Ask the Expert about the Latest Myeloma News
Webcast
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Introduction

Andrew Schorr:
Hello, and thanks for being with us once again on the eighth in our series of live webcasts connecting you with leading multiple myeloma experts, and I'm just delighted to be part of this. I'm a leukemia survivor, so I can relate in some ways, and I've met many myeloma patients and family members along the way, and I know knowledge is power.

Happily, there's a lot happening, and I had the privilege of being at the American Society of Hematology meeting down in Atlanta that met in December, and this is where experts across the blood-related cancers gather from around the world every year, 30,000 people or so, and there was a lot of myeloma news as we've discussed on earlier programs and some very important studies; combinations therapies and studies of drugs related to people who might have transplant or people who were simply having drug therapies.

Well, what does it mean to you if you're living with multiple myeloma or a family member is, and you are trying to live with it chronically and hopefully have a long, full life, and some people have side effects from certain medicines or they wear off after a while, well where do you go next, or how do you limit the side effects? All that has been and continues to be studied, and as always I'll give my commercial for clinical trials. I was in a clinical trial for my leukemia. You have a lot of people to thank, and maybe some of you are in the audience, for the folks who participated in the clinical trials that led to the data that was presented in Atlanta in December that allows us to make decisions and talk about it. So consider for yourself as you go on your myeloma journey being in a clinical trial.

I want to introduce our expert. We will be taking phone calls with your questions as well as e-mail questions. Many people have sent e-mails. We will try to get to as many questions as we can in this hour, but this is not the place for Dr. Lonial, our guest, to practice medicine over the Internet. It wouldn't be fair to you; it wouldn't be fair to him; it wouldn't be fair to our listeners. So what we'll try to do in all cases is take the sense of what you're asking and give you some guidance but also globalize it to our many listeners live, and then also the replays of all of our programs, and as I said this is our eighth one, are all on www.patientpower.info and often on the medical center's websites representing our experts, their institutions, and now we're very excited on a new Microsoft website called

www.healthvault.com, and then you can type in myeloma or multiple myeloma and you'll see little pictures of our web pages on the left and then the transcript, the audio, the article, etc.

Okay, I've talked enough. Let's get down to the nitty-gritty here. I want to welcome back to Patient Power Dr. Sagar Lonial who joins us from Atlanta. He is an associate professor at the Winship Cancer Institute of Emory University, and also he is Director of Translational Research in the B-cell Malignancy Program there.

Dr. Lonial thanks for joining us once again.

Dr. Lonial:
Thank you, Andrew. Glad to be here.

Andrew Schorr:
Okay. Have you got your seatbelt fastened for a lot of questions?

Dr. Lonial:
I'm ready.

What's Encouraging about the Latest Data?

Andrew Schorr:
Okay. Now let me just get your initial comment. So I have mention that this was sort of a pivotal time in myeloma with the amount of research and in some cases the quality of research that you and other practitioners have to go on. Where do you think we are? Are we at sort of a watershed time now in myeloma where really you have more information, more data, and more tools and that that's very encouraging?

Dr. Lonial:
Yes, I think you've summarized it really well. I think that it was pretty remarkable to see at this most recent American Society of Hematology meeting in December that there was an entire session dedicated to large, randomized, phase-III trials for newly diagnosed myeloma patients. I mean, that's unheard of to have that many trials to warrant its own session of presentations that were such high quality that they all deserved to be presented on the podium as opposed to in a poster format, and I think that in many ways that is a testament to the number of drugs that we have available. We have tools now that, you're right, we did not have even as recently as four and five years ago. It's also a testament to the collaborative nature of investigations in myeloma. I think that in the last four or five years now with drugs like Velcade, Revlimid, thalidomide and now Doxil all approved on the basis of large, 600-patient, randomized trials it really is a great testament to collaboration among investigators as well as patients to be enrolled and answer these important questions.

Andrew Schorr:
Now, of course, what happens in oncology then is as you have more tools then, it's a question of which drug or drug combinations, or if we have transplant as an approach too, which do you use when, and of course what frequency and what dosage, and if one approach doesn't work for a patient, what do you switch to? That will be a number of the questions we have. So, it sounds like it gets increasingly complex. Should a concern be for people listening worldwide, as it become more complex and maybe I'm treated by a community oncologist who has lots of other cancers to deal with, and hopefully things are happening there, how does anybody keep up? How can I make sure that the best thinking about myeloma and my myeloma situation is brought to bear? Any guidance there?

Dr. Lonial:
Yes, I think absolutely that that's a very challenging issue nowadays because with more data unfortunately we don't have more answers. What we have is more questions and more things that we want to find out about and answer and ask in terms of treatment options. I think that myeloma has become sufficiently confusing enough now that for every patient at some point in the course of their initial diagnostic workup that it would be reasonable for them to be seen at a large, tertiary myeloma center because I think what that offers you is a perspective from somebody who does in fact specialize in the care of that specific disease. It's not something that means that you're committed now to therapy forever from that tertiary center, which may be two hour, four hours, or six hours away from where you live. I think that the community oncologists are really quite good at delivering care, but I think because the questions have become confusing enough in terms of what's the best induction; what's the best workup for a newly diagnosed patient, is the FISH analysis being done in a good laboratory? That's enough up in the air that I think you want to be at a center where you have access to people who do this on a daily basis and let them help guide the therapy down the road that you can receive from your local oncologist.

