Allogeneic Transplants for Multiple Myeloma with Dr. Bensinger

March is Myeloma Awareness month and we are exploring the allo transplant therapy route for myeloma patients in our talk with Dr. Bensinger. Why are allogeneic stem cell transplants risky for multiple myeloma patients?

When does possible benefit outweigh the risks?

RSVP to participate by asking a myeloma question LIVE on the talk to our panel of experts and patients.

To mark the Myeloma month of awareness, we have extended our show time by 15 mins where we will have Sarah Kaufmann-Fink of MMore joining us to talk about MMores new research and crowdfunding venture.

Full Transcript:

Priya Menon : Good evening, everyone. Hello and welcome to Cure Talk. I am Priya Menon, Scientific Media Editor at Cure Talk, joining you from India; and I welcome all of you this evening to a discussion on multiple myeloma on Cure Talk's 84th episode. March is Myeloma Awareness Month and we are having an extended broadcast today. We will first hear from…, about allogeneic transplants for myeloma treatment and then have the opportunity to listen to about a new myeloma therapy under research. My co-host for the talk is myeloma advocate, Pat Killingsworth, and supporting Pat is our esteemed myeloma panel consisting of advocates, Gary Petersen, Jack Aiello, and Cynthia Chmielewski. We are truly excited to have amongst us a very distinguished expert, Dr. William Bensinger. Dr. Bensinger is Director of the Autologous Marrow Transplant Program at Seattle Cancer Care Alliance, a member in the Clinical Research Division at Fred Hutchinson Cancer Research Center, and a Professor of Medicine at the University of Washington. Dr. Bensinger, welcome to Cure Talks

Dr. William Bensinger : Thank you. Happy to be here.

Priya Menon : We will be addressing questions sent in via email towards the end of the discussion. If you have a question for our expert, you can let us know by pressing 1 on your keypads. With that, now its over to Pat. Pat, you are on air.

Pat Killingsworth : Hello, doctor. Thanks so much for joining us.

Dr. William Bensinger : Its a pleasure.

Pat Killingsworth : Now, I have to say… I… I checked your…, your title and I…, and I see that you focus primarily on autologous stem cell transplants and yet almost all the questions we have this evening are allogeneic, but I am…, I am guessing that's…, that's not a…, that's not an issue.

Dr. William Bensinger : So, I am… I am the Director of the Autologous Marrow…, or the Autologous Stem Cell Transplant Program at the Hutchinson Center in the Seattle Care Alliance, but that doesn't prevent me from doing studies and investigating allogeneic transplant treatments for whatever…, whatever disease is appropriate, but in this case multiple myeloma.

Pat Killingsworth : Of course and I… That…, that's good and I believe we met at ASH this year, didn't we, in San Francisco?

Dr. William Bensinger : I believe we did. Yes.

Pat Killingsworth : It was…, it was wonderful for you to take the time to…, to speak with me and so I would like to start out with a question about auto transplants before we move into the donor…, the donor around here. Over the years, I have heard from a number of…., of patients that had transplants, I hate to use the word "failed" but have transplants that…, that didn't work well or…, or really didn't help much at all and…, and now I find myself…, and actually I was one of those people three or four years ago and now I find myself facing a difficult situation where I am running out of options and…, and a doctor that I respect, a specialist I respect, has recommended that I transplant again and…, and I…, I wondered if I could get your thoughts on…, for me and…, and so many others, if you are going to transplant again, do you…, do you…, do you do something different? If…, if melphalan doesn't really do the trick, do you…, do you add things to…, to maybe try to help the effectiveness on a second try?

