

Promising Therapies For High-Risk Melanoma

September 16, 2009

Kim Margolin, M.D.

Tracy Filipi

Please remember the opinions expressed on Patient Power are not necessarily the views of Seattle Cancer Care Alliance, its medical staff or Patient Power. Our discussions are not a substitute for seeking medical advice or care from your own doctor. That's how you'll get care that's most appropriate for you.

Introduction

Andrew Schorr:

A simple mole or a bump, could it be melanoma? Melanoma is one of the most dangerous cancers, but promising therapies are giving patients with advanced stages of melanoma hope for recovery. Hear from a Seattle Cancer Care Alliance expert, a high-risk melanoma patient and the role of clinical trials for this type of cancer, all coming up next on Patient Power.

Andrew Schorr:

Hello and welcome to Patient Power sponsored by the Seattle Cancer Care Alliance. I'm Andrew Schorr. If you have an unusual bump or mole on your skin it can be skin cancer, and one fear is that it could be malignant melanoma. Now, melanoma can show up in other parts of the body. If it spreads it can be very dangerous, and over so many years, let's face it, we have not had great therapies for it beyond cutting it out with surgery.

Well, there is promise now for therapies for high-risk melanoma. We're going to hear about that today on our Patient Power program and hear the research that's going on across the country but also at the Seattle Cancer Care Alliance, and we'll hear from a leading melanoma expert, a medical oncologist. But before we do, let's meet one of her patients. That's Tracy Filipi. Did I say it right, Tracy?

Tracy's Story

Tracy:

You did, Andrew.

Andrew Schorr:

Okay. Tracy is 52 and lives right outside Bellevue, Washington, not far from Seattle. And let's go back to 2006, Tracy. What did you notice on your cheek?

Tracy:

I noticed a bump, a small bump to start on the right cheek, and it just wasn't going away. And it was like a pimple, but it continued to get larger and had a little stinging touch to it.

Andrew Schorr:

Now, it was red, right?

Tracy:

It was red.

Andrew Schorr:

So anybody would say, well, I've got some kind of little pimple. I'm not a teenager, but it will probably go away. But yours wasn't.

Tracy:

No.

Andrew Schorr:

So you checked with your general practitioner, and you're told, well, it's probably, what, a spider bite?

Tracy:

A spider bite, uh-huh.

Andrew Schorr:

Oh, my. You go to the dermatologist, and you want to find out what it is, and eventually they do a biopsy. What did the biopsy show?

Tracy:

It showed that I had a malignant melanoma.

Andrew Schorr:

That's terrifying. Had you heard of melanoma?

Tracy:

Oh, yes. Yes. I'm the last in my family to get it.

Andrew Schorr:

Wait. You mean there were others in your family who had developed melanoma?

Tracy:

Yes. They had skin melanomas. My melanoma is different, but they all, five members have had skin melanomas. My melanoma grows from the inside and then out.

Andrew Schorr:

Well, nevertheless, now, were they able to survive the melanoma?

Tracy:

Yes, uh-huh.

Andrew Schorr:

Well, that's good news. But the point is you had this that was growing, so you get referred to the Seattle Cancer Care Alliance and a renowned cancer surgeon,

Dr. David Byrd. What was Dr. Byrd able to do back in 2006 with the spot on your cheek?

Tracy:

Dr. Byrd, we decided to do a wide area incision to remove the melanoma, and so that's basically cutting out about the size of a silver dollar around the melanoma to make sure that they got it all.

Andrew Schorr:

And you had reconstruction then.

Tracy:

Yes, I had a plastic surgeon.

Andrew Schorr:

And they looked of course to see, was there any evidence, they did a sentinel node biopsy, was there any melanoma that had spread, and at that time it appeared it had not.

Tracy:

At that time it appeared out of the node that they removed there wasn't a melanoma.

Andrew Schorr:

But we should tell our listeners, and I think we all know this if we've been around cancer care for a while, cancer is pretty wily and it can hide, and even just a few cells can spread, and it's very hard sometimes to detect them. And so in 2008 you're, I think, on a business call or something and something popped. That was that?

