PATIENT POWER

THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER
Making Cancer History®

Advances in the Treatment of Myeloproliferative Disorders

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Marty Prager

Introduction

Andrew Schorr:
Myeloproliferative disorders can strike at any age, and they have no known cause. Symptoms, prognosis and progression vary. Some patients may have slowly progressing disease that may not require any treatment beyond careful monitoring while others may progress to more advanced stages, or even in some cases, AML, acute myelogenous leukemia. We'll learn all about this next on Patient Power.

Hello and welcome once again to Patient Power. I'm Andrew Schorr. I want to tell you in this broadcast about myeloproliferative disorders. They can strike at any age. They have no known cause, but at M. D. Anderson there is some encouraging research, and so it's very important to get to a specialty center like M. D. Anderson, because depending upon where you are the doctors may not be knowledgeable, and we're talking about rare conditions, and we're talking about a variety of conditions, but there is encouraging research, the latest genetic research and news coming out of that. We're going to hear all about that in our program.

And as we like to do, we like to introduce you to a patient who has really lived this story. So let me introduce you to Marty Prager, who joins us from Burbank, California. Marty is 60 years old, almost 61. Married, two kids, and he is in the motion picture business. And then, Marty, you go for an annual physical, 2006 you go for an annual physical, and what did the doctor say from the routine blood test?

Marty:
I had my physical in 2006, and my physician said that I had myelofibrosis and said I had three to five years to live.

Andrew Schorr:
Oh, my goodness. Now, this is something you never heard of, and life-threatening condition. So one of the doctors, I know, and you were in an HMO, says, well, do your research, get on the internet, learn all you can. And when you did you connected with an advocacy group that had information, and you even saw there was a conference coming up of all the leading doctors, right?

Marty:
That's correct.

Andrew Schorr:
So you said, I'm going.

Marty:
That's right. That's what I did.

Andrew Schorr:
So this is really a powerful patient taking the bull by the horns. Were you just feeling in Los Angeles that you just weren't encountering an expert, and you had a concern that whatever was the latest information could make a difference?

Marty:
Well, it's such a rare disease that I felt that a gathering of the acknowledged experts in the field is where I should be, and that's why I went to Scottsdale. It's not that far away. It seemed like the logical thing to do.

Andrew Schorr:
So this is a conference put on by the CMPD Education Foundation, right?

Marty:
Yes. That's correct.

Andrew Schorr:
All right. So you go, but before you go you hear that one of the speakers there and one of the leading experts is Dr. Srdan Verstovsek, who is a medical oncologist and associate professor in the leukemia department at M. D. Anderson, an expert in this. You actually got in touch with him, right?

Marty:
Yes. We exchanged a couple of phone calls and a couple of e-mails.

Andrew Schorr:
So you said I got to meet this guy, and so he gives a speech at this conference and you come up to him afterwards, and what do you begin to talk about as far as research that could make a difference?

Marty:
Well, I explained that I understood that he was conducting a clinical trial and the trial was due to start soon, and I honestly didn't know how to approach someone about participating in a clinical trial, so I just introduced myself and told Dr. V. that I was interested in the clinical trial, and would I be suitable for the trial.

Andrew Schorr:
Now, at this same time as time was going on, you're getting transfusions because your anemia is quite significant. I think normal hemoglobin is about 14, and you had dropped to seven, right?

Marty:
That's right.

Andrew Schorr:
But you're still trying to work, so you're getting transfusions every three weeks to kind of pump you up, but even so you had what was believed to be a life-threatening condition.

Marty:
Yes. That's correct.

Andrew Schorr:
Yeah, that's no way to live. Okay. Well, you mentioned Dr. V, so again, that's Dr. Srdan Verstovsek, and this is his field.

Dr. V, so this is a wonderfully proactive patient who approaches you, and it's at a time when now finally there is some promising research. What was going on in the research world? Was this out of the human genome project, or what was happening, where for a rare condition you might have something new.