Dr. William Bensinger : So, to start with, as you…, as I am sure you are aware, multiple myeloma is a very heterogeneous disease and there is a number of different subtypes that have more or less aggressive features. What that means is that patients as individuals will differ with respect to their response to any form of treatment and autologous transplant is no different and so there are patients who derive tremendous benefit from an auto transplant just as there are patients who won't respond or derive little or no benefit. The way we measure the benefits is to try to include a large enough series of patients on any studies to see if overall there is benefit for this. Now, in terms of a prior transplant in…, in which a patient has relapsed, we often try to judge the length of the initial remission after transplant as a gauge to where…, whether we think a…, a second transplant will benefit. Generally speaking, patients that have a…, a disease-free interval of about two years, we think its worthwhile to consider a second transplant. In patients whose remission lasts a year or less, we do not generally think a second transplant is likely to provide much benefit. There are some studies that have attempted to improve on single-agent melphalan. To date, there is no data that suggests that any one regimen or any different regimen is better than single-agent melphalan. Having said that, there are some groups that will use a regimen commonly known as BEAM, which is a four-drug regimen that includes melphalan for a second transplant. Other groups have added in one or more of the proteasome inhibitors such as bortezomib or carfilzomib to a melphalan-containing regimen, but there really isn't any data to say definitively that that's going to produce better results.

Pat Killingsworth : I appreciate that. So, just to follow up if… So, maybe there isn't necessarily a direct correlation between… Oh, let me give you an example. So, if…, if I had a transplant that…, that wasn't successful, I guess in my mind I was thinking, well, that means down the road, melphalan-prednisone wouldn't be a successful therapy for me, for example, but it sounds like you are saying maybe those two things aren't necessarily connected.

Dr. William Bensinger : Well, they are not, but again, when you…, when you say a transplant is not successful, you have to define what you mean by that. If a person goes three years and then relapses, well, ultimately that transplant was not successful, but the fact that they went three years in remission is in fact the measure of success.

Pat Killingsworth : Yes. Oh, I would call that successful. No, when I say not successful, that means they went in with a 0.4 M-spike and they came out with a 0.4-M spike or they… In my case, I went in with a 0.1 and I came out with a 0.5. So No, I am… To me, I guess, a year or two years or three years I suppose, you have to define what success is. The median is around two years, isn't it? I just… I just… I just meant a lot of patients get what seems to be very little or no benefit out of…, out of the transplant process. So…

Dr. William Bensinger : Yeah. I mean I… I don't know what to tell you on that.

Pat Killingsworth : Sure. Okay, but what I am saying sounds…, I mean I am not incorrect what I am saying, right? I mean, that's all I am asking.

Dr. William Bensinger : Yes.

Pat Killingsworth : I don't want to… I don't want to be passing along incorrect information. So… Okay, great! That…, that was helpful and then I have… I have an allo question to kick us off and that… When I look at mortality rates for donor transplants or allogeneic transplants, it…, it always seems that they are higher for multiple myeloma patients and I …, and I have asked a number of specialists about that and I get several different answers, but I also get a lot of shoulder shrugs and…, and honest I am not sure why that is, but why…, why doesn't mortality rate tend to be higher among multiple myeloma patients?

Dr. William Bensinger : So, patients with multiple myeloma have, by virtue of their disease, an underlying immunodeficiency. They typically have lower or abnormally low levels of antibodies in their blood. Antibodies are one of our immune systems that protect us from infection. As a result of that, they tend to be more prone to develop opportunistic infections after an allogeneic stem cell transplant; and certainly historically, the mortality after high-dose therapy and allogeneic stem cell transplant was extraordinarily high in the 30% to 50% range and high enough that many of us abandoned that strategy a number of years ago because we felt the mortality was too high. Now, since that time, there have been a lot of improvements in supportive care for patients with myeloma and this has reduced the mortality of ablative transplants down to the 20% range. That's still very high. Another strategy is to use the so-called non-ablative or reduced-intensity transplant. These are much lower doses of drugs designed not so much to attack the myeloma but to prevent rejection of the donor graft and so allows the donor graft to be…, to take over and develop its own immunity within the patient. This type of strategy is much less toxic to patients and associated with a considerably lower mortality, in the range of 10% to 15%. This appears to be in line with what we see with the majority of other hematologic malignancies that receive similar conditioning. So, things have improved quite a bit, but, you know, there is still a higher mortality with allogeneic transplants compared to what autologous transplant, but the mortality there is typically only 1% to 2%.

Pat Killingsworth : Sure. That's a great answer, doctor. Thank you very much and I believe our next questioner, you may have even met him at ASH, he was with me, Gary Petersen, and, Gary, are you with us?

