

Non-Myeloablative Mini Transplants

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Rainer Storb M.D.

Hosted By Andrew Schorr

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Introduction

Andrew Schorr:

Hello and welcome once again to Patient Power. I'm Andrew Schorr. Another one of our programs connecting you with leading experts from Seattle Cancer Care Alliance. One of the things that has made Seattle famous in medicine of course has been bone marrow transplant pioneered at the Fred Hutchinson Cancer Research Center, and one of the pioneers is with us today, and that's Dr. Rainier Storb. He's head and member of the transplantation biology program at the Fred Hutchinson Cancer Research Center and the Seattle Cancer Care Alliance. He's also professor of medicine at the University of Washington. And one of the most exciting areas of transplantation now as it continues to evolve is doing what's called non-myeloablative or mini transplants and allowing people to have this approach who couldn't before. Either they were thought to be too old or too sick. So our program today with Dr. Storb is to help us understand what is that approach, who is it right for and where is it headed.

Dr. Storb, thank you so much for being with us on Patient Power.

Non-Myeloablative "Mini" Transplants vs. Conventional Transplants

Dr. Storb:

You're welcome.

Andrew Schorr:

Dr. Storb, let's define the term first. Many people, and of course you've been one of the pioneers of it, have come to understand bone marrow transplant and whether it was your own cells or someone else's trying to help someone who was very sick with a leukemia or multiple myeloma, one of those illnesses, to have their immune system be restored but often have to go through total body irradiation, all that, sort of drive them, their immune system down very low or not at all before they could accept the transplant. What does it mean to have a non-myeloablative transplant?

Dr. Storb:

The non-myeloablative transplant, in contrast with the conventional transplant, relies on a conditioning regimen that does not necessarily really touch the tumors. It's so mild, if you wish, that the tumor cells actually remain on board, and its only purpose is to immunosuppress the patient to a point where the patient will accept the transplant from a donor, which the donor can either be a sibling or an unrelated individual. So the actual regimen is mild. So if the graft fails for instance for one reason or another the patient returns to status quo. With a conventional transplant the patient would not return to status quo and would remain seriously aplastic, that is the patient wouldn't produce any blood cells and would eventually be at risk of dying. So the non-myeloablative transplant allows marrow recovery in case the graft fails to function.

Andrew Schorr:

So I'm going to state this back a little bit, see if I understood it as a lay person. With a traditional bone marrow transplant you're just pretty well knocking out that ailing patient's immune system. In the case of a non-myeloablative transplant you're just sort of nicking it. You're just sort of knocking it back a little.

Dr. Storb:

That's correct. You're essentially nicking it, as you said, in order to give the transplant a slight edge, if you wish, immunologically. As a result the transplant gets established, and the tumor eradication is actually solely dependent on what's called graft versus tumor effects. Graft versus tumor effects are immune reactions of the transplanted donor lymphocytes and perhaps other cells which are called natural killer cells against cell surface determinants that are expressed on tumor cells, whether they're leukemia or myeloma or lymphoma, and these immune reactions eventually lead to eradication of the underlying cancer.

Andrew Schorr:

So is the idea that the sick immune system, if this were a boxing match, I have this visual image, but you take the sick immune system, which is one of the players in the boxing match, and you kind of tie one hand behind its back, and then you have the healthy donor immune system that gets in the ring they're probably going to win because you've given them an edge.

Dr. Storb:

Yes. That's actually a good analogy. So what's happening is that not only does the sick immune system get knocked out but also the tumor cells, and that has to do with as I already indicated the presence on virtually all body cells but especially also on the blood-forming tissues of cell surface determinants that are unique to the patient and which the donor recognizes as something that doesn't belong there. So you get an ensuing immune reaction. It may take sometimes, I think in our longest patient it took two years or two and a half years before the last vestiges of

tumor were gone as evidenced by testing with incredibly sophisticated molecular technologies that allow us to determine one cell in a million, if you wish. So the immune system of the donor sets out to eventually eliminate the tumors.

