are in a very deep cytogenetic response at last assessment on the IRIS study. So, for many patients, it's certainly adequate.

Where we stand here in 2011 is that we don't have the follow-up with the newer drugs that we have with imatinib, but if we take the position that cytogenetic response is a surrogate endpoint for improved outcomes, both these studies showed superior complete cytogenetic responses at 12 months relative to imatinib. And you've seen the molecular response data as well.

And so I think that it's going to take a long time before we show the impressive progression-free survival differences between these two agents, simply because patients are going to be doing reasonably well on imatinib as it is.

I would say that many patients tolerate the second-generation drugs better than imatinib. While we think of imatinib as a very well-tolerated drug, let's remember that we compared it to interferon, which was a rather toxic agent. And now these newer agents are being compared with imatinib. And in many patients' eyes, they're actually better tolerated. And I think there's very little reason to suspect that the patients are going to do more poorly on the second-generation drugs, and so my feeling is there's enough data at the present time to justify, in my practice, preferentially starting a patient on a second-generation drug. But I certainly would not criticize any physician who wanted to continue to start a patient on imatinib in the present time with the newly diagnosed chronic phase CML.

DR LOVE: Susan, here are the updated data from the ENESTnd study, and then we're going to show the DASISION study. These are the kinds of things that oncologists look at in terms of trying to figure out toxicity profiles, but there's also talking to people like you and just saying, "What do you actually see in terms of quality of life, in terms of the frequency of specific problems with all three of these drugs, Susan?"

DR O'BRIEN I mean, obviously, we know that Grade III to IV toxicities are minimal with all of them. On the other hand, if you're a patient who's going to be on a drug for years, a Grade II toxicity is going to get old. And my own experience is that with both of the second-generation TKIs, I think both of them are generally better tolerated than imatinib. There's less fluid retention, less cramps, less GI toxicity, and I think it's a nice thing that the drugs that we think are probably more effective — and so far, do look to be more effective — actually also have less side effects.

DR LOVE: What kind of rash is seen, Neil, with nilotinib? Is it the TKI kind of rash that oncologists are already familiar with?

DR SHAH: Yes, in general, it is. I mean, it can involve more extensive areas of the body. It's generally not a huge symptomatic problem for patients, but if it does involve certainly more than 50 percent of the body, then it's, of course, recommended to switch therapy. But in most cases, it doesn't get that far.

And that's one of the toxicities that's more common with nilotinib relative to imatinib. But in general, as Dr O'Brien said, it does appear to be as well if not better tolerated in most patients' eyes than imatinib.

DR LOVE: Susan, what about dasatinib, and particularly the pleural effusions, that your patient had? Can you give more of a clinical feel for a typical presentation and management?

DR O'BRIEN: Yes. Usually they can be easily managed without a thoracentesis or doing anything that dramatic. What we tell the patients is if they get a cough or they feel a little bit short of breath, to let us know. So usually we'll detect them early. They'll say, "Oh, I have this dry cough. It's just not going away." You do a chest x-ray. They have an effusion. Generally, we'll hold. I sometimes do a Medrol Dosepak, wait until the effusion resolves, and then start at a lower dose.

And it's interesting that with imatinib you really have a very narrow dose range, unless you're going to get to a level that's not going to be very effective. With the second-generation TKI, my sense is, going forward with the dose reductions we're doing, we're still seeing very good responses with significant dose reductions, much more so than you would see if you had to dose-reduce imatinib like that.

So, again, the patient I just presented is only on 20 milligrams of dasatinib a day. Now this is a patient, of course, who didn't start with hematologic disease. She started with just cytogenetic disease. So she's starting with a much lower tumor burden when she goes on it, also. And that may be relevant, too. But nevertheless, she's doing quite well at a relatively low dose.

DR LOVE: Neil, any thoughts in terms of what the mechanism is of why you see pleural effusions or edema with dasatinib?