Dr. Verstovsek:
Yes, this is the beginning of 2007, and a couple of years earlier, in earlier 2005 there was a major discovery made in the field of myeloproliferative disorders, discovery of a mutation in a gene called J-A-K 2, or JAK2, which makes the protein, and the mutated JAK2 protein appears to be contributing to the continuous unregulated growth of cells in these myeloproliferative diseases. So at the conference in 2007 we were talking about future studies with the specific targeted therapy, JAK2 inhibitors that were supposed to inhibit that mutated JAK2 protein and hopefully help the patients, and Martin is one of the patients participating in these early studies.

Myeloproliferative Disease Types

Andrew Schorr:
All right. Let's understand. When we talk about a myeloproliferative disorder, first of all, what was Marty's specific diagnosis? How common is this? What is the range of these problems? What's going on, basically?

Dr. Verstovsek:
When we talk about myeloproliferative diseases we in principle talk about the so-called Philadelphia classic chromosome-negative Myeloproliferative diseases, which are three. One is called essential thrombocythemia, or ET, where the major problem is high platelets. It's a pretty benign disease, and patients live long life by controlling the platelet number. Polycythemia vera is the second one where patients have a high number of red blood cells, white cells and platelets in the blood, and again usually patients live a prolonged period of time, decades, by controlling the numbers and don't suffer much from the disease.

However primary myelofibrosis, or MF, is the one that Marty had, and this is the one where the bone marrow reacts to the presence of the disease by producing fibers, and the bone marrow very quickly becomes fibrotic like a scar tissue in the bone marrow limiting the number of cells, so the patients instead of having too much cells present like Martin had, with anemia. Many also suffer from cachexia, meaning losing weight because the disease takes a toll on the body, the weakness. The enlargement of the spleen and liver can happen because these organs take over production of blood cells from the bone marrow. And this disease, because of all the signs and symptoms, significantly shortens the life expectancy to several years. Usually people say about five to seven years on average, but it's been from few years to more than a decade.

JAK2 Trial

Andrew Schorr:
So there's this study of this protein, and you see this JAK2 protein. So what does that mean when you identify an opportunity on a cell, does that mean you can try to create a medicine to deal with the problem?

Dr. Verstovsek:
That's correct. So in these situations we look at patients when they come to an institution like ours and try to identify biological markers of a particular case, and in about half of the patients with myelofibrosis we usually identify mutation in the JAK2 protein. We would say that in these situations that the mutated protein definitely helps the growth of the abnormal cells in the patient. The interesting part here, and it's an important one to understand, is that half of the patients do not have a mutation in the JAK2 protein, but nevertheless they present in the same way and have the same outcome, which would say that we need to learn much more about the disease and see what else contributes to the disease process. And we are only at the beginning of significant discoveries.

On the other hand we should look at this as a positive sign because we are now in a position to identify one abnormality that identifies bad cells and distinguish them from the normal, and we can target that abnormality, this particular protein, JAK2 protein, with the medications to try to inhibit it.

Andrew Schorr:
Okay. There's a lot to try to go over. So first of all let's go back to Marty for a second. So, Marty, you participated in this trial. We're talking about a medicine that's a liquid, and you can mix it in orange juice, something like that?

Marty:
That's correct.

Andrew Schorr:
And you take it twice a day?

Marty:
Twice a day.

Andrew Schorr:
So you've been doing that. Now, you went to Houston, you're in the trial, and you continue that at home back in Los Angeles. Twice a day you mix up this stuff. How are you doing?

Marty:
I'm doing fine. My energy level is near normal. I'm working nine hours a day and lead a fairly active life on the weekends. I'm as normal, just about as normal as I could be.

Andrew Schorr:
Well, this is incredible. So, Doctor, help us understand what's going on. He's taking this very targeted medicine. Is it finding the cells that otherwise would be inappropriate? And what is it doing? How can you just take a little liquid, take it twice a day, and a man who is near death is now leading a normal life?