Candidates for Transplantation

Andrew Schorr:

Well, it's certainly cool just thinking about this battle and how it goes on over time but hopefully with these donor cells being the eventual winner on the patient's behalf. So that brings us to who can be a patient. What were the criteria traditionally, and how have those changed?

Dr. Storb:

For a sibling transplant in most academic centers the upper age range was 60. For an unrelated transplant again in most academic centers including ours here it was at around 50 years of age. Anything above that the feeling was that these patients won't do well. Secondly, even in younger patients, say, the existence of an infection, say a fungal infection, disqualified the patient for a transplant. Further, the existence of a heart problem, a lung problem or say a patient was on renal dialysis because of a dysfunctioning kidney, that all disqualified patients from a conventional transplant. The feeling was that these patients just couldn't be managed without incredibly high risk of dying from the transplanted procedure.

Now all of these rules have been loosened, if you wish, and as a result for instance we have transplanted patients up to 78 years of age. I remember very vividly a patient last year, a gentleman from the Midwest who was 78, had a history of cardiac problems, several stint placements, had a history of epilepsy and lots of other things, and yet we accepted him for transplantation. He had his share of problems but eventually was discharged home at three months after transplantation. And I just happened to receive a letter from him, that's why I remember him, about a week ago where he reported he's doing well.

Andrew Schorr:

Great.

Dr. Storb:

So those are the kind of patients who are now actually acceptable for transplant.

How do Non-Myeloablative Transplants Relate to Other Cancers?

Andrew Schorr:

Now, what about the illnesses that you're focusing on with non-myeloablative transplant now?

Dr. Storb:

They are first of all malignant diseases, such as the acute lymphoblastic and myeloablative leukemia's. They are the chronic leukemia's, such as chronic myelocytic and lymphocytic leukemia's, the myeloma's, and then a whole slew of different non-Hodgkin's lymphomas. These are again usually patients who have reached the end of the line as far as conventional therapies are concerned.

Additionally we have myelodysplastic syndromes, myeloproliferative diseases, Hodgkin's lymphoma and then some rare instances of Waldenstrom disease and so on.

As far as nonmalignant diseases are concerned, usually we talk about children with genetic diseases who have complications that prevent them from getting a conventional transplant. Among these genetic diseases you have a whole slew of different immunodeficient diseases, and owing to the immunodeficiency, many of these patients have serious infections that the physicians just can't get rid of until they have a normal immune system, so those patients are also candidates for many transplantations.

Optimism in the Future of Transplant Therapies**Andrew Schorr:**

Dr. Storb, now where are things headed? That's where you are today. What's sort of looking forward where you think perhaps there's an opportunity?

Dr. Storb:

Well, the current regimen still includes a drug called fludarabine, which is often used in cancer therapy, and it includes a very small dose of total body radiation. It's a total of two gray, which can be administered in the outpatient setting. What I'm hoping eventually is to replace both the fludarabine and the irradiation with modulators of T cell function. Specifically, there's a whole slew of molecules that can be produced or have already been produced that block, if you wish, the T cell core stimulation. Specifically when an antigen triggers the T cell receptor the T cell in addition needs core stimulatory signals from the antigen presenting cell that if interrupted lead to apoptotic cell death of that T cell which has been activated.

So the idea is to eventually pretreat the patient with a small infusion say of a donor mononuclear cells along with a set of these core stimulatory blockers or down regulatory molecules. And that actually instead of using radiation and fludarabine will set the stage for, if you wish, tying the hand behind the patient's immune system back. So we will get the graft on board with just very mild pre-transplantation therapy. That's number one.