Tracy:

Yes. I was, sometimes anger saves your life. I was a little fed up with a particular customer of mine who was having an issue, and so anyway my blood pressure went up, and I could just feel my neck tightening and then (?) poof! I heard a pop in my ear. And I immediately put my hand on my neck, and I felt a bump. I say it was hiding. It had been hiding behind the vocal cord or whatever muscle was down there, and it was about the size of a BB. And it was about two inches south of the original tumor, so I knew immediately that I had a problem. On Monday morning made a doctor appointment with my GP again and started the rounds. I saw him, I went back to the dermatologist.

Andrew Schorr:

Back to Dr. Byrd. And I guess your worst fears were realized in that it was, it did turn out to be a spread of the melanoma.

Tracy:

Yes.

Andrew Schorr:

To what? Near the salivary gland?

Tracy:

Yes.

Andrew Schorr:

Okay. So surgery again, more extensive.

Tracy:

Yes.

Andrew Schorr:

And so when it spreads then, as many people know, then you start saying, well, is there some sort of systemic therapy to go after the melanoma wherever it is.

Tracy:

Yes.

Andrew Schorr:

And that brings up to a medical oncologist who specializes in melanoma at the University of Washington and Fred Hutchinson Cancer Research Center and of course the Seattle Cancer Care Alliance, and that's your doctor, Dr. Kim Margolin, who is a professor there. Dr. Margolin, so melanoma. It is a wily cancer and it can be an aggressive cancer. So in this case where it had progressed with Tracy, would you call that stage III?

Dr. Margolin:

Yes. It had progressed to a stage III.

Andrew Schorr:

All right. And that's where some kind of systemic therapy is called for?

Dr. Margolin:

It's very important that we find an agent that can reduce the likelihood of a relapse in patients with stage III, but we don't have any good drugs yet. So it's called for, but what's really called for is our ability to discover something that works really well. The available therapies don't work well and they're highly toxic, so we're looking for something that both works better and is less toxic and can be given to everybody.

Andrew Schorr:

Well, let's go over the history of what you have had. Melanoma, when it spreads, and certainly it advances and can spread to organs around the body, it is really a tough go, isn't it. And you just have not had the tools historically, have you?

Dr. Margolin:

That's correct.

Andrew Schorr:

So therefore research comes into play, and you're very much involved as a clinical investigator. So did you then discuss with Tracy that maybe a clinical trial could be a reasonable option?

Dr. Margolin:

Yes.

Andrew Schorr:

And what trial was available as Tracy was showing up as someone with high-risk melanoma?

Trials for High-Risk Melanoma Patients

Dr. Margolin:

Well, as it just so happens at about the time we first met Tracy we were just about to sign the final papers on a very interesting trial that was based on a promising melanoma vaccine that had shown some activity in patients with advanced melanoma. It's important in many instances that we, before we start using these drugs or these agents in the postoperative setting where we can't really see what the effect is on an individual, that we at least be using something that has demonstrated activity in patients where we could actually observe the activity. So that means that almost everything that we use, or that we test in the postoperative setting, which we call the adjuvant treatment setting, has shown some activity in patients whose disease has spread and which we can follow.

So this is a melanoma vaccine that's based on an antigen or a substance that about two-thirds of melanomas produce, and you can check it by doing special pathology tests on the tissue that was taken out of the patient and stored in a wax block. And patients whose tumors do have that particular antigen can then go on a study where they have about a two-out-of-three chance of being randomly assigned to receive a vaccine that's based on that antigen versus a one-in-three chance to receive a placebo. The placebo is important because we don't always know what the side effects might be from a particular treatment, particularly if that treatment is given over long periods of time as well as it may be a very low-risk treatment the side effects of which might mimic life in general and the little things that people run into such as a flu or a chill or some muscle aching, and that's what we often see with vaccines. So it's important to know which of those effects came from the drug and which ones may have just come because the patient is just in the world.