Gary Petersen : Sure, I am. Hi! Hi, Pat! Can you hear me?

Pat Killingsworth : How are you doing?

Gary Petersen : Yes. Doctor, thank you so much for being here.

Dr. William Bensinger : Oh, you are welcome.

Gary Petersen : Yeah. I… I looked at, you know, the Be The Match, I think its what it is, and they have some great information on it and…, and…, and I have got to tell you this. One of the things is that the Seattle Care Alliance is one of the very few who publish their survival data and I have got to congratulate you for that and obviously that's one of the reasons because you track your survival and because you, you know, do the analytics behind it that you guys do a better job than most at survival, but I looked at eight of the largest

centers and the average one-year survival was 67% or one in three patients do not make it one year; however, your Seattle Care Alliance has an 83% on your survival rate. What are you doing differently that others that do not…, with allos that others do not do and…, and you have a, I believe it is 45, in the last three years you have done 45 allo transplants on myeloma patients, which doesn't seem to be a lot, but that happens to be the most of any single institution in the United States. So, what are you doing differently?

Dr. William Bensinger : (Laughter) Well, its hard for me to put a handle on it. We certainly have the longest experience with allogeneic transplants of any center in the country, if not the world. So, we have been doing allogeneic transplants for 30 plus years and what we have tried to do over the years is learn from our results and our experiences, good and bad, and we are very regimented about supportive care, proper antibiotic use, use of other agents to prevent infections such as IV immunoglobulin. We have implemented some strategies that we think reduce some types of graft versus host disease and all of these things are probably incremental in terms of their benefits on patients, but as an aggregate, I think all of these strategies have resulted in a reduction in the transplant-associated mortality with our allograft patients.

Gary Petersen : Oh, thank you very much, doctor. I appreciate that and… As a matter of fact, not that long ago, as I recall, you know, your… I think… one another… one of the, you know, presentations or… I think I was managing myeloma and one of the things that you said was that, its a…., the myeloma is just a very…, you know, what do call it, a disease, an orphan disease, and as a result people don't get to see that many of them and…, and you are saying that its so, so, so important that you get somebody who knows about this disease and has had hundreds of patients because that's the only way that you are going to get adequate care and I totally agree with you and I was wondering what your thoughts were with regard to that.

Dr. William Bensinger : Yeah. So, I…, I do think that getting the advice and a second opinion of a specialist at a center that sees more than a handful of these patients is extremely important. Now, that doesn't mean that you have to move and leave where you live and go within the city where the specialist resides, but you can…, you can basically have your doctor partner with a specialist, have your physician…, have you seen by a…, a specialty group, wherever that center is and work with them in terms of designing a particular treatment program, making decisions about when transplant is appropriate, making decisions about maintenance therapy, and…, and really engage that specialist to help manage your disease. I think that's the winning strategy if you are a patient with myeloma and you don't have to live, you know, at a…, at a big major center to benefit from that.

Gary Petersen : Well, thank you, doctor, and…, and Pat, if you want to go on to others, I got a couple more questions, but I'll…, I'll ask them later and…, and, doctor, thank you. Its the same strategy that Danny Parker uses. He uses Dr. Wolf in… and I think its in San Francisco…

Dr. William Bensinger : Yeah.

Gary Petersen : …or in California anyway and he uses Dr. Wolf and…, and he lives in Florida and he lives in Florida, so talk about a…, talk about exactly what you just talked about. That's, I guess, as extreme as you can get.

Dr. William Bensinger : Yep.

Pat Killingsworth : Thanks, Gary. Cindy, are you with us?

Cynthia Chmielewski : I am. Can you hear me, Pat?

Pat Killingsworth : Yeah. Let's get a woman's perspective here. What do you think? Right away.

Cynthia Chmielewski : I… Well, I think that allo transplant seems scary whenever anyone brings that up for me, I guess, because I have heard about high mortality rates and I…, I was just wondering if there are certain types of pre-testing that are recommended before you would be even configured to undergo an allo

transplant to make sure that your body is in good enough shape to handle what's being thrown at you. So, are there certain testing that you do ahead of time? …preliminary testing?

