News from ASH: Updates on CML
ASH Conference Coverage
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Introduction

Andrew Schorr:
Hello, this is Andrew Schorr from Patient Power. We are in San Francisco at the big Muscone Center at the 50th annual meeting of the American Society of Hematology. I like to come every year. I haven’t come for 50 years, but I’ve come for the last few. One of the most exciting areas has been over the last few years, the therapies and knowledge that’s developed in chronic myelogenous or myeloid leukemia, and at Oregon Health and Science University they’ve really helped lead the way, Brian Druker and a whole team. Another member of that team is sitting across from me, Dr. Michael Deininger, and Dr. Deininger, am I saying that right by the way?

Dr. Deininger:
Perfect.

Andrew Schorr:
Okay, well thank you so much for being with us and taking a break because there’s always a lot going on about CML, and that’s what we want to bring our audience, many families around the world touched by this.

You have three approved medications now and maybe others in development, so the first thing I want to ask you about is coming out of this event is there the suggestion of any changes in first-line therapy for people diagnosed with CML?

Dr. Deininger:
That’s a good question. We still have to see that data that are going to be presented on Sunday and Monday. Really the question is whether we are ready to make a change based on what are phase-I trials. There is clear indication that what we call second-line agents such as Tasigna/nilotinib or Sprycel/dasatinib have a very high efficacy, very high rates of complete chromosomal responses that happen very early on. So I think there is clearly a tremendous degree of activity; however, in order to change the standard of care I think we really need comparative trials, prospective trials where we test these new agents versus what is the standard therapy as of now; Gleevec, which we know works very well for most patients and is a very safe agent as well.
So I think what we all see is that people will start pushing more for these trials, but I don’t think we are ready to make a change to the standard of care.

Now the other very interesting question that we’ll learn about is whether more aggressive Gleevec treatment from the get-go is going to be beneficial or not. As most of you will know, there has been a great push to use what we call high-dose imatinib that is 800-mg per day rather than 400-mg per day for newly diagnosed patients, and there is quite a bit of evidence, I think, of the circumstantial evidence that the response rates are better and that even maybe the progression-free survival is better.

There are two trials that are going to look at this specific question. There’s one called the TOPS trial, which is an international trial sponsored by Novartis that looked at 400 versus 800 mg, and the other trial is an Italian trial, Italian/Scandinavian trial, that looked at the same question specifically in chronic-phase patients with a high initial risk.

Now as far as the TOPS trial is concerned, I think we are a little disappointed because what we see is that responses in terms of cytogenetic responses and molecular responses happen earlier with the 800 mg dose, but at one year really they have caught up with each other, so you get the response faster, but what we don’t know yet is whether you really are less likely to have disease progression during that time.

Andrew Schorr:
Yes, is it a sprinter or a marathon runner?

Dr. Deininger:
Exactly. It’s like the turtle and the hare, the rabbit, so it’s going to be interesting to look at longer follow-up in these patients, and maybe there will be some data presented on that.

Andrew Schorr:
All right, let me go over this with you. So Gleevec still, it’s not an old drug but an older drug, still has great utility.

Dr. Deininger:
I think absolutely. So it’s a great drug. We know it is safe. We know that for perhaps seventy percent, seventy-to-eighty percent of patients diagnosed in chronic phase it’s an effective agent, and they will be on therapy after six or seven years.

There is of course a subset of patients that fails, and for those patients we need more, better agents up front, and of course it’s an effective salvage therapy.
Alternative Treatment Options to Gleevec

Andrew Schorr:
Dr. Deininger, related to the other two therapies that are approved for use in CML, one from Novartis and one from Bristol Meyer Squibb, how do you differentiate between them and decide when Gleevec stops working for a patient which one to use?

Dr. Deininger:
This is the “Holy Grail.” So all I can say it is only partially evidence based, based on incomplete evidence. I think if you have the choice, things to look at are what is the side effect profile of the two drugs, and is there anything in a given patient that would tell me that he or she may be at a higher risk for a certain side effect.

For example, Tasigna/nilotinib is known to cause pancreatitis in some patients, so in somebody with a history of pancreatitis this is clearly not the first choice. Conversely dasatinib or Sprycel is known to cause pleural effusions, so if somebody has already a history of recurrent pleural effusions because of cardiac disease, I would probably be very cautious with prescribing that. So that is one avenue.