The Role of Transplant

Andrew Schorr:
Yes, I think that's great advice. That's what I did in my leukemia, and it gave me a lot more confidence, and I think my community oncologist really appreciated it and appreciated the connection with a specialist in my illness because my community oncologist had to worry about colon cancer, breast cancer, and prostate cancer, everything, and so I think he appreciated the connection with a specialist. The way it worked out for me, and it might for you our listeners and certainly people who are newly diagnosed is, a myeloma specialist like Dr. Lonial, if you have a consultation with them, may in the end make a recommendation that can be a blueprint for your care with the new landscape in myeloma treatment and then hopefully with the concurrence of your local specialist. It's not to put them down;

it's with a great deal of respect. They may be sort of the general contractor. They may be delivering the care according to a plan that was recommended by a myeloma specialist, and then that relationship, that dialogue continues really over the rest of your life, and I think that's very valuable.

Dr. Lonial, just a couple of other questions. I don't want to beat a dead horse, but there's been debate on our programs before depending upon who the practitioner is who has been on, and you've been part of that, the role of transplant now. I know some of the studies came out and talked about how to make transplant more effective. So what's your view at Emory now about the role of transplant? Still very valid and are there now drugs to help it be better?

Dr. Lonial:
I think that, to answer the second question first: Are there drugs to help it be better? We actually have an ongoing phase-II trial combining bortezomib or Velcade with high-dose melphalan and have shown a very high response rate for patients who essentially did not have a good response to their initial induction therapy. So I think that there are ways to enhance the efficacy of high-dose therapy by using novel drugs either as part of the induction or as part of actual transplant maneuver itself.

I think to answer the first question; there are a lot of emotional issues on both sides of the transplant issue. Should you have a transplant? If you go to one transplant meeting, the answer is yes for everybody. If you go to another meeting, you may hear everybody say, 'No, transplant has no role,' and I think that the answer is probably somewhere in between.

In our approach is that for young, well patients we will collect grafts on everybody, and the real question for us becomes when do we transplant? Do we transplant early on in the setting of first remission, or do we transplant in the setting of first relapse, early on in first relapse? And are there subsets of patients for whom high-dose therapy may not offer much of a benefit at all, and that's something we didn't know five and ten years ago when a lot of these studies were done, but I think we're identifying potentially cytogenetic subsets of patients that don't seem to gain a lot of benefit from high-dose therapy as well as cytogenetic and FISH subsets of patients that may actually gain a lot of benefit from high-dose therapy and autologous transplant.

So I think it's a moving target, and if you hear, and I'm always a little cautious of people that are too much on one extreme or the other; no, it has no role; or yes, you have to do it for absolutely everybody. I think that somewhere in the middle is probably the best way to look at it, and there's not a downside to collecting stem cells early on in the course of a patients disease so that you always have options later on.

Dr. Lonial Answers Questions from Listeners

Andrew Schorr:
Okay. Now, I recognize that we have some people who are new to multiple myeloma who are listening, and so sometimes we'll define these terms. There are a lot of acronyms in oncology and hematology. FISH testing, of course, is very sensitive testing to look at a patient's individual situation, and you mentioned about genetic abnormalities, and here's a question we got in from Paul, and he doesn't say where he's from, but here's his story, and again, with these questions we'll explore someone's personal situation, but we're going to globalize it as best we can.

Paul writes in, and he says, 'I was diagnosed five years ago. I've been on just about all the treatments currently available. I've been on Revlimid for two months with pretty good results; however, my remissions have been short according to my multiple myeloma specialist physician due to the partial deletion of 13 and some other genetic irregularity. What novel treatment or clinical trials would you suggest as a possibility when Revlimid has run its course?'

Dr. Lonial:
Yes. Even something as what we thought was straightforward as deletion of chromosome 13 it turns out is actually a lot more complicated now as we get more and more data. So, I think that when you talk about deletion of chromosome 13 there are two different ways to get that result. The first way is using routine cytogenetics, which is a test that they do on the bone marrow where they actually look at the dividing cells and the chromosomes themselves and can identify that a part of chromosome 13 is missing.

The other way it can be identified is through FISH testing, which is as Andrew mentioned a much more sensitive test, but actually when you do FISH testing for deletion 13, 50% of myeloma patients have it. So, if you're talking about a prognostic feature in which half the patients seem to have it, what real utility does it offer?

So what we've looked at now is looking at survival and duration of remission for patients with deletion 13 by routine cytogenetics as well as deletion of 13 by FISH, and it turns out that deletion of 13 by FISH really doesn't have any prognostic implications anymore at all, so that the only deletion 13 that's really potentially a negative adverse factor is when you see it by cytogenetics alone.

The second thing to say about deletion 13 is that all of the data that suggests that patients who have it by cytogenetics do poorly is data using convention, what I call "old fashioned" agents; steroids, chemotherapy, radiation. But there is data

emerging now that says that new drugs like Velcade and like Revlimid deletion 13 doesn't necessarily carry a negative prognostic feature.

So I think in many ways those prognostic factors that we look at may have to be redefined in an era where we use predominately novel agents or novel agents in combination with old drugs because the rules may have changed.

Andrew Schorr:
He also asked about so when Revlimid has run its course, so if you have a drug that may not be as effective, what do you switch to?

Dr. Lonial:
I think that, again, our approach has been often to use combinations. So, if you're not getting what you want out of Revlimid, we will often add Velcade to it. I think that there are other trials now looking at Cytoxan plus Revlimid. I think that there are at my center alone two or three trials now combining new drugs that are not approved with Revlimid or new drugs that are not approved with Velcade, and I think that's really the way to go. Once you've seen the commonly available agents, and even if you haven't, I think a clinical trial is a good option, but this is a perfect setting in which you might benefit from either a combination of either Rev or Vel in the setting of a clinical trial agent.