Dr. William Bensinger : Yeah. So, I… I agree with you that allogeneic transplants are scary. They do have the potential to have a higher risk of…, of dying from the treatment. As a result of that, we typically only offer allogeneic transplants to patients who have certain high-risk features of their disease that predict that they will do poorly with just the…, the drugs that are available today with or without an autologous stem cell transplant. So, we know, for example, that patients who have a 17p deletion or a 414 deletion or have extra copies of chromosome 1q have a more aggressive disease; and studies looking at the outcomes of these patients after induction treatment and autologous transplant suggest that these patients have a much shorter length of remission and a poor overall survival. These are the kinds of patients that we generally recommend to consider an allogeneic transplant. The idea of an allogeneic transplant is you are…, you are basically relying on the immune system from the new donor. Its actually the oldest form of immunotherapy. So, its the first treatment that was developed involving the…, a way to reverse the…, the deficiencies in the immune system that allow the myeloma to grow in the first place and it is the…, the treatment that is associated with the longest survival. I have a particular patient I am fond of, who we transplanted more than 25 years ago from her brother and she is alive and doing well and is free of disease. So, it is associated in some patients with long-term disease control and I would dare say, after 25 years of cure. Now, going into this transplant, we do have to make sure that the patient has a suitable donor and so its important to do tissue typing between the patient and the donor. This is accomplished by a simple blood test or even a swab of the…, of the cheek area where you can get some cells for DNA analysis. This can be used to perform what we call HLA typing, which are antigens that are part of the histocompatibility complex and they determine graft rejection, graft versus host disease. What you want is a fully matched donor ideally. Once you have found a donor, the patient…, it needs to be evaluated, not only for their disease status but to make sure that they are healthy in other ways. They have to have reasonably normal heart and lung and kidney function and so they undergo testing to make sure that they don't have any major medical problems that might interfere with their therapy, but once those things have been done, if everything looks okay, patients can move forward with a donor transplant.

Cynthia Chmielewski : Okay. That sounds… Now, would you recommend for that patient, maybe a young patient, who has these high-risk characteristics, to go right…, right after induction into an allogeneic transplant or would you want to see how he responds to an autologous transplant first?

Dr. William Bensinger : Well, generally, we know if a patient has high-risk features. They are going to have a relatively short remission with an autologous transplant. Each time the disease comes back, it gets a little bit harder to treat and this is especially true if the…, if the patient has high-risk cytogenetic features. The disease tends to come back more aggressively with each subsequent relapse and so if its appropriate for that particular patient, we think the best time to consider doing the allogeneic transplant is as part of their initial therapy, the induction and perhaps depending on the…, on the regimen perhaps an auto transplant first to try to get rid of as much of the disease as possible prior to going into the allo graft.

Cynthia Chmielewski : Okay. Now, I am… I have heard various places when you are going into an allogeneic transplant, its necessary that you are almost in a very good partial remission or a complete remission. Is that true that you need to have almost all your disease taken away by another method before you go into the transplant?

Dr. William Bensinger : So, here's something to keep in mind. If you are in a remission and we define a remission as no monoclonal protein that's measurable in the blood or the urine, no abnormal cells in the bone marrow, and by all testing that we can do, that patient is in remission. What you need to remember though is that the typical patient who is in remission can have between a 100 million and a billion residual cancer cells in their body, but they are diluted among trillions of other cells and so they have still a significant disease burden left behind, but you can't detect it because its below the limits of our testing to do that. At that time, we think its the best time to consider doing a donor transplant. There is… The transplant from a donor relies on his immune effect, we call it a graft versus myeloma effect. If you have a large amount of residual

disease, however, it becomes more difficult for the graft which has to grow and develop in the patient to a…, to a reasonable size to…, to basically be effective. It becomes much harder for that graft to deal with a larger volume of tumor rather than a patient who is in remission. So, remission, keep in mind, is…, is generally associated with still a significant disease burden, its just that we are unable to detect it at that level.