Dr. Verstovsek:
This is an excellent question, and we don't really understand every single bit of the answer. But let me try to explain this a little bit in more detail. The JAK2 protein is important for everybody here. It is important for normal cell growth in our bone marrow. For our blood to become normal we need to have active JAK2 protein, and our body activates the JAK2 protein when it is needed. Like if I would bleed my body would activate the JAK2 protein in the bone marrow cells and I would make more blood. In the patients this protein is active all the time without any signal because it is mutated, and this appears to be driving the disease process. And therefore by inhibiting the protein we would limit the number of bad cells that are growing in the patients and allow normal cells to grow to some extent. So we would shift the balance between the abnormal cells that grow and the normal cells that are suppressed.

And I think this is what we see in patients like Marty where we see that patients benefit from the medications, perhaps not by eliminating the disease, because the disease is still present, but to less of an extent, and we have many more normal cells in the patient. His anemia has resolved. His strength is back. All signs and symptoms of the disease get under much better control, and patients continue to live a productive life.

Andrew Schorr:
It's just an amazing story. Now, there's another part that I didn't quite understand. So you look at somebody and you say, are they a candidate for this trial, as Marty has been, and you say, okay, we're going to try the medicine on them. But then you see other people where they don't fit that same model, and you try the medicine on them, and it's working there too. That's amazing to me.

Dr. Verstovsek:
That was a surprise to us as well at the beginning. And it seems to have something to do with this activation of the JAK2 protein in the normal cells or in the bad cells without mutation. And the biology behind this clinical finding of everybody responding to the JAK2 inhibitors is not quite clear. It seems that we don't really need to identify patients with the mutation for patients to benefit, and therefore the studies that we have, and there are a number of studies over the last couple of years that we have conducted here at M. D. Anderson, does not discriminate patients based on a mutation or not.

It is also important to say that over time, since 2007, we have discovered some additional mutations in myeloproliferative diseases that try to explain to us what is going on. These are mutations in MPL, Mpl receptor for thrombopoietin. This is a growth factor for platelets, also TET2 mutations, so we are here witnessing a rapid gathering of knowledge in the field which hopefully will give us a new target for these patients and a better indication even than what we have right now.

Andrew Schorr:
It sounds like this is a very exciting time in this area.

Dr. Verstovsek:
It is, like it's exploding in front of our eyes over the last four or five years.

Determining the Need for Treatment

Andrew Schorr:
Now, you mentioned that there are some people who are just watched, and it can be very slow. They lead a normal live, you monitor. So how do you determine who needs to get active treatment and who doesn't?

Dr. Verstovsek:
This is an excellent question for practical purposes because, first, we have to realize that we don't have any medication that has been approved as a therapy for primary myelofibrosis, the most difficult of the myeloproliferative diseases. We have no knowledge of a medication that would alter the natural course of the disease. In this situation, therefore, any therapy that we have been using over the last decades was applied or given to the patients with the purpose of helping the patients overcome perhaps anemia or any other signs or symptoms of the disease. So a rule of thumb is to treat the patient when there is a real need to treat the patient, to correct something that impacts on his or her quality of life, not just because the patient has the disease.

So this is what we are applying when we have clinical studies as well. Patients who really suffer from the disease requiring frequent transfusions or losing weight or having a big organomegaly, like a big spleen or liver that's causing a lot of

symptoms, these are the patients that are participating in our studies. If a patient has the disease that does not cause major problems, those patients are usually observed.

Andrew Schorr:
And what is the name or the investigational name for the medicine that Marty has been taking?