Andrew Schorr:
Joan in Nashville is listening, and she just wrote in, 'Please address relapsed myeloma choices. Is low-dose Revlimid as effective as high-dose Revlimid, and how does one determine what to take?' Her key question I think for everyone is how does one determine when to stop one therapy and move to another?

Dr. Lonial:
So, the question about low-dose Revlimid versus high-dose Revlimid I think is, I'm not sure if that's maybe being confused with the low-dose dex versus high-dose with dex with Revlimid. I mean, Revlimid I think for most of us when used with dexamethasone is started at 25 mg, and then the dose is reduced based on side effects or toxicity, but I'm not sure I would recommend the use of a lower-dose Revlimid with dexamethasone in the setting of relapsed myeloma except in the context of a trial or when you're using it in combination with Velcade where we know 15 mg is the dose to start with for Revlimid and 1 mg/m2 of Velcade.

I think the other question about how do you know when to switch is also a good question. In our literature, we define progression as an increase of 25% from the lowest number of the M spike. So, for instance, if you M spike got down as low as 1, then when it went back up to 1.5 or 1.25 or 1.3, so we're in that ballpark, that would be considered progression for most of the study. So when you look at that failure-free or progression-free survival, all those things, that would get you a tick mark on the survival curve, but practically speaking, just because a patient's

biochemical number goes from 1 to 1.5 it doesn't mean that they necessarily need to be treated immediately, and what we will often do is follow them to get a sense for the tempo of the rise in that number.

I know that patients always like to say, "is there an absolute number at which you say I'm going to start you on therapy no matter what?" And the answer is no. There isn't an absolute number because what we look for is some kind of a symptom that tells us that this level of protein is causing harm to the body or potential risk for the patient, and that can be simple things like increases in the creatinine that suggests the kidneys are now starting to get compromised; the development of a high blood calcium; progressive reduction in the hemoglobin or development of anemia; drop in the white count; drop in the platelet count; new bone lesions or bone fractures. Those are all things that I look for that say well, I can't really watch this patient any more because the numbers are going up, but in addition to that they're developing a lot more symptoms.

So, it's really more of a judgment call as to when you start, and often I will tell my patients, you know you don't have to start today, but your numbers are looking like it's moving in the direction that we need to start doing something, so we can talk about doing it now. We can see again in a month where you are, but at some point in the near future we're going to start you back on therapy.

Andrew Schorr:
Let's talk for a minute about when someone is on therapy, when do they call the doctor or the nurse? Here's a question we got in from Yvette in Denver, and she writes in, 'My father-in-law was diagnosed with multiple myeloma four months ago. He's losing a tremendous amount of weight and is receiving chemotherapy twice a month along with pills. The last few days he started getting blood in his stool. Should we be concerned or is this a side effect from chemo?' And I would broaden this out, Dr. Lonial. So they're worried about blood in his stool, and also other people have numbness and pain, so this whole dialogue about what's a side effect, when should we be concerned, when should we call the clinic, or when should it result in a change in therapy?

Dr. Lonial:
Yes, I think blood in the stool is always something that you want to let your doctor know about, so that's one of those relatively straightforward ones. It may not be a big issue or a major emergency, but it's something that somebody ought to at least know about and potentially look into and determine whether or not they need additional workup, follow the hemoglobin, endoscopy or something along those lines, because often blood in the stool can be associated with a drop in the platelet count, and that certainly can be something that can be very serious and requires more aggressive therapy or modification of the dosing.

I think that the question about neuropathy is also another important one because we've found in the large, randomized, phase-III trials that we were able to minimize the incidence of grade 3 and grade 4 neuropathy, which is the worst of the neuropathy, simply by making appropriate dose modifications and dose reduction, and we find that that's not always 100% translated into the community because for instance when somebody sees me, my whole team asks them every time they come in, tell me about your numbness. Is it worse? Is it better? How is it? So, we're pretty sensitive to asking those kinds of questions, and unless you're in an office that is used to doing that, especially with drugs like Velcade or thalidomide, you as a patient may not know to offer that information up, and so I think in that situation changes in numbness or tingling, the development of pain, those are all things that I think the oncologist needs to know about so that they can make appropriate dose modifications or hold the dose of therapy for a period of time to allow that to get better before resuming therapy.

Andrew Schorr:
Now, related to pain. How much is pain related to the therapy or just the effects of myeloma on the bone, and what do you do about that?

Dr. Lonial:
There are different kinds of pain. Obviously there's bone pain, and that can be associated with the disease itself. There is pain that is associated with medicines like Aredia and Zometa. Sometimes we hear patients say that they got really bad bone pain a day or two after receiving that infusion, and then there's pain associated with neuropathy. So, obviously you have to tease them out.

I think it's important that your doctor know before you start where you are and what's causing the pain. A lot of bone pain may resolve with appropriate therapy, and we've seen that in a number of patients where they didn't have a fracture, but they just had a lot of bone pain, and they had a lot of lytic disease by x-rays, and once they got through a cycle or two of therapy as their numbers got better and as their disease got better, the bone pain started to melt away, so I think it's really an acute or an abrupt change in the kind of pain that you're having or progressively getting worse pain over a period of time that that's worth letting the doctor know about.

Andrew Schorr:
Regina writes in from Union Dale, Alabama, a question that I think anybody who's diagnosed with cancer wonders. She says, 'What can I do to help myself?' So, you get asked that all the time. 'Doctor, you're going to do X or Y; what can I do?'