Cynthia Chmielewski : Okay. One last question before I go on. You were talking earlier about matching to get a matched donor and that like, perfect match is the best thing. What about the person who really can't find a match through graded or through one of the Be The Match kinds? Have there been cord blood allogeneic transplants for myeloma patients?

Dr. William Bensinger : They have been done, but they are very rare. We have only done a handful of the cord blood transplants. Part of the problem with cord blood transplants is that the cell dose in a cord blood is rather limited; and for a large adult, that lower cell dose may be insufficient to get a reliable graft. The other area where there seems to be some promise and its still in the early stages is doing, what are called, the haploidentical transplants. So, these are transplants using a brother or sister who is not a complete match, but we have learned some technologies and techniques for markedly reducing the graft versus host disease by killing off the…, the cells that lead to graft versus host disease at an early stage after the transplant. We still haven't done very many of them, but there are beginning to be some greater experiences with these haploidentical transplants and I think they are going to be promising in the future.

Cynthia Chmielewski : Oh, that's exciting. Okay. Thanks, doc, and, Pat, why don't you go on to Jack?

Pat Killingsworth : Thanks, Cindy. Jack, are you with us from California?

Jack Aiello : I am and I look forward to seeing Dr. Bensinger at the IMF this weekend.

Dr. William Bensinger : Yeah, I am heading.. I am heading down there tomorrow in…, in about roughly 24 hours.

Jack Aiello : Uhmm… I will see you there.

Dr. William Bensinger : Okay. You go ahead, Sir.

Jack Aiello : I have a few questions. My followup on Cynthia's, is there definitely a correlation between successful allos for myeloma patient and the donor stem cell sources where source is going to be a… a matched sibling, a matched unrelated donor called the MUD? Do you prefer matched sibling before a MUD?

Dr. William Bensinger : So, our preference is always a matched sibling. Having said that, there are not huge differences between a matched unrelated donor. Typically what we see is with a matched unrelated donor, somewhere in the neighborhood of 5% to 10% greater incidence of graft versus host disease. However, this only has a minor effect on overall survival, so that using a matched unrelated donor produces about the same outcomes as using a matched related donor. You get a little more graft versus host disease, but you probably get a little bit better anti-myeloma effect because of that and they sort of balance each other out.

Jack Aiello : Along those same lines, would you prefer a matched unrelated donor to the haploidentical sibling that you mentioned?

Dr. William Bensinger : At the… At the present time, I would, but I… As I said, I think that there is starting to be some promising work being done with the haploidentical donors and I think in a few years my opinion could change.

Jack Aiello : Is there any correlation of successful allo with the patient donor gender? I have actually heard that its better for a…, a male to donate to a female or is there any such thing as that, for example?

Dr. William Bensinger : Yeah. So, the…, the male…, male donors are associated with less graft versus host disease and the reason for that is that the…, the majority of the female donors undergo some degree of sensitization during pregnancy and so their T cells are more allo reactive because of prior pregnancies. As a result of that, female donors are associated with a… Again, similar to the unrelated donors, there is somewhat greater risk of graft versus host disease, but at the same time a lower risk of relapse. So, its…, its kind of similar when you parse that out between male and female donors. You get a similar result of the difference between matched related and matched unrelated.

Jack Aiello : So, its not an opposite sex attract, its more the preference for male donors in general, whether its male-male or male-female.

Dr. William Bensinger : Mainly because…, mainly because of this issue of sensitization.

Jack Aiello : Yeah. Okay. Should allo transplant patients get re-immunized with their childhood vaccines or do they already get these from the donor transplant?

Dr. William Bensinger : At one year, what we do is we test patients for a variety of the typical pathogens that we immunize for and look for antibody development. If they are deficient in…, in any of these, we re-immunize them.

Jack Aiello : Is that what you do for auto as well?

Dr. William Bensinger : Yes, but in auto we do it at six months.

Jack Aiello : Okay. Got it and then finally, when doing an allo, how do you decide between the reduced intensity or mini technique or non-myeloablative, whatever you want…, want to call it, versus the full or myeloablative technique?