Dr. Verstovsek:
Marty has been taking medication called CEP-701, C-E-P 701, one of the several JAK2 inhibitors that we have been investigating. There are about five or six now. Other JAK2 inhibitors that have been in clinic since, and the response and the quality of response is different among them. The toxicity, some of them have been seen on occasion. So there are differences among them. They are not all the same, but on the positive side it is so exciting to have a variety or race to get to the good quality JAK2 inhibitor for the patient's benefit.

Andrew Schorr:
No kidding. This is a happy story. I'm delighted to help tell it.

We're going to take a quick break, and when he continue we're going to get deeper into the story. We'll also hear some advice from Marty Prager about advice for people listening on how with these rare conditions you connect with the latest research and a treatment center that's right for you to give you the best chance for a long life and a high quality of life. All that coming up as we continue Patient Power right after this.

Connecting with an Expert

Andrew Schorr:
Welcome back to Patient Power sponsored by M. D. Anderson Cancer Center. I'm Andrew Schorr. And we are talking about myeloproliferative disorders, and we have with us someone who has benefited from the latest research at M. D. Anderson. He came from Burbank, California, to go down there. That's Marty Prager, almost 61 years old, who was told that his life was going to be ended by a serious myeloproliferative disorder, and he wanted to seek out really what the latest was and to see if it could make a difference, and it did. And it continues to as he takes an oral liquid medicine twice a day, and he continues to work at a major motion picture studio, active, not feeling tired anymore and doing well. We hope that goes on for a long, long time.

We're also visiting with his doctor who is a renowned researcher in the field, and that's Dr. Srdan Verstovsek. And Dr. Verstovsek is a medical oncologist, associate professor in the department of leukemia at M. D. Anderson. Doctor, let's go back and learn a little more. So here we are, there are a variety of conditions. You talked about sort of what was the indication of treatment, and you have a number

of medicines now that you're learning to use. But they're still all investigational. So these experimental medicines are not available everywhere. How does a patient connect with the right trial investigation for them? How does that happen?

Dr. Verstovsek:
There are several possibilities here, and internet obviously opens a door for people to explore possibilities in much more detail. Traditional way is for an investigator to present the findings of the trials or announce the trial at a major medical meeting where participants in the public, this would be local oncologists or hematologists, will learn about it and perhaps call up the office, like my office, and inquire about possible participation of his or her patient, but now we have a way of communicating through the internet and having, for example, a web page. Like M. D. Anderson has a dedicated web page for myeloproliferative disease, and we list all our clinical studies and eligibilities for everybody to see and learn about. It does list everything in detail including the follow-ups, so the patients can directly learn about it and contact our office.

Or an electronic newsletter through membership of American Society of Clinical Oncology or American Hematology Association doctors, which would be about 20,000 doctors. This comes out every month. Then the specialized meetings for myeloproliferative diseases, the one that Marty participated is quite unique on its own. It is a physician-patient conference that happens in Scottsdale in Arizona every two years, and it is unique in that we really engage together in trying to address the more important factors, not just from the physician's perspective but from the patient's perspective in a unique setting. And that gets recorded on DVDs and on the web, transcribed for patients to exchange over the blogs on the internet. So the connection and information sharing has quite advanced over the last few years.

Andrew Schorr:
Right. And Marty, I wanted to get your perspective too, when you're talking about a rare condition and you'd never heard of this, right?

Marty:
That's correct.

Andrew Schorr:
And for me chronic lymphocytic leukemia, although more common, still nothing I'd ever heard of other than to be terrified, I got on the web too and connected with other patients. Because you've never heard of it, but it doesn't mean nobody has ever had it, and a lot of patients now become very knowledgeable, and they're sharing their information. So, Marty, it was really through help connecting with the CMPD Education Foundation that you began to get educated, right?

Marty:
Yes, that's absolutely true. The CMPD Foundation was founded by Joyce Niblack.

Andrew Schorr:
Yes, I know Joyce.

Marty:
And Joyce just passed away just in the last couple of months, tragically.

Andrew Schorr:
Oh, I'm sorry to hear that.