Dr. Lonial:
Yes. Well, there are probably several things, but I think that the most important thing that I tell patients is to try and stay as physically fit as they can because ultimately our ability to deliver therapy is limited by patients who cannot get

around. They can't care for themselves. They can't get up and walk. If you're physically not fit, that is going to change the doctor's perception of what they're going to use to treat you and how they're going to treat you, so that's incredibly important, doing your best to maintain muscle strength during periods where you are receiving steroids, and that is a real challenge because as you know steroids break down muscle mass. So, I think that that's important.

I think a well-balanced diet is important. There are lots of things on websites all over the Internet that talk about use this supplement, use that supplement, don't eat sugar, do eat sugar. I thing that there are a lot of myths, and there is very little hard scientific data about any of these processes, and so what I tell patients is eat a well-balanced diet, not too much of one thing or too much of another, and take a multivitamin a day, and that's usually sufficient to guarantee that your body is getting what it needs and that you're keeping yourself in a position to stay well for as long as possible.

Andrew Schorr:
I just want to make a personal comment. So when I was diagnosed with leukemia, and a kind of leukemia I'd never heard of, like maybe many of you had never heard of multiple myeloma, but chronic lymphocytic leukemia, so my wife saw somewhere on the internet, well don't drink coffee and only drink carrot juice. So, she was making these carrot juice shakes, and remember I live in Seattle where Starbucks is headquartered, and we have one like every 10 feet, and I was a coffee drinker. So I went a year without drinking coffee.

Well, I have to tell you folks, now I'm happily, you know I've had a remission; I'm a 12-year survivor in a long remission, and I drink coffee a lot. I can't tell any difference, so I'm just trying to enjoy life and stay healthy, but some of the things can just be crazy making, and then it's so stressful to go through that. So, I certainly endorse what you said, doctor.

Okay, we have a question we received from Barbara. Barbara's been a regular listener I guess to our series, and as I said, this is the eighth program in our myeloma series. She says, 'One of the transcripts from a previous webcast mentioned getting Revlimid by intravenous infusion at the doctor's office, and this made a huge difference in the cost of the medication to the patient versus pills. Has anyone gotten Revlimid by IV, and was there a cost difference?'

So, can it be administered by IV? What about this, doctor?

Dr. Lonial:
It actually can't. It's an oral agent. It's not available by intravenous infusion. That's not an option.

Andrew Schorr:
Okay, and then I want to mention for people, several people have written in, 'Well, what are good sources for information?' Well obviously our webcasts and the transcripts, and also the International Myeloma Foundation has a wonderful hotline, and I want to give that number: 1-800-452-CURE, and that works out to be 1-800-452-2873. They have folks there to help you gather information that's valuable for you, and also they can also let you know where there are myeloma specialists.

Now, here's kind of a complicated question we got in from Bill in Baltimore. Let's weave our way through it. He says, 'What do you recommend for relapsed patients who experience a high temperature, over 101 degrees, when they're on Velcade/Revlimid, and blood cultures are negative and the fever is of unknown origin because it seems to be a sensitivity where taking Benadryl can reduce the sensitivity of the chemo.'

I'm not sure I follow all that, but he's worried about the fever when, I guess, nothing shows up as an infection. So, does fever come in as a sensitivity to taking these medicines, and do you do anything about it?

Dr. Lonial:
Yes, I think we have a number of patients whose disease itself has fever associated with it. So, I think one of the questions is, is the therapy that you're receiving really working? Because if it is, then that's not something to worry about, but oftentimes we'll see patients who have what we call "tumor fever" associated with their relapsed disease.

The second is that we've certainly seen it, and it's been reported among patients receiving their first few doses of bortezomib or Velcade, that they will get a fever. Often it can be as high as 102 or 103, and it usually again for patients who respond it usually goes away, and that may be an associated release of growth factors associated with death of the plasma cells that's causing that fever, but if it's persisting for two and three cycles of therapy then that's not likely the major issue.

I think that myeloma patients are so immunocompromised that a lot of times, if you look at just regular blood cultures or routine things, you won't always find something, but you really have to look a little bit harder sometimes and do things like make sure that there aren't fungal infections, and the most common obviously is yeast and other things like that and that there can be other types of infections, even aspergillus or mold infections that can be an issue in patients who have myeloma.

So I think it really, if it persists for longer than three or four weeks, then it probably does require in our hands here pretty extensive CAT scanning as well as a lot of different kinds of cultures to make sure you're not missing some less common bugs or organisms.

Andrew Schorr:
Here's just one question before we take a break, and then of course we invite a lot more. This is from Peter in Holmdel, New Jersey. He says, 'When do you begin treating the patient who has relapsed after a bone marrow transplant? Do you treat when the M spike has reached a certain number, and if so, what would that be?'

Dr. Lonial:
Yes, I think that that's often a challenging question, and we don't have a specific number that we treat. We really look for symptoms more than anything else. Is the hemoglobin starting to drop? Are the blood counts starting to drop? Is the renal function starting to get worse? We look at the whole picture. Is the patient just not doing as well as they were three or four months ago, and that usually drives our decision to start on therapy, not necessarily an absolute number.

Andrew Schorr:
Okay, we're going to take a quick break. We're doing our eighth live webcast, a wonderful resource for you, and all the replays. So tell your doctor or tell other people you know, and today's guest is a great one we've had before, Dr. Sagar Lonial, who is an associate professor at the Winship Cancer Institute of Emory University in Atlanta. We'll be back in just a minute with more of your questions on Patient Power.

And here we are back very fast. Hopefully, myeloma, there can be bumps along the way, but it can be a long-term, chronic condition, and I am going to go down to spring training this week. For me, the Seattle Mariners play in the Cactus League in Arizona, so I'm going to go down with my son. We go, we've gone, this is like the fifth year in a row, I'm watching him grow, and we share our love of baseball, but the reason I'm mentioning this is the new pitching coach for the Seattle Mariners, many people remember him as just an outstanding New York Yankee and Yankee pitching coach, is Mel Stottlemyer, and many people have read the book that Mel wrote, but he's living with multiple myeloma and has been for a number of years, so think about it. Here's a guy; he's in great shape, been an athlete all his life, has the diagnosis of multiple myeloma, and yet the Seattle Mariners, which hopefully can do well in the postseason, have really entrusted their pitchers to him, and I'd like to be able to think of myeloma that way.

What do you think, Dr. Lonial? When people come to you they're terrified, they're newly diagnosed or a family member is, and they say, 'Well, what's life going to be like after this diagnosis?' It's not for sure, and it's individualized, but there are people like Mel Stottlemyer who just go on with their life and certainly are very productive.

Dr. Lonial:
Yes, and I think that that's a big part of what we're all striving to do as we talk about treating patients with myeloma is to get them back to their usual functional status. It's not uncommon for me to see a patient at one-year post transplant, for instance, whose disease is under good control, and I ask them , so tell me what you're doing in a day, and they say, 'Well, I mess around the house a little bit,' and I say, 'Well, why aren't you out doing more?' And their answer is, 'Well, I'm not just sure that I can do it, and I don't know how long I'm going to feel this way.' And I understand that concern, the anxiety about, you know, is this sort of a ticking time bomb kind of an issue, but I think that a main goal for all of us who treat myeloma is that we want patients to be back doing what they normally do and enjoying life and spending time with their family, and that may involve an aggressive treatment course for a short period of time, but at the end of the day if you're not able to do those things, then all that effort and time we spent trying to make patients better is really for naught because they really should be out enjoying life and spending time with your family, so I think that's a major goal for all of us.

Andrew Schorr:
Yes, I think that's great advice, and I would urge people to do that, and I see that across all these serious illnesses. This weekend, again, I'm going to have a new friend on, Mary Sharkey, who is a six-and-a-half-year pancreatic cancer survivor, and there are not many, and she did have aggressive treatment, and it worked for her, and she's going about her life. She has her checkups, but she's going about her life, and that's what that aggressive therapy was there for, for her.

Here's kind of a complicated question, what I call a "grad school" question, from Scott in Buffalo, New York. So, our newbies just bear with us, but we'll try to define things for you. He writes, 'Recent findings have potentially linked the eventual relapse of multiple myeloma and some other cancers to the chemo-resistive properties of the cancer's stem cell. Would you comment on any of the therapies in clinical or preclinical trials that you're familiar with that have supposed cancer stem cell efficacy?' And then he asks about a couple of drugs, which maybe you've heard of; GRN163L or another one cyclopamine, if I got that right?

Dr. Lonial:
Cyclopamine. Yes, I think that there is a lot, again, just as there is a lot of information and hype on the web about you should use this supplement or you should use this nutritional approach, there's a lot of hype as well from the physician side and the basic scientist side about this so-called myeloma stem cell, and I think that intuitively it makes sense to me that there probably is a less mature cell that does not divide as much as the average myeloma cell does, although to be perfectly honest with you, a typical myeloma cell does not divide that often, so it's not like a leukemia that divides much more rapidly. Myeloma cells tend to be a lot more indolent, at least in most subsets.

I think that there probably is some truth and validity to this so-called stem cell that may give rise to all the subsequent cells, and that might explain why we can eradicate large amounts of the disease, and yet patients are not truly cured because this cell is still alive, but I think it's also important to realize that none of this has been proven in patients. There is no clinical data that suggests that any one agent or any one approach can hit the myeloma stem cell in a patient. There's lots of animal data. There's lots of mouse data. We know that we can cure mice of their myeloma, which I always laugh a little bit at because mice don't get myeloma, so curing them of a disease that they don't ever really get, what's the real importance of that in my mind? But I think that it is helping us to ask important questions about the disease biology.

Right now I would say that there is no drug that's tested or proven to have any efficacy against any kind of a "myeloma stem cell" and that I think if you want to take these agents, I think I would do it as a part of a clinical trial to really answer that question.

Andrew Schorr:
Okay. Now, Beth has called in from New Jersey. Beth, welcome to the program. Beth, I understand it's your husband who has a diagnosis of multiple myeloma?

Caller:
That's correct, yes.

Andrew Schorr:
When was he diagnosed?

Caller:
He was diagnosed in 2003 and underwent a stem cell transplant in 2004. My question is, it's been recommended at this time that he begin Revlimid and dex because he seems to have come out of his remission, and he has some reservations about this combination, particularly the side effects of blood clots. Due to the nature of the disease, he experiences a lot of pain, in his legs in particular, and is concerned that he won't be able to differentiate between the pain of a blood clot versus the pain that he already experiences, and therefore he's a little reluctant to begin the drug. Is there any way that you can make him feel a little bit more at ease or explain to him how this is going to go?

Dr. Lonial:
Sure, sure.

Andrew Schorr:
Sure, and Beth, what's your husband's name by the way?

Caller:
Peter.

Andrew Schorr:
Okay, well let's give some guidance to Peter. Thank you for calling, Beth.

Dr. Lonial:
I think that there are, first of all, there is no absolute right answer for what to do in the setting of first-relapsed myeloma. So I think if at the end of the day or whatever I say or whatever else, if you and your husband are not comfortable receiving Revlimid-based therapy, there are other options. Velcade/Doxil is an option. Velcade is an option. There are a number of other clinical trial options that are available as well. So, there isn't just one option.

