PATIENT POWER

Northwestern Memorial® Hospital

Stem Cell Treatment for Heart Repair
Webcast
February 26, 2008
Douglas Losordo, M.D.

Introduction

Andrew Schorr:
Hello and welcome once again to Patient Power sponsored by Northwestern Memorial Hospital. I'm Andrew Schorr. When you talk about these two words there's a lot of confusion: stem cells. Stem cells, what are they, first of all, and can they be the way to helping people who could be very sick get well in a variety of areas. And one of our biggest health problems is of course heart disease. Can stem cells help repair the heart?

Well, Northwestern has been leading the way, and one of the leaders at Northwestern is Dr. Doug Losordo. Dr. Losordo is the director of cardiovascular regenerative medicine at Northwestern Memorial Hospital. He's also director of the Feinberg Cardiovascular Research Institute, and for many years now he's been studying how to use stem cells in new ways to get people back some better health. Dr. Losordo, thank you so much for being with us and helping us understand this area that can be controversial or at least confusing for some people request and then understand some of the clinical trials you have going on at Northwestern Memorial that for some people with very seriously impaired health, where it could give them the chance of doing better. Thanks for being with us.

Dr. Losordo:
It's a pleasure to be here. Thank you.

What are Stem Cells?

Andrew Schorr:
So let's start with stem cells. What are we talking about and help maybe clarify the confusion.

Dr. Losordo:
I think that's a great place to start, Andrew, because there is a lot of perhaps confusion about what a stem cell is, and I think if you'll excuse the pun that stem from the fact that our knowledge about these cells and about progenitor cells, which are close cousins to stem cells, is really advancing at a very fast pace. So as the science a moving quickly I think the average person's ability to grasp what's happening is really challenged.

But I think the excitement that's come into medicine in the last few years around the potential of stem cells and their use therapeutically really involves the observation that cells from our own bodies may have the potential to repair tissues and to reverse disease processes in a way that we previously really didn't think were possible. You know, for example in cardiology one of the long held dogmas really was that after heart attack your heart muscle tissue was irreversible damaged and there really was no opportunity to salvage or recover that muscle function. And one of the exciting things now that we've shown experimentally, and many groups have repeated these experiments, is that in fact that's not the case. Heart muscle that's been damaged by heart attack it looks like can actually be brought back to life in part by taking advantage of the natural biology of stem cells in our own bodies.

Andrew Schorr:
Wow. I think we need to understand stem cells. So I have this image. I know we make blood cells and other cells in our bone marrow, and these cells then go out and in the stem cells we have create other kinds of cells, bone, muscle, skin, all sorts of things. So is it the idea to take these very early stage cells and use them then to regenerate different parts of the body that have become sick, if you will?

Andrew Schorr:
Right. I think that's actually a great place to kind of focus the conversation because it's a concept that maybe people are a little bit more familiar with it, and that is the stem cell as something that gets transplanted to reconstitute the bone marrow. So almost everybody knows somebody or has a friend or a friend of a friend who's had a stem cell transplant usually in the setting of malignancy, and so as you just suggested the concept that allows that or the feature that allows that to work is that there are cells in our bone marrow that really are in a sense immortal. What is a stem cell? It's a cell that is capable of dividing for an indefinite period of time, that is, the cell will continue to propagate itself we think indefinitely. That's one of the key features of "stemness," if you will.

But the other feature that you just suggested as well is the ability of that cell, which is, if you will, kind of a vanilla cell when it's in its purely stem state, that is, without many features of a specific cell type, that cell can differentiate into multiple different cell types. And previously the concept was really that the bone marrow stem cells were capable exclusively of reconstituting bone marrow and the circulating blood elements. But recent work has really shown us that those same cells are in fact capable of differentiating into many different tissue types.

Our lab's focus has been on the ability of those bone marrow derived cells to form new blood vessels, something that before 1997, just 11 years ago, was not really known, and now it's widely accept that the bone marrow is in fact capable of providing cells that can build new blood vessels in places where they've been lost.

Uses for Stem Cells

Andrew Schorr:
Wow. That is so cool. And first of all, congratulations for the work you've been doing in your lab for so many years now with these discoveries.