Andrew Schorr:

Let's back up for a minute, Dr. Margolin, just to explain some of the science to people. I have had the privilege of interviewing you and other experts for a long time, so I maybe know enough to be dangerous, but many people when they here this term, "vaccine," they think of, you know, the shot, polio vaccine or something you got to prevent a disease. But here we're talking about somebody who already

has a disease. So when we talk about sort of anticancer vaccines for people who already have the cancer cells and we talk about antigen, let's go over that.

So is it the idea, let's see. You're the professor. Let's see if I get a good grade. Is the idea that you're going after some property on the cancer cells and you have some, in this case, medicine that you inject that targets that to try to turn that cancer off after you already have it? Is that the idea?

Dr. Margolin:

Yes, this is, yeah, Andrew, you got a pretty good grade there.

Andrew Schorr:

Okay.

Dr. Margolin:

It's basically that the types of vaccines that we use in patients who have already had a diagnosis of cancer might be called secondary vaccination or secondary prevention. As you say, the patient already has the cancer. This is not preventing cancer. And what we're looking for is the ability to stimulate a group or a subset of the patient's white blood cells to be able to recognize that protein or antigen on whatever residual cancer cells might still be in the body that got into the circulation or got into the channels or into the local skin before the tumor was removed and that cannot be detected in any fashion.

The primary prevention vaccines in cancer almost do not exist although you could say that those papillomavirus immunizations that are given to prevent cervical cancer are a form of primary prevention, but they still rely on individuals having been exposed to the virus.

Vaccine for Melanoma?

Andrew Schorr:

All right. So when the vaccine finds the melanoma cells is it turning them off so they can't proliferate? Is that what the hope is?

Dr. Margolin:

Yes. The hope is that they will actually be destroyed and that they will be eliminated permanently. We do not trust any melanoma cell that's been anything but killed dead. Even if it's stalled or prevented from proliferating, melanomas, as well as many other cancers, are highly susceptible to secondary mutations and they can become activated again, so we try to, we really don't recognize anything between life and death when it comes to melanoma.

Andrew Schorr:

All right. And just to help people, a little bit of terminology. So you mention antigen, so a property on the melanoma cell. What is the name of what you're targeting?

Dr. Margolin:

The name of what we're targeting in this instance is MAGE-A3.

Andrew Schorr:

Okay. And as you said, two-thirds of the people who are getting these shots, an intramuscular injection they get at the clinic, are receiving the medicine. One-third are not, although certainly they are given the best of standard therapy and monitoring.

Dr. Margolin:

They're given the best of monitoring, and standard therapy in this situation is no therapy postoperatively. So, yes, you could say they're getting the best of what we know.

Andrew Schorr:

All right. Tracy, so you were told about this trial, and maybe you knew that the melanoma therapies heretofore were not great. Knowing that there was a one-third chance you'd get a placebo but a two-thirds chance you wouldn't and it could be something very promising, you decided to enroll.

Tracy:

Yes. The alternative was interferon, a choice of that, or not, and then I think we were just so fortunate that this opportunity arose at the time that I needed it as an option.

Andrew Schorr:

Right. So you've been getting shots for about how long now?

Tracy:

Well, let's see. That had been during the snow, so January. Does that sound right, Dr. Margolin?

Andrew Schorr:

2009?

Dr. Margolin:

Yeah, yeah.

Andrew Schorr:

And Tracy, side effects, things you've noticed from the medicine?

Tracy:

No, nothing, I keep trying to pinpoint side effects. I just don't get side effects, so.

Andrew Schorr:

But you also haven't found another lump.

Tracy:

I have not. Six months clear.

Andrew Schorr:

Okay. All right. That's great news. We want to hear more about research, what's going on there at the Seattle Cancer Care Alliance and, in this case, the fight against melanoma as it may be someone who is at high risk, like Tracy. Want to hear more about Tracy's hope for a long live and also about other research approaches as well. So it's all coming up as we continue our discussion on promising therapies for high-risk melanoma, sponsored by the Seattle Cancer Care Alliance and produced by Patient Power. We'll be right back.