Marty:
And she deserved so much credit for organizing the CMPD Foundation as she did because there's hundreds of people benefitting from this now. I wouldn't have learned about Dr. V., I wouldn't have learned about anything, I think, without her organization.

Andrew Schorr:
Let me ask you about another thing. So you learned a lot, and you found out that the expertise like Dr. V.'s is not on every corner or at every hospital or even in a big city like L.A. and so you chose to go to sort of action central, and the research made a huge difference. So you got on a plane, and that's what seemed to be a wise choice.

Marty:
Yes. One of the things that Joyce taught us, and I only got to meet her once, in 2007, and that was you have to be your own advocate, and you have to be extremely proactive. I am a proactive person in my daily life and in my work, but as far as being my own advocate, that was something new to me. But I put this into practice, especially like when I met Dr. V. at the conference and it's worked out very well for me. I think this is a really important aspect that people overlook. They tend to accept the medical community's diagnosis, and perhaps eventual outcome without challenging it. We're all different. Each one of us is an individual, and we all are going to react differently to different diseases, so I figure that to be an advocate is essential.

Andrew Schorr:
Well, you touched on something else. I agree with everything said. So Dr. V., we're talking about a range of disorders, and you're talking about all sorts of genetic mutations and trying to understand of these fortunately growing list of experimental drugs you have, which is right for which patient when. So it would seem like with myeloproliferative disorders it is very important to at least consult with a center such as yours where you all have experience with a range of incarnations, if you will, of these disorders.

Dr. Verstovsek:
I think this is crucial for the overall good outcome of any therapy because you have to put this in perspective, like you said, how many patients have these diseases. So ET and PV, being the easier ones that the patients live longer, much longer, decades with it, and that everybody needs even therapy, you have about two new patients diagnosed with these diseases per 100,000 people in the United States, so maybe 6- to 8,000 patients newly diagnosed with each of these every year. But when you come to primary myelofibrosis, the number is even lower. It's about one new patient per 100,000 population, so maybe 3,000, maybe some say a little more, up to 5,000 new patients every year. So if you see how few patients actually get to be diagnosed with this and you spread that over the United States, not too much people see too many patients with these diseases. And you need the expertise to judge correctly what would be the best therapy and when to institute the therapy, how to address the needs and problems that the patient has.

Andrew Schorr:
Right. And as I realize so much now, so you're a medical oncologist, but you work with colleagues who are pathologists who are looking at the slides and the samples and many other specialists who work as part of your team, all of you specialize in looking at this group of illnesses, and that is not in many places. So my message, and, Marty, I bet you back me up, is if you're diagnosed with one of these conditions and you have these acute symptoms as you did, you've got to as quick as you can get in some sort of a relationship with a center where they specialize in it.

Marty:
Yes. I heartily agree with that statement.

Andrew Schorr:
Okay. And how was your experience at M. D. Anderson?

Marty:
Incredible, in a word. I can't say enough about the organization.

Research and Treatment for the Future

Andrew Schorr:
Well, Dr. V., so let's look ahead. So you're very encouraged now. You said it's exploding. So for people who do need treatment do you believe now that the options will either continue to increase or with the tools you have now just in the last couple years that you'll learn to use them even better?

Dr. Verstovsek:
So in terms of where we're heading just in the near future, among these five or six JAK2 inhibitors that are in clinic right now and that are being developed as a therapy for the most difficult myeloproliferative disease, the myelofibrosis, I think that within couple of years, two or three years maximum, at least one of these

medications will be close to be approved by FDA as effective therapy because we see tremendous change in the quality of life in symptoms and signs control of the disease like Marty has experienced, and I think this is very important for patients where we don't have any other medications to use.

The new developments with the new discoveries of abnormalities in myeloproliferative diseases will bring us a new layer of perhaps different targeted therapies that we may either use as a single agent or combined with the JAK2 inhibitors for even better results. So I think the field is really booming in that aspect, and there is in my view huge hope that maybe five years down the road we'll have several new options on the market.

Andrew Schorr:
Well, I'm delighted to help tell this happy story. The other thing is, you know, when somebody is diagnosed with something really serious and then they hear there are things in research or in the lab, it's often frustrating that they're in the lab and not in the clinic, but it seems like this is an example where you all were working really, really hard to make this available to patients like Marty even in an investigational way.

Dr. Verstovsek:
I think for the success of any new therapies there is a need for a team effort. And you have companies or academic centers that are even developing new medications, but this is really a drug development part. Then obviously you would need physicians who are focused on a particular group of diseases or one disease and invested in clinical development of these medications. But the most important is for the patients to participate and realize the abilities and potential of new medications helping out the patients, and it may not help them right away directly, for the patient's community to benefit from that in the long-term. So the patient's participation and the close relationship with the investigators and with the industry is crucial here, and I cannot emphasize this enough.

Andrew Schorr:
Marty, let me ask you about that just for a second because there may be people listening to our program and they hear these words clinical trial, and they say, not me. I'm not going to be, guinea pig is probably the worst characterization. But for you it's been maybe lifesaving, and you made an informed decision, just as I did to be in an M. D. Anderson phase II trial. What would you say to people as far as participating in research and what a difference it could make?

Marty:
I'd have to say it's a personal decision, and I think that personal decision is driven by possibly the severity of the disease, length of time, the quality of a person's life, that sort of thing. I mean, when you're given three to five you're going to be a little more open-minded about research. This, I think, is what helped me make the decision. And the fact that I met Dr. V., and we hit it off immediately, I felt very comfortable with him, I felt that he wasn't going to subject people to drugs that

might harm them, that he had a very personal level of interest in me, and I felt very good about it. Just as I felt very bad about the first doctor I met in my HMO, I felt very positively about Dr. V. I don't know, I had a relative back in the 1960s who was dying of liver cancer, and she said she'd go to Africa if there was a cure. Well, I only had to go to Houston.

Andrew Schorr:
Well said. And I'm glad it's worked out. So what's your view of the future, Marty?

Marty:
I pretty much take it day by day. I'm trying to get a little more quality time in with my wife. We're doing a little more traveling than we were in the past. I'm trying new things. You know, this could all end very quickly, it could last a long time, but I'm not taking any chances. I'm being a little more adventurous than I used to be.

Andrew Schorr:
Well, good for you. But certainly your current condition sure beats the alternative, doesn't it?

Marty:
Yes, very much so. It's been like opening a new door in my life.

Andrew Schorr:
Well, I'm going to look for some more motion pictures that you're involved in. I'll look for you on the credits, okay, Marty?

Marty:
I'm towards the end.

Andrew Schorr:
Towards the end of the credit, but not towards the end of your career.

Marty:
That's right. Towards the end of the credits.

Andrew Schorr:
I'll look for that. Thank you for joining us.

And, Dr. V., it probably does your heart good to hear Marty tell his story and how he feels and remember when you first met him, that it's worked out this way so far.

Dr. Verstovsek:
Oh, this is an amazing story. The primary myelofibrosis is a pretty difficult field because we haven't had anything to offer to the patient, and it just was devastating to all of us. And now we cherish all the successes that we see, like Marty has lived through, and I hope that this is going to last for a long, long time.

Andrew Schorr:
Amen. Well, Dr. Srdan Verstovsek at M. D. Anderson and your work with your colleagues in myeloproliferative disorders, we wish you continued and growing success, okay?

Dr. Verstovsek:
Thank you very much. It was my pleasure.

Andrew Schorr:
Thank you for joining us.

This is what we do on Patient Power. I'm so delighted we have support of M. D. Anderson. I learn so much from the patients and the experts, and you can see how devoted all of them are to helping you. Remember, knowledge can be the best medicine of all. Thanks for joining us.