The second avenue is that what we’ve learned over the last couple of years is that some patients have kinase diminutions that make their disease resistant to Gleevec, and it turns out that the specific type of mutation, or what we like to call the genotype, tells us to some extent what is likely to work and what is not likely to work.

The most pivotal example of that is a mutation called T359, which is not responsive to any of these drugs. So if a patient has that mutation he’s not going to benefit from either Sprycel or Tasigna, but there are a couple of other mutations that respond better to one or the other agent, and so if somebody gets diagnosed with a mutation I think the physician should take a careful look at the literature and if in doubt call up one of the centers and get some advice as to which agent to use.

Andrew Schorr:
Yes, of course my view as a patient is I think the patient would do well to often drive that and either have a consultation or treatment at a center like OHSU where you deal with this all the time, but that’s their call certainly.

Dr. Deininger:
Right, I mean I do have to say we are happy to see patients any time, and there aren’t any huge waiting times, but even if that is not feasible, we are always ready to advise through the telephone.

Andrew Schorr:
Right. Thank you for that. I have one follow-up question. So you said there’s a percentage of patients who won’t respond to any of the three approved drugs. What do you do then? What can you offer them then?
Dr. Deininger:
Correct, and these are really patients with the T359 mutation, and then the choice becomes more difficult. First of all, really backing off a little bit, anybody who fails on Gleevec should be reconsidered for an allogeneic transplant. I think it should be part of the evaluation process if a patient is a candidate in principle, and if so one should get all the machinery going, do the HLA typing, do everything so that if the second-line therapy doesn’t work we don’t lose time, and I think that happens many times in the community, and then a patient has blast crisis and has very few options and no donor identified. This is not good practice.

In terms of treating T359, there are some agents that have activity. One has a considerable activity and is available within clinical trials. Sometimes it’s even appropriate to try something like Hydrea because we’ve seen the mutation disappear in patients matched with this very conventional agent.

Thirdly, there are clinical trials testing new agents, kinase inhibitors, that do have activity against this particular mutation. There is one made by a company called Exelixis, another one is made by an Italian company called Nerviano, yet another one is made by ARIAD Pharmaceuticals. So if patients do experience or develop this mutation, I think it’s prudent to contact one of the centers to see whether such a trial may be available, and we do have a trial open at OHSU that actively enrolls as we speak.

Andrew Schorr:
I was in a phase-II clinical trial for my leukemia, CLL, and I was able to get therapy that now is used world-wide, and I’m in PCR-negative remission, so I’m a big proponent of clinical trials, and I urge people to check that out.

We were talking about first line choices mostly there. What about, what are you hearing here or involved in the discussion of related to changing second-line therapies? Where are we with that?

Dr. Deininger:
I think at the moment we are still in a learning process. There will be updates on the second-line inhibitor studies in chronic-phase, accelerated-phase, or blast crisis, and we’ll see where that is going. I think what is becoming clear is that responses are generally durable in those patients who are treated in chronic phase and to attain a rather profound and fast response. If you take a long time to respond, if you go there from blast crisis, responses tend not to be durable. For those patients I have to say an allogeneic transplant remains the only, for most of them, will remain the only curative option.
Developments in Biomarkers

Andrew Schorr:
Dr. Deininger, so obviously the whole discussion we've had as the new drugs have come into use is about developing resistance. Where are we now with information on shutting down resistance so you don't get to that point?

Dr. Deininger:
I think progress is being made, and I think progress happens on two levels. First of all I think we are getting better in terms of identifying patients who are at high risk of having a progression event in the first place. There is biomarker development, and one I think important biomarker that is emerging is called OCT1. This is a drug shuttle that pumps imatinib from the outside into the cells, and it turns out that those patients who have very little of that pump have little likelihood of responding, so it makes perfect sense. If you don't have the shuttle you don't get the drug in the cells.

Andrew Schorr:
I just want to understand what you mean by shuttle. Do you mean another drug that transports Gleevec into the cells?

Dr. Deininger:
It's not a drug. It's an enzyme that sits on the cell membrane. It's a pump basically.

Andrew Schorr:
It's a carrier.

Dr. Deininger:
It's a carrier, correct.

Andrew Schorr:
A little freight train.

Dr. Deininger:
A little freight train, and so it turns out that those patients who don't have a lot of that, in those if you really prop up the dose to 800 mg you can make a difference, and so using that biomarker we might be able to distinguish between those patients who are likely to benefit from a higher dose from those for whom it really doesn't make a difference because they pump it very effectively anyway. So that is I think a very interesting development.