Andrew Schorr:

Welcome back to our discussion on malignant melanoma and promising therapies for people who have high-risk melanoma and where we really worry about it spreading further and shortening their life. And as we talked about earlier, the available therapies over many years now beyond surgery, which really has played a key role and we have had other programs with Dr. David Byrd from the Seattle Cancer Care Alliance about that, what about systemic therapies and ideally targeted therapies. And even carrying it further we're really coming into the age of personalized care for the cancer you have, not just the name of it, let's say, in this case, melanoma, but the characteristics of your melanoma.

So Tracy Filipi from outside Seattle in the suburban area, Fall City, and works in Bellevue, Washington, she's in a clinical trial for just that approach right now, targeting characteristics on her melanoma cells. And there are other trials under way as well, so to help us understand that we're going to go back to Dr. Kim Margolin who is a melanoma specialist and a medical oncologist.

Dr. Margolin, it sound like melanoma therapy is coming of age, if you will. It sound like a lot of work is going on there. Are you encouraged?

Dr. Margolin:

I am optimistic and encouraged about the tremendous explosion of knowledge about what make melanoma cells tick over the last several years. And I think that, unlike what happens in some cancers where we may almost stumble upon a blockbuster drug and then kind of go back to the laboratory to figure out precisely how it works and then how we can dissect the patients who most benefit from it and the combinations we can use, I think melanoma is acting more, as it were, like AIDS perhaps, where we have had nothing but bad outcomes and bad luck and all of our bad luck has led us to tremendous efforts to sort out the genetics and the inner workings of the melanoma cells and to get an understanding of the fact that it is not just one tumor but many different species. And then we now have many agents and strategies for development that will allow us to much more intelligently select and test agents or combinations that may be far more promising than anything has been in the past.

Understanding the Patients Specific Disease

Andrew Schorr:

All right. Let's talk about what that means. So people may be listening anywhere in the world to this program, and they may go to their local doctor or their local hospital, and if it's diagnosed as melanoma there have been certain standard approaches. Maybe it's been, we'll cut it out as we can. Tracy mentioned interferon therapy, which can be a tough go, but it's been around for a long time but not highly effective for this. But maybe there wasn't a genetic workup. Help us understand about where genes and damaged genes come into play and what you do at the Seattle Cancer Care Alliance to try to understand that specific patient's scenario, if you will. Not just one disease but what's their disease.

Dr. Margolin:

Well, most of this work, which is very promising that I've been referring to, is still in the laboratory, and it's not quite ready to apply routinely to treatment selections for melanoma or to putting patients into different categories such as we now are able to do for almost all breast cancer patients, and vast majority of lung cancer patients and a substantial percentage of colorectal cancer patients. Nevertheless, in conjunction with all of the clinical trials that are being done, all of the ones that I'm aware of that are being done currently and that are being designed for the near future, there is a strong component of laboratory analysis and molecular and genetic analysis of the tumors so that at the end of the day, at the end of the trial we will be able to go back and say, well, patients who did well had the following gene signature or pathway activation pattern, whereas patients who didn't do well had this other signature, this other pattern or some immunologic features that would suggest the likelihood of a poor response.

Now, in melanoma I think there may be some unique features that have much more to do with the interrelationship between the tumor and the host or the patient than is the case for other tumors. So for example in breast cancer you might say that the vast majority of breast cancers, if they respond so Taxol it's because the Taxol kills the cell, and if they don't it's because they pump it out or because they've got some other mutation. Whereas in melanoma many of the strategies that are currently being tested have to do with either stimulating the immune system of the patient, so it's at least as much about the patient as it is about the tumor, as well as some of the newer targeted agents that may have several targets and they're not as focused as we think. And they may be designed for example to inhibit a particular pathway that is overly represented in a melanoma tumor that's growing quickly, but they may have as a secondary target blood vessel formation around the tumor or something again to do with the immune system that we may be able to take advantage of, so that we have to really cast a very wide net and look at a whole number of different things in all of these research correlates that we do.