Now, I think that Revlimid/dex is certainly a reasonable choice to make in this clinical situation, and the risks of clotting and thrombosis is an issue, but I think with appropriate prophylaxis and with appropriate observation, it can be minimized to probably an area of about five to seven percent, somewhere in that range there. If you look at the incidence of thrombosis in myeloma patients across the board, it probably is somewhere around five to seven percent anyway in the relapsed-myeloma setting.

I think that the symptoms of thrombosis are not really usually pain. It tends to be more asymmetrical swelling. So, if you get a clot, you may get swelling on the right leg or the left leg out of proportion to swelling on the other side. So, the main symptoms are usually not pain per se as much as they are the swelling associated with one side or the other, so I think that if pain is an issue and you're worried about confounding pain, that really should not be a major issue, but I think it's important that anybody who receives Revlimid-based therapy be on some kind of prophylaxis to minimize or prevent the risk of clotting, and there are a number of ways to think about what to use for prophylaxis.

There is a paper that just came out in the journal "Leukemia" which is a consensus statement for many of us who wrestle with this problem on a daily basis, suggesting a couple of strategies for prophylaxis when you use Revlimid-based therapy, and again there's no one accepted opinion, so I'm not going to tell you exactly what I would do in this situation, but there are options to reduce the risk of clotting significantly.

Andrew Schorr:
Okay and I think this underscores for Beth and Peter and others is for many myeloma patients your clinical situation is kind of a moving target and the knowledge about both the treatment of the disease and managing of side effects or potential complications, that's moving too. So, I think you not only want to stay up to day yourself as best you can, but have a consultation and have a relationship

with a myeloma specialist so as you heard Dr. Lonial allude to, he is reading that journal article that just came out in "Leukemia" and focusing on it because he's been dealing with these issues all the time, so obviously he'll be discussing that with his patients. Whether you're one of his patients or consult with him or another myeloma specialist, I think it's good to have that relationship.

Here's a question we got in from Robert in Arlington, probably Arlington, Virginia, and I'll read through this one. "For smoldering myeloma, stage I, asymptomatic, newly diagnosed, are bisphosphonates such as Aredia not appropriate to start as adjunctive preventive therapy to strengthen the bones in advance of myeloma's destructive work, or are bisphosphonates only appropriate to repair ongoing, already damage bones?' And he was referring to Mayo Clinic's consensus statement. So the idea is, what preventive strengthening do you use for the bones or not, doctor?

Dr. Lonial:
Right, right, and again, I think you highlight a very important couple of pieces of information there. The first is the Mayo Clinic consensus statement, and I think having been one of the reviewers of that consensus statement, I can tell you that it was a consensus among Mayo physicians. It was not a national consensus statement. So many of us do not actually agree with their guidelines for use or not use of bisphosphonates.

I think the second piece of information I would offer is that for patients who truly have asymptomatic myeloma, part of that definition means that you don't have bone disease, and so if you don't have bone disease to date there have not been any demonstration that the use of bisphosphonates in that setting offers any significant benefit, and if you do have bone lesions, many would argue that you're not asymptomatic myeloma, that you actually are symptomatic myeloma, so I think that that is an important distinction. Oftentimes I'll feel tempted in patients who I think are high risk of progression to symptomatic myeloma to start them on bisphosphonates early, but again remember that there are certainly some risks associated with bisphosphonates; the risk of osteonecrosis of the jaw, if you need any kind of major dental work done you don't want to have that done while you're on bisphosphonates because of that risk going up.

So our approach has been to try and hold off unless there are patients who I know have a single, isolated bone lesion, and I don't want to start them on therapy even though they technically fit the definition of symptomatic myeloma. So, in our hands, we're not starting bisphosphonates for smoldering myeloma.

Andrew Schorr:
Okay, we gave a very definitive answer. Thank you. Now, our listeners you may gather are not only patients and family members but actually healthcare providers tune in, and I think this question is from one of them. Linda, in my old home town

of Charlotte, North Carolina, up the road from you in Atlanta, she writes in, 'I have patients who are treated mitoxantrone for multiple sclerosis. Recently I had a patient who received a total of 70 mg/m2 over four years ago, and then they developed multiple myeloma. Have you seen any indication that mitoxantrone might cause multiple myeloma because there's nothing in the MS literature about this as a problem, and the patient is 60 years old?'

Dr. Lonial:
Yes, I think that there are certainly secondary leukemias that can be seen with the use of prior chemotherapy. Those tend, again, to be leukemias not multiple myeloma, so I'm not aware of anything that says that the use of mitoxantrone or other anthracyclines can increase the risk of developing myeloma. What is curious though is that MS in many ways is an autoimmune phenomenon or an autoimmune disease in many ways, and we know that myeloma is abnormalities of plasma cells, which are part of the immune systems.

So, if you create this unusual or abnormal clone of cells that causes you to have MS, it is certainly highly possible that that same abnormality may trigger something like myeloma. Just as in, for instance, in HIV patients we know the incidence of myeloma is actually higher, and the incidence of lymphoma is actually higher as well, so if you have an abnormal immune system, your risk of blood cancers in general may be a little bit higher.

Andrew Schorr:
Now, of course, people worry about their family members, so if someone is diagnosed with multiple myeloma, they worry about other family members, and here's a question we got like that from Terry in Franklin, Massachusetts. Terry writes in and says, 'Well my husband died in 1995 from multiple myeloma, and our 32-year-old daughter has been diagnoses with' and she uses an acronym here, and I'm not sure what it is, 'CIDP. What is the latest research on each of these conditions being hereditary?'

Dr. Lonial:
So for myeloma, there are a few subsets of familial myeloma that's been documented now in the literature, and it presents, we haven't exactly identified all the genes or chromosomes that are associated with it, but that compromises maybe one percent of the total number of myeloma cases around the world. It's not a huge number of myeloma patients that have hereditary myeloma, although it can be seen again in a small proportion of patients, so I think the likelihood of if dad had it the likelihood of a daughter getting it is not exceedingly high because it's just not transmitted that often through heredity.

Andrew Schorr:
That's good to know. Now, I know in my own leukemia there's research going on. I know you deal with B-cell malignancies, CLL, where we do see it to some degree run in some families, so this is all being studied.

Now maybe you can explain this one. This question came all the way from Maureen in Australia, and she says, 'Is there a multiple myeloma type that does not give off the P protein, and how can this be monitored?'

So, what does she mean by the "P protein?"

Dr. Lonial:
I wonder whether she means the paraprotein.

Andrew Schorr:
Probably.

Dr. Lonial:
Yes, which would be the same as the M protein or the myeloma protein. There are non-secretory myelomas, meaning that they don't make a blood or a urine protein, and that used to comprise probably about ten percent of myelomas historically in the past, but now that we have some newer technology, things like the Freelite assay, that ten percent that have non-secretory is now down to probably about one or two percent that truly don't have any marker you can follow, and in those patients who have non-secretory myeloma, oftentimes the only thing you can do is serial bone marrows to get a sense for what the disease looks like, but it's much less common nowadays because of this Freelite assay.

Andrew Schorr:
Well, that brings up a question then because we have people living around the world, what would you recommend and what do you do in Atlanta at Emory at the Winship Cancer Institute when someone is suspected of having multiple myeloma? What diagnostic tests do you do to really get a clear picture of what you're dealing with, and then what would you recommend to people?

Dr. Lonial:
Our initial diagnostic workup starts with basic laboratory measures, chemistries, routine chemistries, and a CBC. We get a beta-2 microglobulin. We get a skeletal survey. We get a bone marrow with flow cytometry, and we also get routine cytogenetics, and we run in-house FISH analysis on that as well.

Now, for newly diagnosed patients, one thing that we do that we think is actually very important is our center is one of the now 15 centers in the Multiple Myeloma Research Consortium, or the MMRC, and part of what we do for every newly diagnosed and certain patients in the relapsed setting is we actually send a sample

of the bone marrow with the permission of the patient to the MMRC for sequencing, and actually there's a very exciting and interesting whole genome sequencing project for newly-diagnosed myeloma patients that we try and send as many newly-diagnosed samples to so that we can again identify the different subsets of patients. For the patient's that actually go on that specific study, they actually can get a copy of their whole genome sequencing for their malignant plasma cells at some time down the road, so we find that to be important not just from the disease standpoint but also from the future aspects and therapy standpoints as well. I think that that in a nutshell comprises most of what our initial workup is.

Andrew Schorr:
Okay, now there are some people who might say, well you're at a university center, and you're doing a lot of clinical research, and you take a bazillion tubes of blood and do this and do that to further research. So in the community setting, though, if you said, 'Well if you call me and you're way out in the hinterland, even if you don't come see me, I would really like you to get test X, Y, and Z.'

Dr. Lonial:
Yes.

Andrew Schorr:
What's sort of the baseline that you really think people need so the practitioner's know what they're dealing with?

Dr. Lonial:
Right, right. I think you need to have obviously a serum protein electrophoresis, quantitative immunoglobulins to know what all your other immunoglobulins look like, immunofixation on the blood, 24-hour urine collection for urinalysis of protein, a Freelite assay, and I still think you need bone marrow for cytogenetics and for FISH analysis.

Andrew Schorr:
Okay. Now if some goes to, as you said, a tertiary center, normally you want people to bring their test results, right?

Dr. Lonial:
Normally I'd like to do them myself here, but I would accept the test results from outside, but some things like a bone marrow I may still want to repeat.

Andrew Schorr:
Right, right. I have to mention, I've had a number of bone marrow biopsies, and I have to say at the leading academic centers you have people who do it all the time, and so I was very daunted by the prospect of it, but for me at least it wasn't that big a deal.

Dr. Lonial:
Yes.

Andrew Schorr:
But I know that people worry about it.

Dr. Lonial, let's kind of look at this more globally for a minute. So things are changing. There's new research. They have subspecialists like you keeping up with it and more and more clinical trials. I mentioned that I thought clinical trials were really important. Can clinical trials potentially give people the benefit of tomorrow's medicine today, and is it appropriate for newly diagnosed people or just people who've failed all therapies?

Dr. Lonial:
I think you're absolutely right. I think the clinical trials offer a patient hopefully the best treatments for tomorrow, and they offer them today. I think that patients at every stage of disease have clinical trial options that are available to them. We wouldn't have that wealth of randomized phase-III data that was presented at that session at ASH if newly diagnosed patients had not gone on all these studies.

As I often will say, the best place where the most number of patients get enrolled is in Europe. It's not in the United States. They enroll more patients in Europe to large, randomized phase-III clinical trials than we do in the United States, and there are a number of reasons why that occurs, but I think that if we're really going to be able to make the kinds of advances we need to make in a moment-by-moment day-by-day basis to treat this disease more effectively to get more drugs to the clinic and approved, we need to really all work together to enroll patients on studies to answer that, and that includes relapsed/refractory, that includes first-relapse, but most importantly that includes the newly diagnosed because I think that what we're on the verge of doing is changing the whole way we approach therapy for the newly diagnosed patient, and instead of saying it doesn't really matter what you give, what drugs you give at the beginning, I think it does matter now, and I think that in order for us to prove that, we need to have the data from trials of newly-diagnosed patients to prove, to once and for all say you *do* do better if you get drugs X and Y as opposed to A and B at the time of newly diagnosed disease.