Other things that are happening on that front are gene expression arrays that we developed in Oregon to see whether we can develop prognostic markers from the get-go to identify those patients who are least likely to attain a complete chromosomal response, and you know that once you are in a complete chromosomal response you're very likely to
do well. So we really want to figure out what is going on in those patients who don’t even go there, and there are some promising data emerging.

In the future this could mean that perhaps you come to Oregon, we do a ChIP analysis, and we tell you you’re very likely to be a cytogenetic responder and you go with 400 mg of imatinib, or you really have a disease that if you look down the microscope it doesn’t look any different from what we see in all the other patients, but something is wrong with these cells that we see on the molecular level, and you need stronger treatment up front or maybe even at some point need an allograft. So I think using that we can stratify up front so that is I think one avenue to improve results.

The second avenue is of course to improve our strategies for those patients who have progressed and have progressed into accelerated phase or blast crisis, and there are a number of agents that are emerging that are targeting cells that are not entirely dependent on BCR-ABL anymore because this is the big problem, I think. What we are very good at and getting even better by the day is developing drugs that shut down BCR-ABL irrespective of mutations, and one drug made by ARIAD Pharmaceuticals is in clinical trials at our institution, and as I said it’s extremely effective.

The problem is if a disease is at an advanced age, as I like to call that, it starts to become BCR-ABL independent, and then targeting BCR-ABL doesn’t get it anymore. So we need to understand what the mechanisms are and then develop new treatments to target the cells once they have grown into BCR-ABL independents, and there are a number of I think abstracts at this meeting that look at new agents for that.

Progress in Finding a Cure

Andrew Schorr:
Okay. So let’s carry this one step further. Where do you think we are, looking in your crystal ball, with the hope of eradicating the disease?

Dr. Deininger:
I think let’s start with defining cure. What is cure? Is cure the death of the last leukemia cell or is cure something that we can define operationally as not needing any more treatment, and I would be inclined to use the second definition because the first definition we might never be able to validate because we can’t tell beyond a certain level of sensitivity.

Now if we use the second definition I think there are a couple of really interesting things happening. First there are two studies, one from France and one from Australia, that look at what happens if you stop imatinib in patients with a complete molecular response, so no detectable disease. It turns out that about fifty percent or so of these patients actually remain in remission, so the disease does not come back, and the relapses that do happen tend to happen rather early. It’s not black and white, but the bulk of the relapses happen early.
That could mean that, well, there is some, I don’t know what it is, an immunological control, something is good in these patients that controls the disease, and talking about immunological control, a really interesting observation is that those patients who had exposure to interferon at some point during their disease history have the highest likelihood of remaining in remission, which I think is very interesting because many times this is very longstanding disease. It’s not that this is the newly diagnosed patients with low disease burden. It seems that the exposure to interferon plays a major role, and I think that in turn points to the immune system taking control of the leukemia cells, and of course that opens up a whole arena of potential applications using interferon.

Andrew Schorr:
I just want to make sure I understand this. This sounds very exciting. So the idea is if you could knock the disease back to such a low level, after all the immune system let the patient down in the first place because the disease developed, right, so now if you could knock it back to a certain point whether they had received interferon or whatever you learn about assisting it, you’re suggesting in that patient the immune system may take over and do a better job than it did the first time around?

Dr. Deininger:
Correct, but bear in mind it’s both fascinating and complicated, and the complication is that if you treat patients with Gleevec the very antigens that are recognized by the immune system are actually down-regulated so the cells become little stealth fighters, right? So they basically are not recognizable by the immune system because the cell surface changes in a way that the immune system becomes blind to it.

So I think what would be a logical thing is to use some kind of a priming strategy. So you start with some interferon. You sensitize the T-cells. There are a lot of CML cells around; all these bodies are there; and so the T-cells learn how to recognize them. Then you treat with Gleevec and get rid of the bulk of the disease because the T-cells would always be overwhelmed by this huge proliferation, and then you come back with interferon and stimulate the T-cells that are already primed to recognize the leukemia cells, and you control them.

This is all hypothetical, but I think it’s...

Andrew Schorr:
It’s like a mopping up operation.

Dr. Deininger:
It’s a mopping up operation, right.
Andrew Schorr:
It’s so cool. I always think of Star Wars, you know, like a de-cloaking device to say here were these stealth cells. Nope, there they are. They’re all around you, and have a drug that can knock most of them out and then your own little ray guns to shoot the rest of them.