Number two; with a number of diseases across the board we actually still experience a failure of transplantation in the form of relapsing disease. So what we hope to do in the future, and this is really fairly futuristic, is to eventually be able to determine what antigenic differences exist between the patient's blood-forming tissues and the donor's blood-forming tissues and then isolate those peptides which we by then have recognized as relevant and immunize the donor cells against those particular antigenic differences between donor and host and thereby increase the tempo of the graft versus tumor effects and the magnitude and thereby we hope eventually eliminate the issue of relapse.

Andrew Schorr:

Wow.

Dr. Storb:

So those are some of the things that we're working on. You know you can now do actually a shotgun sequencing of somebody's genome in about a week actually at fairly low cost. At the moment it's still about \$2,000 per run, but that's going to come down, and that would eventually allow us actually to carry out these studies almost in a routine way. There's machinery coming along that's pretty spectacular actually.

Andrew Schorr:

Well, I would say what you've done over your career is pretty spectacular. It's just amazing, and for you to see this coming even if it's not just around the corner is incredible too.

Now, we've had a question and I'm sure it's one you get asked all the time. If you've made all this progress with these less toxic approaches to transplant, where is still the need for the traditional approach? What illnesses, what situations?

Dr. Storb:

Well, that's a very good question. And for the patients with say acute myelocytic leukemia and certain myelodysplastic syndromes that have progressed to acute myelocytic leukemia and have been brought into remission with chemotherapy, one must realize that that's not curative chemotherapy, so they're in apparent remission but they still have tumor on board, for those patients we believe the non-myeloablative transplant is as good as a myeloablative transplant. We for that reason have begun a randomized prospective study comparing the two modalities in younger patients. The problem with that is it's very difficult to actually get this across to the patients. They just don't like to be randomized and as a result have preferences, and I'm not sure that we will be able to complete this study in due time. So that's one group of patients where we believe the non-myeloablative transplant approach is as good as anything else. And the same is beginning to be true for patients with non-Hodgkin's lymphoma and for patients with multiple myeloma. So I think we are begin to move downwards in age.

Andrew Schorr:

Okay. But as far as a place for the traditional transplant are there some diagnoses, some situations where you say, We've got to go there, we're not confident that the non-myeloablative transplant approach would apply to you?

Dr. Storb:

I think that's true for almost all patients with a high disease burden. Say an acute myelocytic leukemia patient whose disease has refused to go into remission, say, that patient is at the moment still candidate for a myeloablative transplant. And the same is true for acute lymphoblastic leukemia and perhaps for certain patients with non-Hodgkin's lymphoma whose disease seems to be entirely refractory to any therapy and has very large disease burden. So I think there the myeloablative transplant at the moment still here the Hutch has priority.

Defining a "Mini" Non-Myeloablative Transplant**Andrew Schorr:**

Okay. Dr. Storb, now what about this word "mini"? So we've been saying non-myeloablative. Some people and maybe around there too it's called a mini transplant. It's certainly mini compared to the traditional approach, but it's still, it's still a big deal. So maybe you could put it in perspective as what, and you said along the way that it doesn't always work. So help us understand a realistic picture of what is it and what expectations people should have.

Dr. Storb:

The word "mini" really is only refer to go the magnitude of the conditioning regimen. So for a, say, myeloablative transplant the patient either receives something like 12 to 14 gray of total body radiation plus high doses of a drug called cyclophosphamide or something similar or high doses of a drug called busulfan combined with a drug called cyclophosphamide. So these are all very intense conditioning regimens that cause a lot of morbidity and mortality.

The mini transplant is characterized by the three doses, and the myeloablative transplant is always done in a fairly intensive care setting inside the hospital. The mini transplant relies on the three doses of fludarabine, which are given over three consecutive days, and those are given in the outpatient department, and this is followed by two gray instead of 12 to 14 gray of total body irradiation. That's in a range where we do not expect issues of sterility. The patient does not experience for instance side effects such as vomiting, diarrhea, mucositis, hair loss or anything like this. So the "mini" basically indicates that this transplant is fairly mild. It can be done in the ambulatory care setting. The actual transplant of stem cells of bone marrow is just the regular, old-fashioned transplant. So it's a full transplant. The subsequent complications that might arise, such as graft versus host disease, while perhaps a little less frequent and a little less severe are still issues that we have to

deal with. Then finally we still are dealing with issues such as relapse. It isn't working in every case, nor is the conventional transplant working in every case, and so these are the issues that we have to deal with.

And we are working on novel and hopefully more effective approaches at graft versus host disease prevention, but these are at this point in the laboratory and we hope will be applied somewhere over the next three to four years clinically. And also, as I indicated, we hope that we will eventually use genomics approaches for specific sensitization to peptides expressed on hematopoietic cells that will enable us to induce much more effective graft versus tumor effects than we currently can do. So currently we're still basically flying blind. We cannot predict which patients will develop graft versus host disease and which will not. We cannot predict exactly which patients will relapse and who will not. So those are the things that actually the future will have to address, and I'm hopeful that we can in the long haul.

Andrew Schorr:

Dr. Storb, you and your team have paved the way in this approach, not just in the Seattle area but for patients from around the world. This approach now, beyond being done at the Seattle Cancer Care Alliance is it very common, obviously you all have sort of invented this, but is this something that people can find many places elsewhere or it really is something that you've specialized in?

Dr. Storb:

No. From the very outset actually we have attempted to export this technology, and we are working with a number of academic centers both in the United States and in Europe who are using the protocols that have been developed here and who meet with us actually once annually here in Seattle for continually developing these protocols. So it can be done in other centers.

Graft-Versus-Host Disease

Andrew Schorr:

So looking at this now then, you mentioned about graft versus host disease, and you mentioned about the man who is now 79 who wrote you and seems to be doing well. If somebody sort of comes out the other side of this and it seems effective in the short term and the graft versus host disease or other complications are minimized or maybe don't happen for them, what can they look forward to in going ahead with their life?

Dr. Storb:

Well, if they don't have ongoing graft versus host disease and say have reached a time point of two to three years after transplantation the risk of relapse actually diminishes at that point, and frankly they should be able to lead perfectly normal lives.

Andrew Schorr:

Wow. It's really, it's just, I have to ask you, Dr. Storb, so now you look back on this kind of continuum where you had these very, very major therapies and now you've refined it and expanded it to more and more people, more illnesses. You're looking at where you've done the traditional transplant, and now you can do the non-myeloablative, and you're looking at new areas now to set the stage where for it being more successful more of the time. How do you feel when you look at all this?

Dr. Storb:

I don't know, it just feels perfectly normal. Part of my job is to develop new ideas and then be driven by curiosity and being driven by what you see when you're attending on the transplantation services. I attend two months a year, straight two months, and I see a lot of issues and problems, so that drives me back to the laboratory wanting to deal with these problems. And as I said the major ones are really graft versus host disease and relapse of underlying disease. For both of these we hope to develop novel approaches over the next several years in order to deal with it. So I don't feel in any special way, shape or form special. I just, it's just part of my job, and I enjoy actually what I'm doing.

Future Challenges and Current Progresses**Andrew Schorr:**

Well, Dr. Storb, I've met a number of people who have had transplants the Hutch and Seattle Cancer Care Alliance and I know they would feel I was remiss if we didn't say a big thank you to your and your team, Dr. Thomas, just everybody. And looking forward to this then, then the question comes up, sort of getting back to reality here, and that is, well, should this approach be used earlier when somebody is diagnosed? You mention about other people where other options have been tried, but if it can be so highly effective and if you can develop ways of making it more effective for more people, then where does it fit in the continuum of treatments that are offered, drug therapies, etc.?

Dr. Storb:

You know, at the moment I think the procedure still has an associated mortality ranging from 10 to 20 percent at three years, and I think that's what keeps physicians and patients away from having these transplants done earlier. And so they are exploring the newly emerging drug therapies that are continually developed by pharmaceutical industry before they consider throwing in the towel and undergoing a transplant. So I think unless we bring down the mortality rate significantly we are still going to be faced with the issue of having late referrals.

Andrew Schorr:

And as far as bringing the mortality rate down, so you've talked about the complications of the side effects, graft versus host, and also being able to look at

somebody on the front end and say how can we make this transplant most successful for them. It seems like that will make a big difference if you can conquer those two challenges.

Dr. Storb:

Yeah. For instance for the sibling transplantations we now have a fairly conventional treatment regimen that has brought down the serious graft versus host disease rate to about four percent acute graft versus host disease. It's staged between grades two, three and four. So the grade three and four rate is down to four percent. So on that front we have made progress, and that should bring the mortality rate down. We really don't have yet long enough follow-ups on those patients, but it should bring it down.

As for unrelated transplants, again we have a three-armed prospective randomized trial going on that has accrued about 105 of the 150 patients who will be entered. That will tell us whether we have made any headway in that setting. In the laboratory we're working on totally novel approaches that if they work, and that's a big if, would actually avoid the necessity for this long-term post grafting immunosuppression. Now, currently the standard is actually a minimum of six months, and in many patients it's longer. What we hope to accomplish is that we will deal with this really right up front, within the first week or so, and then eventually induced graft versus, leukemia graft versus tumor effects by these sensitizations that I mentioned to you earlier, all of that is at the laboratory level at the moment and probably won't see the clinic for the next five or so years, but if we accomplish that I think transplants will become much safer.

Andrew Schorr:

Dr. Storb, there's just one last area I want to ask you about and it's not an idle question for me personally since I'm a chronic lymphocytic leukemia survivor and I've had a long remission and I'm familiar with Fludara, fludarabine, which is part of the regimen. But I've wondered for me or other people if we don't have a living sibling and then you look through the registry and we don't find a perfect match, are we out of luck or is the technology changing where even as we get older a non-myeloablative transplant might be available to us where there's less than a perfect match.

Dr. Storb:

The answer is there are options available, two options specifically. One is cord blood transplant. There are now increasing numbers of cord bloods around the world, and we have and others have non-myeloablative regimens that use cord blood instead of unrelated donor for blood stem cells.

The second option is a relatively new one, a protocol that was developed with colleagues at Johns Hopkins, which employs bone marrow from so-called HLA identical donors. And these could be siblings; children of the patient or parents of

the patient who share one HLA type and are dissimilar for its other. So these two methods probably will satisfy donor availability for virtually every patient.

Andrew Schorr:

Wow. Well, amen to that. That would be terrific. And I think for those of us who whether we need this approach now or might in the future, I think the progress is incredible. And again I just want to say thank you on behalf of the listeners, the people who are affected by this, to you and your team, your colleagues and the other practitioners you're working with around the world to make this more available to people.

Dr. Rainier Storb, I want to thank you so much for being with us on Patient Power and wish you all the best in your work day-to-day in the lab and in the clinic.

Dr. Storb:

Thank you. It has been my pleasure.

Andrew Schorr:

Thank you.

Just for our audience I want to mention that the Seattle Cancer Care Alliance is working a number of areas, and they're encouraging women to access the latest technologies in mammography, and they actually have a Mammovan that is in the ongoing fight against breast cancer. And you can take advantage of this mobile mammography van to reverse the downward trend in women who actually get an annual breast examination. You can find out more by calling the Seattle Cancer Care Alliance at 206-288-7800. Or just go to the website, sccammammography.org.

Our next Patient Power webcast of the Seattle Cancer Care Alliance will be March 12, and that will discuss state-of-the-art colon cancer treatments with Dr. Tony Back. And as always replays and transcripts of our program are available at sccapatientpower.org and also on the patientpower.info website.

I'm Andrew Schorr. You've been listening to Patient Power brought to you by the Seattle Cancer Care Alliance. Thanks for joining us.

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