DR SHAH: Yes. That's an area of investigation. People have actually looked at whether these patients are less likely to respond well or more likely to respond well. It turns out they actually may have a higher response rate than patients who don't develop pleural effusions. The pleural effusions tend to be

lymphocytic exudates. Another thing that's associated with better responses on dasatinib is the development of lymphocytosis, peripheral blood lymphocytosis. And whether there's a link between those two, whether dasatinib has some other mechanism of action in addition to inhibiting BCR-ABL is an area of active study. But we really don't understand too much about the mechanism. It does occur. It's almost uniquely a dasatinib-related toxicity. But as you can see from these numbers here, that it's 10 percent, all grades, and it's essentially Grade I and Grade II. So another way of looking at it is that the majority of patients are not having this toxicity, in which case their side-effect profile tends to look substantially better than imatinib. But it's something to certainly be aware of and to have a high index of suspicion of in any patient that develops new dry cough or shortness of breath, as Dr O'Brien mentioned.

DR LOVE: Susan, actually I think we'll skip your second case so we can get to the other topics. But I did want to share with you what these 25 oncologists said in terms of these more than 200 patients in their practices with TKIs. This obviously is not a study of any type, but more of a survey, but supporting the fact that even with imatinib, most patients generally tolerate it well.

Overall, globally, Susan, how do you look at these three drugs in terms of the fraction of patients who cruise through as opposed to those that you have to manage in terms of toxicity?

DR O'BRIEN: I think that the numbers that you see here are actually fairly representative. I think anywhere from 60 to 70 percent of patients really, as you said, cruise through. And then there's patients who have some toxicity. The one difference I might take with this slide is that I would say that some toxicity — and, of course, it depends how you define that — is probably a bit more common with imatinib, as I mentioned earlier, particularly in terms of cramps or edema. And then in terms of really significant toxicity, I think it's pretty minor with all of these drugs.

DR LOVE: I thought it was interesting that for both of you, in your practices, there are 75 to 100 patients with CML. You estimated a much higher number for problems with imatinib, more along the lines of around 30 percent. But I want to ask the audience. We know that the average oncologist has around 10 patients with CML. But I want you to assume, audience, that you have 10 patients — let's say that's the number in your practice right now — who are on a TKI for CML, whatever the TKI is. What would you guess would be the number out of that 10 patients who would have enough of a problem with adherence that it might theoretically threaten their outcome? And while they're estimating that, Neil, you're in a tertiary center. I'm not sure how typical this problem is, but what's your assessment in terms of how often adherence is enough of a problem that you're concerned?

DR SHAH: It certainly does come up. I mean, we're sometimes referred patients because they've lost a response. And at the heart of it may be adherence. And it obviously can be a difficult thing to try to tease apart. And then of course, we do see some of our own patients that are diagnosed at our own medical center, and for one reason or another you cannot seem to convince them of the importance of taking their medication. So this is, I think, another thing to keep in mind here, that as patients hear more and more about how well they're doing with time on therapy, the threat of their disease really becomes relatively diminished in their minds relative to the threat of side effects or the cost or just the sense that they don't want to be on a medication. So it really does require probably a little bit more hand-holding on the part of physicians to say, "You need to continue to take this very seriously. Yes, we have these great drugs and, yes, you can feel like so far you've dodged a bullet, but we can't assume that you can stop therapy without any untoward complication."

DR LOVE: It's interesting, Susan. You can see the audience here tonight kind of reflects the same predictions of the docs in practice, as well as you two, that maybe 10 or 20 percent of patients have issues with adherence. And one of the people in our group looked at that and said, "Wow! That's pretty good, 80 or 90 percent adherence," but again, CML's a little bit different, huh, Susan?

DR O'BRIEN: Yes. I mean, I'm not surprised by these results, but I think that one question is, "What does the doctor consider adherence?" Does the doctor think that if they miss their pills 10 or 20 percent of the time, that's adherence? Of course, we don't know the answer to that from this. So I think that's an important question. Adherence is somewhat relative.

But let's say they assume that it's 95 percent. Then I think early on it's not that surprising, because these drugs aren't that toxic and, again, early on, patients can generally tolerate Grade I to II toxicity. But if they're going to have to tolerate it year after year, it gets different. So I agree with Neil for two reasons. Sometimes as time goes on is when you have to be more concerned about it, because either the patient, as Neil said, is doing very well and they start to not feel the significance of their disease, or they have mild but chronic toxicities where they're just kind of sick of them. And now you can

probably switch to another TKI, but in the past, before we had the second generation, we really had to encourage some of these people to stay on the drug, even though they weren't having Grade III to IV toxicity, because they just got tired of it after a while.

DR LOVE: Neil, we want to just touch quickly on a couple of practical points about assessing adherence. Frankly, we're trying to plant a seed in the minds of our viewers. I mean, oncologists have to deal with lots of patients on important oral medication: capecitabine, as you were mentioning, tons of different kinds of TKIs. And we want to see if we can push out a little bit the fact that obviously a patient with CML is a little bit different.

Neil, we have what we call the Lisa Carey idea. In one of our breast cancer programs, North Carolina's Lisa Carey said, "Well, I don't say to my patient, 'Are you taking your medicine?' I say, 'How many doses of medicine have you missed in the last couple of weeks?'"

What are some of your clinical pearls, Neil, that maybe you tell your fellows about how to assess adherence with CML?

DR SHAH: This is obviously an important issue, as we've been discussing. And at least in my own practice, what I like to try to do is what I call normalize the process of nonadherence, meaning first of all put the patient at ease that I'm not judging them and say something along the lines of, "Most people have trouble remembering to take every last dose of medication in an average month. How many pills do you end up missing for one reason or another?"

That's my way of approaching it. But this is another satisfactory one, to ask, "How many times in the last couple of weeks?" It should be clarified that this issue of adherence, we know clearly it has a substantial impact on outcomes in patients treated with imatinib, as we may discuss in just a moment.

We don't yet have those studies for the second-generation drugs, but I think we have to assume that if a drug isn't taken, of course, the patient's not going to do as well.

DR LOVE: I want to just briefly show you in the spirit of edutainment — we like to get people's attention — one of the questions we asked the 25 docs was, "Were there any interesting or unusual or amusing answers you've gotten when you ask people, not just with CML, but in their practice, 'Are you taking your medication?'" And I'll ask the audience if there are any ones that you want to add to this list.

But, Susan, here are some of the ones I thought were kind of interesting: "The dog ate my medicine," "My child threw the pills out the window on the turnpike," "It interferes with my golf game" — I'm assuming that was an LHRH agonist — "I don't take a pill that's that color," and, "It inhibits my creativity." So we just throw those out to you to get your attention a little bit.

But, Susan, what about the issue of how much adherence problems have to exist in terms of being concerned. Here are a couple of papers that attempted to correlate adherence — in this case, with imatinib — with outcome. And there are obviously tons of studies like that in the literature, but the graphic, Susan, that caught my attention the most was this paper from the *JCO* when they broke patients down into greater or less than 90 percent. And you can see what the MMR was. Any thoughts, Susan, about how many pills a month do you need to miss to be concerned?

DR O'BRIEN: I think that's a very good point. And these are people who have to take pills every single day — and with nilotinib, twice a day — and sometimes more than one pill, depending on what the TKI is. So you're right. You don't really have to miss too many pills to be less than 90 percent. And so I think that this was a very striking article, which really is something that is pointing out that it doesn't take a lot to have a significant impact on the outcome.

DR LOVE: We want to finish up and talk about a couple of other important topics in the field, but first I've got to throw out another question I just got from the audience. I think it's interesting. And actually, we know from talking to oncologists that this is actually a very common question, Neil, which is, "Can we ever stop treatment in patients who've been stable for years?"