Dr. Deininger:
Correct, right.

Andrew Schorr:
Yes, it’s so cool. So here we are at this meeting. When you come year after year, and obviously you’re going to other meetings in the interim, and you’re doing a lot of work at OHSU, for people living with this condition, I don’t know if the word is “excited” but are you hopeful that we can do even better in CML?

Dr. Deininger:
I’m sure we can still do better. We do very well, but there are still areas where we can improve. One in is to prevent relapse in the first place and target our therapy, more aggressive therapy to the right population, develop better biomarkers of predicting response.

The other thing, as we discussed, we’d like to come to an operational cure so that patients could really stop all treatment. Maybe the pharmaceutical companies will not like that, but this is really where the field would like to go.

Andrew Schorr:
I just want to ask you about that. That’s kind of a scary proposition for the patient though emotionally unless you can really predict it, because if they’ve had a drug like Gleevec or one of the others and they’re doing well, and then you say well, we have a good bet that you can stop taking this and your immune system will take over, it’s like flying blind, you know, flying naked.

Dr. Deininger:
Well, you shouldn’t fly blind. I think you need a physician who does PCR testing on a regular basis, and if you do that you pick up a relapse early on, and it turns out that those patients who do have, you know I shouldn’t call it a relapse, it’s a recurrence. It’s like you know you have diabetes and you stop insulin and then the sugar levels rise.

Andrew Schorr:
It flares, yes.

Dr. Deininger:
If you do PCR monitoring I think you can pick it up very early on, and if you restart the drug you attain responses again. So for those patients who don’t have an operational cure, there may not be that much danger associated with a trial, but I think at this point
all that should be done within clinic studies, I really want to stress that, don’t go out and now say okay I’m going to stop it on my own. It needs to be closely supervised to avoid any danger.

**Andrew Schorr:**
And you’ve suggested dosages different for different patients, and that’s not something they should do. They have their bottle of Gleevec or whatever, they shouldn’t be changing the dosage on their own either.

**Dr. Deininger:**
No, they should certainly not do that. I think what we’re learning is that a lack of compliance for whatever reason or sometimes what I call economic drug resistance, which unfortunately is not uncommon in the faltering health service of this country are major causes of what appears to be resistance and in fact it’s just the inability to afford or the inability to stick to a regular schedule. So you’ve got to take your pills every day. It is really important, and wait until your doctor tells you whether you should increase the dose, reduce it, or perhaps stop it all together within a clinical study.

**Listener Questions**

**Andrew Schorr:**
Right, we need to understand what’s right for you. We did have an e-mail question that came in, in anticipation of this interview, and I just want to pose that to you. This is from Miles in New York City. Miles writes in, ‘My thirteen-year-old with CML is having problems keeping weight down with Gleevec medicine that needs to be taken. How are patients deal with the side effect?’ Is that a familiar side effect to you related to weight?

**Dr. Deininger:**
I think it is actually quite common to see a significant weight gain that is related to the drug. It’s not the disease being taken care of, so it’s not people who lost weight and then regained it, it’s a real weight gain. That can be difficult to manage, and what I recommend are the obvious things; exercise, try to control your eating as much as you can. If this is excessive and becomes morbid, then even a change to a second-line agent might be an option to consider, although I do have to say that these agents are not currently approved for use in children, so it is an individualized decision, but if it is really significant it is something to consider.

**Andrew Schorr:**
Okay, I think we’ve covered a lot of ground, and I know you have a lot to do at this conference. We’re going to let you go. We will be having other updates on CML from ASH with some of your peers, but I want to first of all just congratulate you on the work you’ve done now with the whole group at OHSU and really leading the way for the whole world in CML and congratulate you and thank you for your dedication to patients.
Dr. Deininger:
A pleasure Andrew, thank you.

Andrew Schorr:
Thank you. Well, Andrew Schorr reporting live and now on tape depending upon how you’re listening to it, from the American Society of Hematology meeting in San Francisco. We’ve been visiting with Dr. Michael Deininger who’s an Associate Professor at the Center for Hematologic Malignancies at Oregon Health and Science University in Portland, Oregon. Just one other pitch is he made whether it’s OHSU or another key CML center, I believe as you hear what’s changing, it’s very important to at least have a consultation or have your doctor if you’re at a community oncology clinic check in on whether there is new knowledge from a conference like this that would apply to you.

Andrew Schorr reminding you knowledge can be the best medicine of all.

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