And I have little doubt that within the next five to ten years, hopefully sooner, we will stop lumping melanoma patients together to select therapy, and we will start really looking at seven or eight different groups of people who are characterized by genetics, by their own genetics as well as the tumor's genetics and other features and that our job in a sense will be a lot easier and a lot more effective as

oncologists.

Andrew Schorr:

I was in a phase II clinical trial, and in my case a leukemia. I remember the first day they pulled ten tubes of blood. I had never had that before, and I had a bone marrow biopsy and lots of tests and extensive ones that I had not had before. But I recognized that not only was I in a trial but maybe I was on the forefront of change. Tracy, so when you hear, you have these CAT scans and you're involved in a trial, are you glad you came to the Seattle Cancer Care Alliance, and you hear Dr. Margolin where you, do you feel like you're on the frontier but maybe that there's significant change that is just over the horizon?

Tracy:

I definitely think I'm on the frontier. It's an experiment that could ultimately be a cure or a way to extend life or to kill the melanomas. And, yes, I'm a guinea pig, and you have to make that option when you go on these clinical trials.

Andrew Schorr:

I did it too.

Tracy:

Yes, but, you know, I also, even if I am a placebo person I'm still part of the study because I still have an outcome, and I'm very glad to be in the program.

Andrew Schorr:

Now, Tracy, I should mention that you have been married for about seven years now to a wonderful guy, that you ride a Harley. What is it called, a road,

Tracy:

Road Glide.

Andrew Schorr:

Road Glide. And it has a queen seat, and with Leo you sit in that queen seat and you are the queen. So, obviously, that's your dream, that you get to do that, ride off into the sunset many years from now. But we recognize that you have a difficult disease, so we hope that it will, you know, that there will be knowledge that will come out of this. Dr. Margolin, you must really feel a great debt of thanks to people who participate in the trials, because I know not everybody does.

Dr. Margolin:

Enormous.

Andrew Schorr:

Yeah. I feel that too, and I encourage people all the time. Now, you used this word, I don't like to use it too much, Tracy, guinea pig, because it has the sense of stuff being done to you, and, you know, you're not a person, and there is a lot of caring that goes on. Tracy, but still you recognize that there can be knowledge that not only could benefit you but could benefit everyone.

Tracy:
Absolutely.

Andrew Schorr:

Okay. Well, Dr. Margolin, let's talk about some other approaches. So we talked about the vaccine. Are other approaches to repair genetic damage, or what else is cooking in melanoma?

Repairing Genetic Damage

Dr. Margolin:

Well, it's interesting that you have focused a little bit on this concept of repair of genetic damage. I think that's probably the furthest away from the line of ordinary clinics. It's a more difficult concept to really address. There are many different ways of looking at that, and in fact all the way back to why certain patients get certain cancers, they may be born with defects in repair of genetic damage such as the BRCA gene mutations that are known to underlie breast and ovarian cancer in certain families.

However, the more common situation is that cancers are not born out of a known constitutional or inherited problem with DNA, and they're more likely to have arisen from either something we don't know about in the constitutional genome but secondarily environmental damage and any number of things that we don't really understand. All cells are mutating and going through changes, and in fact one of the problems with, one of the many, many features that underlies resistance to some of our chemotherapies is that cancer cells sometimes are particularly good at repairing genetic damage, and because some of our drugs actually work by creating problems with the DNA we're looking for the ability to kill cells that don't have the machinery required to repair it.

Nevertheless, there are a number of other targeted agents and approaches that take advantage of Achille's heels that are generally considered pathways, metabolic pathways or proliferative pathways that are unique to the tumors. In fact some tumors are even characterized by up regulation or overexpression of certain chains of pathways that protect them from undergoing the death mechanism that cells are supposed to do when they've reached their natural lifetime, so that these cells are protected against programmed death and we are looking for agents that can interrupt that protection against programmed death and allow the programmed death to occur the way it's supposed to.