One other point I wanted to make is some of the controversy about stem cells is were they taking cells from fetuses, for example, or cell lives? That's not what we're talking about here. We're talking about taking your own cells and then having them differentiate in ways that you need to grow new blood vessels, as you were saying. So let's talk about the trials you have going on and where this applies to people who really have very serious health problems. I know you have two trials now. What are the health problems that patients who might be in this trial have and how could this potentially be an answer?

Dr. Losordo:
Right. The two studies that we have running right now are, as you suggest, really focused on patients who have really exhausted the conventional therapeutic armamentarium. That is to say that they have taken advantage of the best that medicine has to offer and despite that really have very severe symptoms. And the two patient populations we're talking about are individuals with congestive heart failure and then individuals with severely blocked leg arteries and a condition known as critical limb ischemia. In that latter patient population, critical limb ischemia or CLI patients, these patients have pain at rest because of the very severely reduced blood flow to the legs. Many of them are taking narcotics just so they can get sleep at night and also may have the early phases of tissue breakdown or gangrene as the tissue begins to die because of the severe lack of blood supply.

The congestive heart failure patients are largely patients who have had prior heart attacks, have had bypass surgery, angioplasty or stenting and are taking the best of medicines and despite that are really disabled because of their heart failure. They get short of breath or just don't have the energy to do normal daily activities. So those are the two groups of patients that we're attempting to help with these therapies by replenishing the blood supply either to the leg or to the heart, restoring function by restoring the supply of oxygenated blood.

Andrew Schorr:
Okay. Let me see if I understand. I'm going to spit this back to you in a way that I kind of process it as a lay person. So let's take somebody who has impaired blood

flow to their limbs, terrible pain, as you said. May need to take narcotics, can't sleep. I've read that some people have to sleep in a chair because if they're sitting in that position maybe they'll feel a little better, but nevertheless with reduced blood flow and getting oxygenated blood they may be in a position where they lose their toes or their feet or their limbs, amputations, and I know there's something like a hundred thousand amputations a year in the US. So a very serious health problem.

On the heart side, and I know my dad had had angioplasty and things like that, and it worked for him, but I imagine if the drugs and the angioplasty and the other part procedures don't work you're just in increasingly failing health. You don't have much quality and no way to live. So is the idea then that you can manipulate a patient's own stem cells to let's say in the limbs, create new blood vessels. The stem cells kind of are trained somehow to create new blood vessels or new blood vessels to the heart.

Let's take it in the limbs, for example. What are they doing? Are you injecting them in? Are you infusing them in? What's happening from a science point of view?

Dr. Losordo:
I think you actually put your finger on one of the features of the particular cells that we're using that makes them to us a very attractive therapeutic candidate, and I refer to this as tearing a page out of nature's play book. After we discovered these cells 11 years ago, these progenitor cells floating around the circulation, we started to study how these cells work, what do they do, how do they behave and so forth. And it turns out, just as you said, these cells kind of know what to do once they find themselves in a certain situation.

So for example if one takes one of these endothelial progenitor cells, so these are the blood vessel forming stem cells, we call them EPCs for short. If one takes one of those EPCs or a bunch of them and injects them into a muscle in which the blood supply is fine, the cell will just find its way back into the circulation and go back home into the bone marrow because it's not needed there. You take the same cell and you put it into a muscle that is lacking a blood supply, that is severely ischemic, that's the term we use to describe muscle tissue that's lacking blood supply and lacking oxygen, then that cell and its counterparts will stick around, find its way into an appropriate location to begin assembling blood vessels, will recruit in other cells from the circulation to help in that process, will secrete various growth factors in that neighborhood again to stimulate the formation of those blood vessels and gradually begin to restore the circulation there. So there's a bit of preprogramming in these cells that enables them to form new blood vessels in the appropriate locations where, as I said, in a situation where they're not needed they behave in a completely different way.

Andrew Schorr:
This is so cool. I have this image of these sort of pipeline workers who are sitting around a bar or hotel, they're just lounging around. They don't have an assignment, and then you recruit them and you put them on a train and you take them where they need to go and what these guys need to know how to do is build a pipeline, build a blood vessel. And then they say, Well, this is what we do. Let's go.