DR SHAH: That's an excellent question, and I say that just because I want to be on that first little bit where you have everybody say, "That's an excellent question."

DR LOVE: I like that one. That was good. We might have to keep that one.

DR SHAH: So that is an excellent question. And so this is actually being studied right now. First of all, it's a minority of patients that get to a level of disease response where even PCR fails to detect their disease repeatedly over a period of several years. And again, after about five years of imatinib therapy, we're talking about no more than maybe five to 10 percent of patients. Maybe it'll be higher with the

second-generation drugs that get to that level of deep remission. That doesn't mean that they can stop medication, but the French have done some studies where they've actually enrolled patients in a clinical trial and followed their PCR level after they've volunteered to stop their medication on study.

And what they've found is about 60 percent of patients have a loss of that deep molecular response, so they test PCR-positive once again, usually within six to nine months, which on the one hand is rather disheartening, but if you're an optimist, you look at the other 40 percent who've now been out three years or so and continue to be PCR-undetectable. And so there may be a population, a subpopulation of a subpopulation, that can stop medication. But at the present time, we don't know whether this is safe to do in the long term, whether it's going to encourage the eventual outgrowth of resistant disease. So, at the present time, the recommendation is continuing therapy unless you want to go on a protocol to really try to address this.

DR LOVE: There are a couple of other topics we want to address, again getting at them through your cases. The first is the issue of disease progression, mutations and new agents. And to get into that, Neil, maybe you can present your case.

DR SHAH: This is a woman who came to see us a couple of years ago, who had been diagnosed at the age of 43 with typical chronic phase CML. She was a little bit unusual in that she had some significant constitutional symptoms, some night sweats. She interestingly did not have a bone marrow assessment. She was seen at an academic center, but not in my own. And she was started on imatinib and rapidly achieved a hematologic response but developed recurrence of her constitutional symptoms as well as leukocytosis just nine months down the road despite being adherent with medication. And at that time, she was switched to a second-generation drug. It was dasatinib. And she had a BCR-ABL kinase domain mutation test to try to figure out the reason that she lost response to imatinib. And after two weeks, she had really no subjective improvement or improvement in her leukocytosis on dasatinib. And the mutation test came back positive for a mutation in the BCR-ABL T315I mutation, which is known to be cross-resistant to all three approved kinase inhibitors.

She was offered a nine-out-of-10 allogeneic stem cell transplant at that institution. She investigated that we were doing a clinical study with an investigational third-generation kinase inhibitor called ponatinib, and she came on that study and actually achieved a very rapid complete cytogenetic response and a deep molecular response, as well, and is now two and a half years on that study and really thankful that she's on it at the moment.

DR LOVE: Susan, I like the colors in this slide. And I think there's an important point in there. But maybe you can comment a little bit about the issue of mutation testing. One of the things that Mike Mauro picked up in his survey was, I think it was about 30 percent of oncologists were testing patients at diagnosis. When do you do this test, and what does it mean, and what does this graphic mean?

DR O'BRIEN: Basically, you only do the test when the patient is failing therapy. There's no point in doing it at diagnosis. And there's no point in doing it in a patient who has a very good response, because you're not going to find a mutation. So, don't bother to look then. Look at a time point when the patient is having an inadequate response or is losing their response.

I think the graphic here just shows us that unfortunately right now, all the commercially available TKIs do not have very much activity against the T315I. And so Neil's patient was lucky enough to get on a trial with a new TKI, ponatinib, that you heard about. That's only available on clinical trial, although as I guess we're going to see from the data that was recently presented at ASH, this data looks quite encouraging, and I think that this drug will become commercially available. But right now, having a T315I is a difficult problem, since all the commercially available drugs are just not very good at treating it.

DR LOVE: We want to get on to Susan's case in a second, but accelerated-phase CML to close out. But, Neil, any thoughts about not just ponatinib but some of the other TKIs that are coming along?

DR SHAH: Yes. This T315I mutation was actually the first mutation that was documented 10 years ago in a patient that lost response to imatinib at UCLA. And all these years later, we still don't have an approved therapy for this one mutation. We pretty much have effective treatment options for all the other mutations, so it's nice to finally have something investigational for this, but as will be the case, some patients may have trouble tolerating one particular agent, and so there is another agent that's a kinase inhibitor called DCC-2036, which is in a clinical trial that's also designed to deal with this particular mutation. There hasn't been efficacy data really presented with that yet, and then there's omacetaxine, which is not a kinase inhibitor, protein synthesis inhibitor, which has some activity, is also

investigational. So, hopefully between these three in the coming years, physicians will actually have a number of choices for patients who are unfortunate enough to develop this one particular mutation.

DR LOVE: Let's finish out, Susan, with your case, the 40-year-old man, and we'll briefly touch on the issue of accelerated-phase CML.

DR O'BRIEN: He actually presented in 2002 with high-risk disease. You see a very high white count, platelets over a million, slight increase in blasts, but was still in chronic phase, and initially had a nice response to imatinib, 600 milligrams daily, on a clinical trial. Had some side effects but managed to achieve a complete cytogenetic response. However, about two years later, he lost that response, and, in fact, because he lost the response, we looked for a mutation and found an E355A mutation.

Initially, we tried to increase the imatinib dose, because at that time we didn't have second-generation TKIs to give him, but then a trial opened with nilotinib, 400 milligrams BID. This is back in 2005. Interestingly, when he went on that, he also had clonal evolution, which is why I called him accelerated phase, with an isochromosome 17.

When he went on nilotinib, all of the common side effects that we do see with imatinib disappeared. He had absolutely no side effects with nilotinib. He very rapidly achieved a response, and, in fact, in 2006 he achieved a complete molecular response, so no evidence of disease by PCR, that he's now maintained for over five years.

DR LOVE: Neil, any comments on the case?

DR SHAH: I think this speaks to the power of how you can use tests to guide therapy. In this particular case, this mutation that was detected is not one of the more common ones that's been associated with imatinib resistance, but it's also one that we don't know of to be associated with loss of response to the second-generation drugs. So I think either second-generation drug could have been an excellent choice for this particular patient. And with the large number of mutations that are out there, it can become rather daunting to really know how to optimally treat patients. But I think what I try to advise physicians is, just try to become aware of the ones that you know are clinically problematic for each of the second-generation drugs, and there's only five or six that have been shown to cause loss of clinical response to nilotinib or dasatinib. And if a patient has one of those, then you can guide your treatment appropriately.

DR LOVE: I've got to finish out on my favorite topic, adherence, and ask you, Susan, I'm just curious. And it was interesting that this patient sounds like he cruised through nilotinib without any side effects, just based on what you're saying. How often do you see this, Susan, with the three TKIs? Off the top of your head, what fraction of patients with each of the three cruise right through therapy?

DR O'BRIEN: I think it's higher, as I've mentioned, for both nilotinib and dasatinib. I think it's the majority. I'm going to say 90 percent, maybe 85 percent, because you do have the 10 percent effusions with dasatinib that, again, are usually easy to deal with.

I think cruising on imatinib is much less likely. Almost everybody has some degree of cramps. Again, having a sporadic cramp is not that big a deal. Some people have them quite frequently. Almost everybody has some amount of edema, particularly periorbital edema, which, if you're interested in your looks, can be pretty bothersome. So these are minor things compared to the old days with interferon, but they do bother people. I think these annoying things that prevent people from cruising through are much more common with imatinib and much less common with the second-generation TKIs.

DR LOVE: On that note, I'd like to thank Neil and Susan, and thank you for participating in this conference. Again, I'll send out an email in about a week, announcing the rebroadcast of this program. And hopefully we'll be back in the not-too-far future with another series of webcasts. Have a great night.