Andrew Schorr:

All right. Let me just jump in for just one second because I get the science but not everybody does, maybe. And that is, so what you're looking for is unique things on those cancer cells that can allow you to turn them off when they don't, I always think of it like a copy machine with cancer cells. It won't turn off. It's run amok, and it's producing, it's filling the room with bad paper copies. So how do you turn the machine off, and is there a unique way to do that which will have medicine that

will spare healthy cells. Because isn't it the traditional chemotherapy kind of cuts a wide swath, right, and that's where you get side effects. So the idea is if you have targeted therapy hopefully you would greatly reduce side effects for the patient as well.

Dr. Margolin:

That's also correct, yeah. The problem with the, your analogy is good and you can use that to explain the whole problem, because what you've got is a roomful of bad copies. They're in the way, and so it's not only do you have to turn off the machine that's spewing out the bad copies but you have to have a way to clear the room of them. They're not disintegrating as fast as they're supposed to, or they're not getting picked up by the guy who does the recycling.

Andrew Schorr:

You need the trash man or the recycling.

Dr. Margolin:

Yeah. And unfortunately, because these cells are so smart, it seems that no matter what you do, if you can find one very important pathway or mechanism for their overproduction or their under-elimination and address that effectively, most of the time one or a few renegade cells will figure out a way to change and avoid that, just like the swine flu and all those other things we hear about in the news. Everyone knows what mutations are, changes in the genetic material that make these targets evade the ammunition that we have for them.

Andrew Schorr:

Wow. Well, the point that we're, you know, I'm just excited that we're talking about it at this level because it seems like you're on the right track, I believe. I know there's several tracks being followed. And, Tracy, wouldn't you agree that with Dr. Margolin and her peers around the country and around the world, really getting down to the cellular level, that that should be encouraging for people and families like yours that have been affected by melanoma?

Tracy:

Absolutely because if this vaccine accomplishes what they want it to do and makes my body go after any new cancer cells, then you can pretty well say I'm going to be cancer-free.

Andrew Schorr:

Yay. And lots of Harley rides.

Tracy:

Lots of Harley rides into the sunset.

Dr. Margolin:

But keep your sunscreen on, on the Harley.

Tracy:

I know. I know.

Andrew Schorr:

Let's mention. We have to say that for everyone, you know, you mentioned, Dr. Margolin, about environmental triggers, and we certainly know whether it's more common skin cancers or melanoma, that really protecting yourself from environmental damage from the sun, and no tanning booths, is so important. So I want to underscore that.

Dr. Kim Margolin from the Seattle Cancer Care Alliance and a melanoma specialist, I want to wish you and your colleagues all the best with your research, and hopefully we can do another program before long and you have what I hope is exciting data and maybe, it's definitely going to be with folks, I hope, like Tracy who say, look at this, because it happened to me in leukemia. Tracy, I wish that for you. Dr. Margolin, that's my wish for you, okay?

Dr. Margolin:

Thank you very much Andrew.

Andrew Schorr:

And, Tracy, I just want to thank you as someone who is in a clinical trial. It takes some courage to sign all those papers and go down that road and show up to the clinic for a vaccine with a good chance that you're getting the actual medicine but not always sure, but knowing that you're playing a role, hopefully helping yourself but helping a lot of other people too. Thank you for doing that, Tracy.

Tracy:

You're very welcome.

Andrew Schorr:

This is what we do. I meet incredible people, medical practitioners, researchers like Dr. Margolin and really wonderful people like Tracy. I'm going to wave to her when she and Leo are going down the road past me, and I hope I see that for many years to come. This is what we do on Patient Power sponsored by the Seattle Cancer Care Alliance, connect you with leading researchers and really inspiring patients. And we certainly heard that about high-risk melanoma today. I'm Andrew Schorr. Thanks for joining us. Remember, knowledge can be the best medicine of all.

Please remember the opinions expressed on Patient Power are not necessarily the views of Seattle Cancer Care Alliance, its medical staff or Patient Power. Our discussions are not a substitute for seeking medical advice or care from your own doctor. That's how you'll get care that's most appropriate for you.