Dr. Losordo:
That's a great image. I hope that's not copyrighted because I'm probably going to borrow it the next time I talk to a patient.

Repairing Damage to the Heart

Andrew Schorr:
I think of building the railroads, building the pipelines, and this is what people would know how to do, and these cells seem to have this ability. You just have to put them in the right place at the right time.

Let's talk about the heart. So, as you said, the impression was for so long, someone has a heart attack, there's cut off or reduced blood flow to the heart muscle. The heart muscle dies or some of it that may survive is scarred, but I think you were getting at earlier that there's some heart muscle that has been deprived of some blood but is still alive, and if you could just get more blood flow to it again it could start doing the job again.

Dr. Losordo:
That's exactly right. So it's actually now been pretty well shown that after a heart attack there certainly is damage to a certain percentage of the heart muscle, and that ultimately becomes fibrotic or scar tissue. And then of course there is remaining healthy muscle. But in between there's a pretty sizable zone of muscle tissue that has gotten enough blood supply to stay alive but does not have enough blood supply to function normally. And we refer to that as hibernating myocardium, myocardium being the heart muscle. That hibernation term is I think somewhat self explanatory. Everybody understands that bears hibernate in the winter, and they do so to conserve energy. The muscle tissue in the heart does the exact same thing. It goes into a state of hibernation so that it can remain alive by conserving all of the oxygenated blood that it's getting and using that just to maintain the muscle cells and keep them alive, but it's not getting enough blood supply to function normally.

And we've shown in our preclinical models and the animal studies that if one takes an animal that has had a heart attack and scar tissue and restores the circulation in that hibernation zone then that muscle really comes back to life and starts functioning again and pumping blood again as if it were normal.

Andrew Schorr:
Wow. This is so cool, I have to tell you, Dr. Losordo. So let me see if I can put this in perspective for people. So unfortunately there are millions of Americans with diabetes and have heart problems from that. People have hypertension. People have obesity problems. Smokers. And then some people just have genetics that get in the way as well, lifestyle issues. But no matter what, you end up with either circulatory problems we were talking about or also circulation, if you will, to the heart, and we have the heart problems, heart failure where the heart can't pump efficiently or the other problems we were talking about, terrible pain and lack of circulation to the limbs.

So here we are now thinking of the heart again, what would somebody's options be, trying to unblock the arteries, get blood flow going again or in extreme cases maybe a heart transplant or there are a variety of drugs, I guess, to try to get the heart to pump a little better, but your approach is get some better blood flow going again. Somebody may have already tried angioplasty or could they even have had bypass surgery, but still now we say, well, can we grow new blood vessels?

Dr. Losordo:
Yes, that's exactly right. There is in fact a large number of people out there. The heart transplant population is a good one to mention. Of course there are a number of heart transplants done around the country every year, but there are many, many more people on transplant lists, and that tells us that these patients have really exhausted all the other available options and still have very severe heart failure. In addition to those people who are listed for transplants there are people with slightly less severe heart failure, not bad enough to transplant yet but still quite disabled, and they've had just about everything done, including many of them multiple bypass operations to try to improve circulation, and there just comes a point where those operations are no longer possible.

So this therapy absolutely targets those patients who have really tried everything else, and we think we can help a significant percentage of the folks in that situation. There still will be patients who have so much scar tissue that a transplant remains their best option. But I do think a day will come when by taking advantage of therapies like ours that restore circulation and then other therapies that are being worked on now to take some of that scar tissue and actually restore the muscle cells that have been lost, combining those approaches I think we can perhaps begin to dial back the clock a little bit on folks who have had these severe events and get them out of trouble and maybe reduce the need for transplant.

Harvesting Stem Cells

Andrew Schorr:
Wow. Dr. Losordo, let's get into the nitty-gritty a little bit because I'm sure there are people listening who are hanging on every word and may be in those very serious situations. So first of all help us understand in the trial, what do you do? How do you get the stem cells you need from that patient, and then what is the producer for sending them to where they need to go and over what period of time, and what are the risks and implication complications that go along with it after it is a clinical trial?

Dr. Losordo:
Okay. That's great. In both cases, both the study for improving the circulation in the legs and the study for heart failure patients, a lot of the procedure is actually very similar. Normally in our circulation the number of these circulating stem cells is quite low, and so the first part of the procedure involves giving a medication, a drug that's been used for the past decade or so to increase the number of circulating white blood cells. It's called G-CSF, stands for granulocyte colony stimulating factor, and what that medication does is to stimulate the bone marrow to produce and release these stem cells into the circulation.

So after five days of that drug the patient undergoes an outpatient producer called apheresis. It kind of looks like dialysis, but it really is a method of collecting a population of the white blood cells, the so-called mononuclear cells, which contain the stem cell population. So those mononuclear cells are collected by this outpatient procedure. The patient goes home the next morning. The stem cell population is purified on a commercially available device that's been used to purify what's called a CD-34 cell, which is one of the stem cells that comes from the bone marrow. So those cells are purified on this device. And then for the leg patients those cells are injected directly into the muscle of the leg. It's a simple procedure using a standard syringe, a needle, and ten injections of the cells are administered into the muscle tissue in the area that's lacking the blood supply that I mentioned before, that so-called ischemic muscle, where we think those cells will then take hold and begin the process of restoring the circulation.

In the heart it's a little bit more of a complicated procedure. We still want to administer the cells into the muscle, but this requires a so-called catheterization. It's the same type of procedure that would be done, say, to perform an angiogram to take pictures of the coronary arteries, but in this case a catheter, a specially designed catheter is inserted into the cavity of the left ventricle, that's the pumping chamber of the heart. It's a steerable catheter system that has some mapping capabilities, and that catheter is touched to the inner surface of the heart muscle, a needle is expended, and the cells are injected again in ten locations within the area of the muscle that's lacking the blood supply, so the muscle that's alive but not functioning because it's lacking the blood supply.

<u>Treatment Risks</u>

Andrew Schorr:
Okay. Help us understand any downside to this as far as from the treatment. Obviously people are sick when they have this, but what's the downside? What are the risks? And how long would this go on for a patient? How long would they be in the trial?

Dr. Losordo:
The risks, I guess, can be broken up into several categories. The first would be the risk of getting the G-CSF drug. So because the drug has been around for so long and millions of doses have been given, the risk profile of that medication is pretty well known. So some patients will have some discomfort in their bones as the bone marrow is turned on, if you will, to start producing these cells. Some people get a little bit achy. It can increase the levels of certain blood cells called platelets, so there's a little bit of a risk of clot formation, so that's one of the things that we certainly keep an eye out for. So the risk profile of the G-CSF is pretty well known and pretty well tolerated by most patients.

The next potential issue is the injection procedure. So in the legs it's a very straightforward intramuscular injection, again a procedure that's very familiar to most patients. There's a little bit of pain associated with that when the injection is done but similar to any other injection that you would get. So that's relatively lower risk.

The injection to the heart muscle is trickier, as I was suggesting. So there we're steering a catheter into the heart and extending a needle into the wall of the beating heart, so you can imagine there's the risk that the catheter could make a hole in the side of the heart and cause leaking of blood and that sort of thing. Fortunately the mapping catheter system that we have gives us some capabilities to monitor that very carefully and avoid those complications, but still I think that's a potential risk of the procedure.

Other than that, one of the things that we don't have to encounter as far as risk is the risk of rejection since the patient's own stem cells are being used. Patient doesn't have to take immunosuppressive medications or anything like that. The cells are their own, and so that that risk isn't there.

Benefits of Therapy

Andrew Schorr:
How quickly would someone see a benefit if it is going to work?

Dr. Losordo:
Well, interestingly, and as I think I tried to allude to in one of my earlier comments, we think that the injection of these cells into a tissue that's lacking blood supply stimulates a process, it's sort of like a domino effect is the way we view it. It starts a process that appears at least in our early observations to go on for a few months. And so in reality as opposed to a lot of procedures, an angioplasty the patient feels right away. The blood vessels open up, symptom relief is instantaneous. Here the process of building blood vessels, it appears to take a few months, and so patients tend to in our observations begin to feel better after two, three, four months following the injections. So it is a process that takes some time.

Research and Hope for the Future

Andrew Schorr:
How excited are you? I mean, you've been working on this, you've been spending your career on this, so this has been a long time. At this point where we are now and now with these trials at Northwestern, a lot of questions to be answered, a lot further to go, but how excited are you to be at this point?

Dr. Losordo:
Well, you know, I feel very lucky. It's a very exciting time in medicine. I think the discovery of these stem and progenitor cells in our bodies really has the potential to kind of change a lot of the paradigms that have existed. It really could change the way we practice medicine, and I just feel very fortunate to be involved in this work right now and have the opportunity to move the science and especially the clinical practice of regenerative medicine forward. I think we're going to look back on this time as one of the really golden ages of medicine because I think it stands to benefit patient a great deal.

Andrew Schorr:
Well, we wish you well with that. And of course for people who are in the trials, hopefully they will get some benefit themselves, for sure, and they will be really partnering with you and other researchers to try to answer key questions and improve therapy still further. So I know you're a principal investigator there at Northwestern. Are there other sites where this is happening too?

Dr. Losordo:
Yes, absolutely so. Now in the critical limb ischemia study, that will be a nationwide study with center across the United States. The heart failure study is

being launched here at Northwestern, but after the pilot phase of that it will also be a nationwide study, so patients around the country will have the opportunity to participate in these studies. And I am very glad that you brought up the aspect of patient participation in these studies because of course without the pioneering efforts of patients who are willing to participate in these studies medicine would be at a standstill.

And I have to say that I am in constant awe of the courage of people, first of all the courage that people have when they face these really tough conditions and then second of all the, really, the community spirit and the willingness to help that these people exhibit. Because they know that they're entering into an experiment. They know that what they're trying is not proven and yet despite the fact that they've already been dealt a pretty tough hand as far as the disease they're still willing to step up and help others in the future by their participation in studies. And that to me is a source of inspiration and awe on a pretty much daily basis.

Andrew Schorr:
Absolutely. Now, Dr. Losordo, if someone listening wants to get involved in the trial, how do they do it? How do they do it at Northwestern? Who do they talk to? Who do they call? How do they get the ball rolling?

Dr. Losordo:
Sure. The easiest way is to call me, and my office will always refer any calls about, inquiries about trials directly to me, and then we can answer patients' questions and see if in fact they are appropriate candidates and if they're interested bring them in for a visit. All these trials are listed on the clinicaltrials.gov website, which is a national listing of all clinical trials. And that's actually a nice resource for patients because by entering a few research terms you can usually find active clinical trials pretty easily.

Andrew Schorr:
And I'll also mention that right on the Northwestern Memorial Hospital website, nmh.org, you can just look up Dr. Doug Losordo and away you go, and it has all his information, and you can go from there.

Well, Dr. Doug Losordo, director of cardiovascular regenerative medicine at Northwestern Memorial Hospital and a man who's devoted his life to try and answer some of these questions and with colleagues around the world, really, see how can stem cells be used to regenerate blood vessels, regenerate heart muscle and just help people be healthier. Thank you so much for all your devotion to this, all your hard work, and I wish you a long career and a Nobel Prize some day. Wouldn't that be neat?

Dr. Losordo:
Well, thanks very much. I think the patients get the Nobel on this one, but hopefully we'll move this forward together.

Andrew Schorr:
Okay. Thank you so much.

I just want to mention that on our next Patient Power program we're going to switch gears. We were talking the heart transplant a little while ago. We're going to talk about solid organ transplant. That's a program on March 11 with Dr. Michael Abecassis. We've done programs with him before. It's a fascinating area too. And that's coming up on Patient Power.

Remember, the whole library of programs is in the HealthNet section of nmh.org. Please tell others about it. Look at the replays and the transcripts. And we hope our program today with Dr. Losordo has been very helpful.

Dr. Losordo, all the best, thanks again for being with us.

Dr. Losordo:
Thank you very much.

Andrew Schorr:
You've been listening to Patient Power sponsored by Northwestern Memorial Hospital.