Andrew Schorr:
One of the things I think is changing and across all cancer is how aggressively do you treat a cancer, like multiple myeloma, in someone who's older, and multiple myeloma isn't always but often is in someone we used to consider older. So whether it's yourself who may be listening or a family member your worried about mom or dad or grandma or grandpa, what's your philosophy, Dr. Lonial, on how aggressively you treat it with the newest tools you have no matter what somebody's age is?

Dr. Lonial:
Yes, and sometimes the hard problem is you don't know how much a given individual can really take, and so I may start with something that is fairly aggressive, but if I see that they're not doing well with the first cycle or two, I may change ships a little bit and say well, you know, this isn't going to work out, and that's okay. I think it's okay to change the treatment plan based on side effects and toxicities for a given patient. There have been many patients that I thought were on the borderline of being suitable transplant candidates, and I gave them my best up-front induction therapy, and they just fell apart during the first cycle of therapy, and to me that in many ways that's a stress test. That tells me that perhaps that kind of an approach is not optimal for this patient, and so I switch to something a little bit different.

While it's easy for all of us to say, well this is what I use, this is what I use, this is what I use, there is a lot of play in that decision, and there's a lot of continuous reassessment for side effects, for toxicities, and for quality of life that helps guide me in terms of what I do with a given patient at any visit.

Andrew Schorr:
You touched on something I've asking a lot of experts about. I hadn't really thought about it up until recently, and that is really the question of the art of medicine. So, I think we think of it in surgery, you know, and eminent brain surgeon and they say, 'Well, in my hands most people are cured or live long lives' etc. In oncology you have all these tools now, but it still seems like even beyond the data there's a lot of judgment.

Dr. Lonial:
Yes, I think you're absolutely right, and sometimes you have to know how to balance what you think is absolutely best in a given situation with what the patient is telling you or what you're sensing from the patient in front of you, and times when I've had trouble getting patients through therapy is when I haven't listened to that sort of inner voice that said maybe you shouldn't do this to this one. It happens to all of us where you either underestimate the disease or you underestimate the ability of the patient to tolerate the therapy that you're delivering, but there is a real art to knowing how to do this, and what you do for, you know, I mean most trials will lump patients over the age of 65, but what you do for somebody who is 65 versus somebody who is 85 is very different, and it is not just the difference in age, it's also a difference in function and what they've gone through in their life beforehand that is going to either help you or hinder your ability to deliver therapy.

Andrew Schorr:
Okay, now that leads me to one other question too, and that is as people are older they may be taking other medicines for their heart, blood pressure, or some other

chronic condition they have. How much of a concern are those other meds to the newest medicines to treat multiple myeloma?

Dr. Lonial:
I think as long as we know what we're dealing with it's not as big an issue. Revlimid and Velcade have a few drug interactions but not very many, so I don't think it's as big a deal, but there certainly are classes of drugs that are coming through now like the histone deacetylase inhibitors, and there are at least three or four of them that are in phase-I and phase-II trials in myeloma now where what you can take with those drugs is very different. It's a limited list because of drug interactions. So I think that right now we don't have a lot of issues with potential drug interactions. There are some, but it's not an overwhelming number, but I that that number may grow as we get more targeted agents coming through the pike.

Where is Research Headed?

Andrew Schorr:
So here we are. You've been at this awhile. Where we are today, are you excited, and are you excited about, looking in the lab, where we're headed?

Dr. Lonial:
Absolutely. You know, it's one of the most exciting times I think to be a researcher in this area. You know, there was a time ten years ago where nobody wanted to be a myeloma researcher because there was nothing you could really do. There was nothing. We didn't understand the pathways. We had very limited drugs, and the numbers of patients we thought we had was much smaller than probably the real number. The reason I say that is they're saying that the number now is up to 20,000 a year, whereas a few years ago it was 12,000 or 13,000, and I don't think that that's purely a result of the incidence going up. I think that's because now as we have better therapies the diagnosis is being made earlier, and so patients now have options that they didn't have before, and when you look to the drugs or the monoclonal antibodies or the combinations that are in the lab, it's a new day. It's a completely new day, and I think the real challenge is going to be, as I said before, how do we put these drugs together? What sequence of time do we give them? You know, I'm a believer in multiple combinations and giving as many drugs together as you can to try and eradicate resistant cells early on in the disease course. Others don't necessarily share that point of view, and I don't think we know what's the right answer yet, but I think we have so many new drugs and targets coming that it's never been a better time to be stuck with the problem of myeloma.

Andrew Schorr:
Dr. Sagar Lonial, I just love doing programs with you, and if you're upbeat, I'm upbeat, and I think it's a great message to our listeners. That's Dr. Sagar Lonial, associate professor at the Winship Cancer Institute of Emory University in Atlanta. Dr. Lonial, thanks. We'll do it again sometime soon, okay?

Dr. Lonial:
Great, I look forward to it. Thank you, Andrew.

Andrew Schorr:
Thank you. We'll he's a great guest, and as I said, we have a whole series we're planning as we continue our programs on multiple myeloma. Look for the replay on www.patientpower.info, look for news about coming up programs. Be sure you're signed up for our e-newsletter, keep in touch with our friends at the International Myeloma Foundation, and thanks to Millennium Pharmaceuticals for making a grant to help fund these programs. We really appreciate it. As always, knowledge can be the best medicine of all. Have a great weekend. In Seattle, I'm Andrew Schorr.