Dr. William Bensinger : Yeah, that's a complicated question, but it certainly depends in part on the disease status of the patient. So, if you have a patient who is in a good remission, who has, say, undergone a recent autologous transplant and has recovered and has minimal disease, generally you are going to go with a reduced intensity regimen. If you have a patient who has got pretty resistant disease, who has failed one or more therapies, may have failed an autologous transplant and you are not able to get them to this minimal residual disease state, you are generally going to be looking at a more intensive regimen, tending to be more full-dose myeloablative. There are also some strategies that we are looking at to hopefully give the best of both worlds. So, for example, we have taken the back bone of the reduced-intensity transplant and added into that a radioisotope using an antibody that targets the bone marrow, the lymph nodes, the spleen and the idea is to provide radiation to the major sites where the myeloma tends to hang out and thereby provide a way to control the disease, but at the same time using these guided radioisotopes, we avoid the lungs and the kidneys and.., and the liver, which are major targets for toxicity with external radiation. So, the idea is to provide this targeted radiation as a way to…, to provide what is essentially a more intensive regimen, but yet its going to be safer for the patient.

Jack Aiello : No longer giving TVI before the allo, huh?

Dr. William Bensinger : Correct.

Jack Aiello : Yeah. Well, thanks so much. I look forward to talking with you again this weekend.

Dr. William Bensinger : All right. Look forward to seeing you.

Pat Killingsworth : Thanks, Jack. Thank you, doctor. So, Priya, this is a…, a wonderful opportunity. Normally its hard to get the panelists to stop asking questions and…, and we run out of an hour, so it looks like we have got some time to take…, for the doctor to take questions that people have emailed in or callers on the

line. Do you want to… Do you want to take it from here?

Priya Menon : Thank you so much, Pat. We have a long list of questions which have been sent in via email and while we get going on them, listeners, if you have a question for Dr. Bensinger you would like to ask live, please press 1 on your keypad and we can bring you live to ask your question. Yes, I think we have one person, maybe we should just begin with that. Person calling in from (703)237-9690, please ask your question. (Pause) Person calling in from 237-9690, you are live. Please ask your question. (Pause) Okay, maybe we should just… To start with our list of questions, Dr. Bensinger, first question is, is there an age limit for a patient who is doing well after relapse on Velcade maintenance to go on to an allo?

Dr. William Bensinger : To go on to an allogeneic transplant?

Priya Menon : Yeah.

Dr. William Bensinger : Is that… Is that the question?

Priya Menon : Yes, that's the question.

Dr. William Bensinger : Umm… Its not so much a chronologic age as a biologic age. As a generality, we tend to use a rough age of around 70 in terms of decision making about whether to proceed to an allogeneic transplant or not. Having said that, there are patients who are in their low 70s who are quite robust and their chronologic age of 72 is much higher than their…, what I would consider their biologic age. They may have the… They may be more like a 60-year-old person. These are patients that on an individual basis we would certainly consider for an allogeneic stem cell transplant and then the other side of that is, of course, there are patients who may be in their 50s but have bad chronic obstructive lung disease or bad heart disease and these are patients that are much more likely to develop complications from any type of transplant, perhaps even on autologous transplant and they are patients that we are generally going to discourage from moving forward with these types of treatments.

Priya Menon : Thank you, doctor. The next question is, do you need to be in complete remission to do a full allogeneic transplant as part of a first line therapy?

Dr. William Bensinger : You don't need to be in a…, in a first remission to do it; however, the data that have looked at outcomes suggest that patients who are in first remission have longer lengths of remission and a higher chance of long-term survival and the potential for cure. So, while you can do a transplant in patients who are not in a complete remission, we like, in general, to have patients in that condition prior to transplant because we know that they will have a better outcome.

Priya Menon : Thank you, doctor. The next is, what is the significance of a T cell depletion relative to an allogeneic stem cell transplant?

Dr. William Bensinger : So, T cell depletion is based on the idea that T cells are the cells most responsible for cause of graft versus host disease and that by depleting these T cells from the graft, you can reduce the chances of this complication. That is a strategy that was developed actually at our center almost 25 years ago and we did a variety of…, of transplants using various T cell depletion strategies. The problem is that there were quite a few complications from this. When you T deplete the graft, there is a greater chance of graft rejection, that the graft will not take in the patient because these T cells play an important role in establishment of the graft. In addition, while graft versus host disease could clearly be reduced, there was also a much higher incidence of relapse of the disease and this is true of myeloma, but it was also true of the various leukemias that are transplanted as well and as a result of that, our feeling was that pure T cell depletion by itself was fraught with too many problems and we abandoned this as a strategy at our center. Now, there are some groups that are looking at selective T cell depletion, the term that's often used is graft engineering, where they try to deplete certain populations of T cells that may be more responsible for graft versus host disease and yet would preserve the anti-leukemia or anti-myeloma effect of the graft. These

are strategies that have been in the works for some time, but I have to say there isn't any definitive data about which T cell subsets to get rid of and which way is the best way to go.

Priya Menon : Thank you, doctor. The next is, could you explain in layman terms what the graft versus tumor effect of the allogeneic transplant is and how this is different from the graft versus host effect?

Dr. William Bensinger : Yes. So, graft…, graft versus host disease results from, as I said earlier, T cells. These are T cells that are contained in the graft that will react to antigens present on certain tissues of the patient. These tissues tend to be confined to the gastrointestinal tract, the skin, the liver, and sometimes the lungs. So, this causes these cells to…, these T cells to proliferate and eventually if there is significant graft versus host disease to cause damage to these tissues. The graft versus tumor effect is a similar type of T cell reaction directed against the tumor cells. Now, as…, as you probably know, as most of the tumors that arise in our body are derived from normal cells and normal tissues, so these cells will often contain many of the same target antigens that are present on normal tissues. Sometimes if you are lucky enough, they will contain unique targets that are only present on the tumor, but the goal is to exploit this graft versus tumor effect and avoid the graft versus host disease. As it turns out, when we do analyses of outcomes in patients who have had allogeneic transplants, the patients who have no graft versus host disease at all tend to do worse and this is because they tend to have a higher rate of relapse. The patients who have severe graft versus host disease similarly do poorly because of the damage from their…, to their normal tissues. The patients who do the best are the ones who have a mild form of graft versus host disease, that is easily treated and easily controlled. So, the graft versus host reaction and the graft versus tumor effect tend to go hand in hand and this has made it very difficult for researchers that have tried to separate these two effects by graft engineering. This is why its been so difficult. The same cells that cause graft versus host disease tend to be the same cells that cause the graft versus tumor effect.

Priya Menon : Thank you, doctor. The next question is actually on graft engineering that you just mentioned and the question reads, I read you mentioned graft engineering to improve the graft versus myeloma activity while reducing graft versus host disease in one of your papers. What is actually done in graft engineering?

Dr. William Bensinger : So, this is based on the hypothesis that, in fact, distinct populations of T cells are responsible for graft versus host disease and that these are separate and distinct from populations that lead to the graft versus tumor effect and so, for example, some researchers have separated out T cells that are CDA positive. CDA is a protein marker that identifies a particular subset of T cells and the notion with doing this is that these CDA T cells are the ones that tend to be more responsible for causing graft versus host disease, but at the same time are not as responsible for the graft versus myeloma effect and by depleting this distinct population, you can gain for the patient lack of graft versus host disease and still preserve the anti-tumor effect.

Priya Menon : Thank you, doctor. The next question is, what is the criteria to choose a suitable candidate to be the donor in allogeneic transplant?

Dr. William Bensinger : So, the most common donor is a brother or a sister who is HLA matched and this is… As I mentioned, this is done by a blood test or even a swab of cells from inside the cheek. This is then tested in the lab to look at HLA typing and you are looking for a matching between the donor and the patient. If you have a family with…, with four siblings, each sibling has a 25% chance or one out of four that they will match with a particular patient and so if you have three siblings and the fourth person is a patient, he has three chances, each 25%, that one of those three siblings will match with him. Now, once a donor has been identified, they have to pass a health screening as well, so they have to be in good physical condition and not have any major medical problems. They can certainly have some minor things like high blood pressure or other minor health conditions that won't interfere with their ability to donate cells. