

Dr. Rainer Storb

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Seattle Cancer Care Alliance – a unique collaboration

Andrew: Welcome to HealthTalk. I'm Andrew Schorr, just back from the 38th annual American Society of Clinical Oncology meeting or ASCO in Orlando, Florida, where cancer specialists from around the world, ranging from clinical researchers to community oncologists, have come together to present the latest in cancer research as well as learn about newer approaches to cancer care.

Speaking with us today, also just back from the ASCO meeting, is Dr. Rainer Storb from the Seattle Cancer Care Alliance or SCCA. SCCA is a collaboration between the Fred Hutchinson Cancer Research Center, the University of Washington Academic Medical Center, and Children's Hospital and Regional Medical Center in Seattle. Dr. Storb is a member of the Fred Hutchinson Cancer Research Center, and he's also head of the transplantation biology program at the University of Washington. Dr. Storb, thank you for joining us on HealthTalk.

Dr. Storb: You're welcome.

Andrew: Dr. Storb, first just a word about the Seattle Cancer Care Alliance, since we're doing this program for patients. I understand that that's really a unique collaboration that draws on the strengths of research from folks like you here at the Hutch, the powerful research that's also going on at the University of Washington, and then also Children's Medical Center. Does that collaboration make the care team and the treatments offered for patients more powerful?

Dr. Storb: Absolutely. As you pointed out, the University of Washington, Children's Hospital, and the Fred Hutchinson Cancer Research Center are rather awesome research institutions and also are really in the forefront of clinical medicine. Putting the expertise of these three institutions together makes really for outstanding patient care such that the new developments in research can be translated almost immediately not only to serve patients treated under the Hutch umbrella but also to patients, for example, at Children's Hospital and at the University of Washington the other way around. There is an intermingling of the expertise of these three institutions.

Andrew: Many people who now seek out the Seattle Cancer Care Alliance are looking for leading edge medicine or even the possibility of being in a very advanced, if you

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will, clinical trial. If they've been very sick and really don't have any hope at other institutions, they come here and often they do have hope.

Dr. Storb: That's correct. The Hutch and now the Alliance is really a tertiary referral center where patients who have basically exhausted the abilities of other institutions are being referred. Given the enormous number of laboratories here, at the University and at Children's, these patients are actually experiencing the rapid translation of cutting edge lab research into the clinic.

Andrew: You have the benefit of smart researchers collaborating as well.

Dr. Storb: Yes. Additionally, I should say that a lot of the laboratory-based researchers are also clinicians. It's called a "physician-scientist," if you wish, and so you have people in the clinic who apply what they themselves have worked out in the laboratory. It's actually an incredibly smooth and powerful transition that the patients then experience. That's why I think this is going to be a very powerful combination of institutions in one place. Here on campus is the ambulatory care building, over at the university and at Children's are the inpatient services, and the staff of these three institutions rotates through all of these buildings. By meeting in the hallways, you meet university physicians all of a sudden and researchers with whom you discuss a complicated case, and so all of that has been really facilitated by having these common facilities.

#### Understanding standard transplants and mini-transplants

Andrew: If that's the state of the art in cancer patient care, let's talk about your particular area of research, which has been in transplantation. Transplant really started here, and now you've been advancing that and made a presentation at ASCO about so-called mini-transplant. Help us understand what mini-transplant is and what it means for patients at a center like yours here in Seattle, the Seattle Cancer Care Alliance.

***The mini-transplant shifts the burden of tumor cell kill from the high dose cytotoxic radiation therapy to the donor T-cell.***

Dr. Storb: For that you have to understand a regular and conventional transplant. In the conventional transplants, you take a patient with leukemia or lymphoma or myeloma, expose the patient to an incredibly strong blast of chemo and radiation therapy, and then rescue the patient with a stem cell transplant from a healthy donor. [Medical Editor's note: The transplant is called a "rescue" procedure because the patient would otherwise die from the effects of the chemo and radiation therapy.] In the course of these studies, we recognized that another very powerful ingredient in the ultimate cure of many of these patients was what's called a graft-versus-tumor effect whereby the transplanted donor T-cells

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recognize foreign antigens or cell surface determinants on the malignant patient cells, and become sensitized to them and then by cytotoxic reactions eliminate them. The mini-transplants make use of that principle of graft-versus-tumor effect and the mini-transplant shifts the burden of tumor cell kill from the high dose cytotoxic radiation therapy to the donor T-cell. That's the principle. [Medical Editor's note: Instead of relying on extremely toxic chemo and radiation therapy to do most of the tumor cell killing, the mini-transplant approach relies on the cell-killing activity of the donor T-cells.]

Andrew: Traditional transplant was you would blast the cancer cells in a patient with high dose chemotherapy and high dose radiation.

Dr. Storb: Correct.

Andrew: Often total body irradiation, and of course that would have its own effect on the patient, and they would be in a weakened state. The hope was you would have donated stem cells or bone marrow, and that would create a new immune system and cure the patient if possible. But if I heard you right, you were saying that maybe all that front-end treatment isn't needed in that the donor cells, the healthy donor cells, could do the heavy lifting and do the killing of the cancer cells by themselves or for the most part.

Dr. Storb: That's very well put. There is the recognition that the high dose toxic therapy, which actually can only be applied to younger patients in good clinical shape, by the way, that that really didn't do the trick. It may have done the trick in 30 percent of the patients. The rest of the cures were actually accomplished by the donor immune system recognizing the tumor as foreign, getting sensitized to it, and eliminating it over a period of time.

Andrew: You made a presentation about this. Obviously, this makes this treatment available for sicker people. What were the limits before for standard transplant, and what is opened up now?

Dr. Storb: The upper age limits for a standard transplant from a sibling at the Hutch were about 60 years of age; at many other institutions, 50 years of age. As for unrelated donors, at the Hutch it was 50 years; for many other institutions, it was lower than that. The median age of transplants here at the Hutch for sibling transplants was 40; for unrelateds, 35 years.

On the other hand, the candidate diseases -- say, chronic leukemias, acute myelocytic leukemias, lymphomas, myeloma -- the median ages of that diagnosis are 65 to 70 years of age, so you can imagine the vast majority of patients with candidate diseases did not get transplanted. The mini-transplant, however, is so mild as far as the toxicities of the regimen is concerned, that you can apply it to an

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80-year-old patient without that the patient would actually even need to be hospitalized.

Andrew: What's been your experience with older patients?

Dr. Storb: The experience has been that something on the order of 60 percent of the patients who have been transplanted with this new approach actually never saw the inside of the hospital. The remainder, in part, were already hospitalized because they were so sick to begin with, or they were hospitalized for maybe five or ten days because of a fever that required continuous infusions of antibiotics for a transient period of time.

*Virtually all of the patients whom we have treated so far have advanced stage disease.*

The treatment was very well tolerated. The patients, for instance, don't lose their hair. They don't experience the bad mouth pain, the diarrhea, associated with a regular transplant. They don't experience the incredible drop in peripheral blood counts that are characteristic of a regular transplant. Their blood counts gradually only decline a little bit, and then they recover.

Andrew: And you've had some people with advanced age?

Dr. Storb: Actually, virtually all of the patients whom we have treated so far have advanced stage disease. That's a matter of policy with a new technology.

Andrew: At what age have some of these people been?

Dr. Storb: I think the oldest patient was age 78.

Andrew: Which you never could have done before.

Dr. Storb: Never could have done before. The median age of our patients who are being transplanted on the mini-transplant is about the age group at which the other protocols cut off.

Andrew: They've also been sicker patients who wouldn't have been a candidate just based on that.

Dr. Storb: That's correct. You can also transplant now younger patients who have co-morbid conditions. They have diabetes, have had myocardial infarcts [heart attacks], have had bypass surgery, have pulmonary function impairment [lung disease] or have

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non-functioning kidneys because of myeloma, for example. All of these patients can now be transplanted with a mini-transplant.

### Using mini-transplants in a variety of diseases

Andrew: What this means, then, is that in the transplant category, a mini-transplant is an option, is available to more people, older people, sicker people, and is more part of the treatment mix with the hope of it being a cure.

Dr. Storb: That's correct, and in fact when you look at the various disease categories, we have seen cures in I would say a majority of patients. Best results so far have been seen in multiple myeloma whereby the survival curve currently is at about 84 percent. Intermediate results have been seen with non-Hodgkin's lymphoma. These are very advanced patients with survivals on the order of maybe 70 percent. We have also seen very good survival in chronic leukemias, chronic lymphocytic leukemia, chronic myelocytic leukemia, in acute myelocytic leukemia and so on. The interesting thing is that the remission accomplished with these donor T-cells does not happen overnight. In some patients, it may take a year and a half before the last tumor marker that we have disappears. It's a slow process whereby the donor T-cells nibble away, if you wish, at the tumor. But on the other hand, you have to realize that sometimes the tumor burden means many, many, many pounds of tumor that have to be eaten away. ["Tumor burden" means the amount of tumor in the patient when treatment begins.] But they ultimately get eaten away, and even with the most sophisticated technology using DNA markers, you can't document the presence of the tumor. [The tumor becomes undetectable with even the most sensitive tests.]

***Best results so far have been seen in multiple myeloma whereby the survival curve currently is at about 84 percent.***

Andrew: It sounds a little bit like the tortoise and the hare. Maybe the hare is some of these other therapies, but now you have an immune therapy, basically, with a new immune system that gets there eventually and maybe does a more complete job.

Dr. Storb: It is in all likelihood going to be more efficient than, say, a drug or an antibody simply because the T-cell doesn't rest until the last target has been eliminated. It's the nature of the beast. A T-cell is a cell that ordinarily is involved in defenses against viral infections. When you get infected with a virus, whether it's a flu virus or whatever, the T-cell does not rest until the last evidence of the virus has been eliminated from the body. The same can be said for the tumor.

### Incorporating mini-transplants earlier in treatment

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- Andrew: You alluded to earlier how it's been used on people with advanced disease. Typically that's what happens with new approaches in cancer. Will this become a more prevalent, earlier option?
- Dr. Storb: Yes, ultimately it will, but it requires what we call a phase three study. For example, currently we are in the planning stage with the National Bone Marrow Transplant Network that's sponsored by the National Cancer Institute involving 18 institutions, 18 academic institutions in this country, to carry out a phase three comparison between our mini-transplant from related donors for multiple myeloma versus the current state of the art approach, which involves an autologous transplant and thalidomide therapy. That study is currently on the drawing boards. When that study has been completed and shows that the mini-transplant approach is superior to the state of the current art therapy for multiple myeloma, it will become the state of the art therapy, including younger patients as well.
- Andrew: Then there would be studies in these other diseases you mentioned.
- Dr. Storb: That's correct. We are currently also looking with the Southwest Oncology Group but also perhaps with this national network at a study in elderly patients with acute myelocytic leukemia, specifically patients above age 55 who with conventional chemotherapy have maybe a 9 percent disease-free survival. The plan would be a natural randomization based on the availability of an HLA-matched sibling. We would treat patients at these various institutions with either a mini-transplant or the best conventional therapy, and again, when that has been concluded, then you can say, "Well, this looks good enough to go into younger patients."
- Andrew: It sounds like, though, there are many options shaping up for older people and sicker people, in a number of these hematologic malignancies. Is this a discussion that a patient might have now with their doctor if they have advanced disease about whether they should be referred today to the Seattle Cancer Care Alliance?
- Dr. Storb: I hope it is. We try to inform referring physicians and through meetings like ASCO or the American Society of Hematology meetings or other meetings like this by presenting in the educational sessions. We also try to inform our own referring physicians by periodic letters. There is clearly a need for education that is very important.

### Comparing the standard transplant and mini-transplant regimens

- Andrew: Just so we understand, you've mentioned that the pre-treatment is very mild. There still is a little bit of chemo. Maybe you could describe if a patient came

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here, mini-transplant was going to be used, what do you do versus what you used to do.

Dr. Storb: What we used to do was to give the patient a drug called cyclophosphamide and at incredibly high doses. That in itself is a very toxic treatment. This would generally, then, be followed by a series of total body irradiations extending over three to four days, amounting to a dose of up to 15 gray, which is an incredibly high dose in the super lethal range as far as the bone marrow is concerned. That's why the patient needs a transplant. The patient gets terribly ill, is hospitalized, needs nutrition through the vein because they can't eat anymore; they're just very, very sick.

The current regimen, the mini-transplant regimen, reduces the dose of total body irradiation from 15 gray to 2 gray. That's a sub-lethal dose. It's below the dose at which infertility occurs. It's below the dose at which you lose your hair, for instance. We add to this three doses of a drug called fludarabine, which is given as a kind of immunosuppression, and that's given in the outpatient department. The whole thing, actually, is mild. The patients eat their regular meals throughout this. They don't need the nutrition through the vein. They don't experience the hair loss, mouth pain, diarrhea that is commonly associated with the conventional transplant regimen.

Andrew: They can be an outpatient, either stay at home if they live nearby, or they can just be at a hotel or apartment nearby if they've come from afar.

Dr. Storb: That's correct, and of interest some of the patients do so well that during the time they are in Seattle, we may see them once a week. I do recall a patient recently when I was attending at the outpatient department telling me at the end of when I discharged him back home to Kentucky, he and his wife thanked me for the nice vacation they had in Seattle. It is a different experience than a conventional transplant.

***The one toxicity that both the regular transplant and the mini-transplant have in common are immunological sequelae of the foreign graft coming on board.***

Andrew: There are in some people, though, some toxicity, some things that happen that need more care. Tell us about that.

Dr. Storb: The one toxicity that both the regular transplant and the mini-transplant have in common are immunological sequelae [results] of the foreign graft coming on board. And the syndrome that may occur in these patients is called graft-versus-host disease, which is a disease that affects skin, gut and liver in the form of erythema [redness], diarrhea, or liver function test abnormalities. This syndrome can occur both in the mini-transplant and in the regular transplant.

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Of interest, though, is number one, it occurs considerably later, maybe in the regular transplant it occurs in the first six weeks. In the mini-transplant, it may occur three or four months later. Number two, it occurs at a lesser incidence and in a milder form in the mini-transplant, and there are a number of reasons to explain that, which are complex and immunological, but it is certainly a stunning finding.

When you also then ask the question, "What about mortality from graft-versus-host disease?" We have recently concluded a comparison of a case-matched control study, and the mini-transplant patients have a significant advantage over the regular transplant patients once they have developed graft-versus-host disease. Overall, it seems like this particular toxicity is less severe and less often fatal than in the regular transplant.

Andrew: When you look at mini-transplant and I know it must vary by disease, and people say, when they think of transplant, "What's my chance of getting through this, doctor?" How do you rate sort of percentages of being able to live so many years?

Dr. Storb: There is a group of patients who come to us who have had a transplant before at another center, an autologous transplant or allogeneic transplant. If we then treat them again with a regular transplant here, it's a highly toxic, highly fatal kind of approach. We lose 47 percent of these patients in the first 100 days with a conventional transplant. When we look at the mini-transplants where we have done an equal number of patients, we lost nobody in the first hundred days. That just tells you that this approach is really relatively mild, and has tremendous advantages in patients who have already exhausted other therapies.

If you have multiple myeloma, we can tell the patient that your chances of being alive in two years are on the order of 84 percent with a mini-transplant. If we would have to tell this to a patient who comes for a regular transplant, we have to say it's on the order of 30 percent. There's a tremendous difference in fatality from the regimen.

Andrew: We talked at the outset about your team here at the Seattle Cancer Care Alliance. The mini-transplant sounds simple, but I'm sure it's not, and therefore the idea of them getting a mini-transplant at the hospital around the corner, the community hospital, is not possible.

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***You have to monitor the patient actually every four weeks for disease status, every four weeks also for how much of his or her blood-forming system is now donor.***

Dr. Storb: I would not recommend it at the moment. The reason is that even though it seems simple, there are quite a few things that are important for success. Number one, you have to monitor the patient actually every four weeks for disease status, every four weeks also for how much of his or her blood-forming system is now donor. You want to know that. You have to monitor the patient every few days for whether or not there's graft-versus-host disease.

It may occur that on day 84, when you are ready to discharge the patient home, all of a sudden the disease seems to make a comeback. You can see the disease coming back if you have a marker, for instance, and you may have to decide to stop the immunosuppression earlier than anticipated. Usually, we try to give the immunosuppression for six months after transplant, but you may have to make the decision to stop it right then and there in hopes of eliciting a graft-versus-tumor response.

All of that needs to be monitored on a regular basis. We get shipments of blood from the patient from their hometowns, which we then examine, and based on the findings make a recommendation to the physician over the phone as to what to do. Clearly, you need an experienced team. That's where the SCCA comes in.

Andrew: Sounds like there's as much art as science at work here.

Dr. Storb: There is some art at work. That's correct. But on the other hand, you make those decisions based on pretty hard findings.

#### Moving forward- where the mini-transplant may take us

Andrew: Dr. Storb, let's just look into your crystal ball for a minute, since you're a researcher right at the ground floor of all of this, and that is where will this evolve to, do you think?

Dr. Storb: The mini-transplant? First of all, we already have begun extending it to treat patients with non-cancerous diseases. We have transplanted quite a few patients with so-called inborn errors of metabolism, that is, genetic diseases. The longest patient would be out now four and a half years after transplant. In those patients, we try to make the procedure safer by extending the immunosuppression out maybe to a year. In those patients, we aren't interested in making them all donor. We actually can live with a mixed host and donor combination of blood-forming tissues because the donor cells will bring the missing enzyme in ample amounts.

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***We already have begun extending it to treat patients with non-cancerous diseases.***

Andrew: What sort of diseases?

Dr. Storb: One big disease is sickle cell anemia, for instance, where if you only have 10, 20 percent donor cells, the patient's red cells stop sickling, thereby avoiding all these terrible sequelae from sickle cell disease. Other diseases are immunodeficiency diseases and storage diseases. That's another area where I think the mini-transplant will come in really well because you're avoiding these long-term sequelae from these high-dose therapies that are currently still needed for carrying out transplants in these disorders.

Andrew: Just to be clear, though, do you view mini-transplants still as experimental, still investigational?

Dr. Storb: Yes and no. I believe in their success. They're investigational in the sense that you are trying to really establish how safe they are, how effective they are compared to a conventional transplant. That is still investigational.

The other areas where I see potential for the mini-transplant is certain metastatic diseases originating from organs which have either been surgically removed already or are not important anymore. The tumors I'm thinking about are breast cancer, prostate cancer, colon cancer, ovarian cancer, cervical cancer, pancreas cancer, for instance.

***The other areas where I see potential for the mini-transplant are certain metastatic diseases originating from organs, which have either been surgically removed already or are not important anymore.***

Once they turn metastatic, they are basically incurable, and so the question is, can we in some ways direct the donor T-cells' immune responses toward these metastatic tumors, say in a case of patient who has widespread metastatic pancreas cancer? It doesn't matter whether the normal pancreas gets wiped out. We can substitute with insulin. We can substitute with enzymes so that the loss of the normal pancreas is tolerable as long as you get rid of the tumor metastases. I can foresee if we manage to figure out how to do this, that this would be really a terrific procedure for very frequently encountered tumors.

Andrew: It sounds like you're excited about where the science is going.

Dr. Storb: We are excited, actually. Very excited. I mean, the other group of people who is excited are the transplant surgeons because take for instance a patient whom we just saw back again here with multiple myeloma. She was transplanted here two

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years ago. Her multiple myeloma seems totally under control, can't find any evidence of tumor. When she was transplanted, she had non-functioning kidneys because of the multiple myeloma. She has been on dialysis ever since.

With her being off all immune suppression, having a good graft, leading other than for the hemodialysis a normal life, the bone marrow donor, her brother, has decided to donate a kidney. This kidney transplant will be carried out in Idaho, actually, with our guidance, and will be carried out without the need for any immunosuppression for the rest of the patient's life as unlike what you see in conventional transplant. The reason is that the patient now carries the donor immune system, which will not recognize the kidney as foreign but rather as self.

The transplant surgeons knowing about these kind of things are very excited that maybe the mini-transplant can be used as a prelude, if you wish, to subsequent transplantation of solid organs. That's an area of work that we're working on in the laboratory.

Andrew: It sounds like taking people who've been very sick, had damaged organs, transplanting them and making them whole again.

Dr. Storb: Without that they need to take cyclosporine or azathioprine or prednisone for the rest of their lives. That's one of the hopes. The final thing I want to say is that we try to get away from this last vestiges of total body radiation, and we are looking currently at antibody therapy, antibodies for instance to the recipient T-cells to which we link a very short-acting, alpha-emitting radioactive isotope that has a half-life of 47 minutes to seven hours in hopes of just wiping out the patient's T-cells and then get the graft in and then let the graft-versus-tumor effect take care of the rest. We hope to replace the 2 gray of total body irradiation that's currently still in the regimen ultimately by a much less toxic approach, which we are already employing in the laboratory, namely, an antibody/isotope conjugate, and we have employed this successfully in the laboratory. That would be a very non-toxic approach because the isotope irradiates only across maybe four or five cell diameters but not beyond. It's in fact so safe that you can take the syringe with a hand that has a rubber glove to protect it because the radiation doesn't go through the thickness of the glove.

Andrew: Instead of the much lower dose of total body irradiation, sort of an patient-specific injectible radiation that just goes after specific cells, and then you come on in with the donor cells, and they do all the work that you've described.

Dr. Storb: That's correct. That's where I see the future.

Andrew: Very exciting. Dr. Rainer Storb from the Seattle Cancer Care Alliance and the Fred Hutchinson Cancer Research Center, thank you for taking time out just back

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from the American Society of Clinical Oncology meeting to describe the new hope with mini-transplant and the future of research in this area. It's really exciting. Thank you, sir.

Dr. Storb: You're welcome.

Andrew: For HealthTalk, I'm Andrew Schorr. From all of us at HealthTalk, we wish you the very best of health. This has been a presentation of HealthTalk, the leader in online talk shows for people living with cancer and their families.

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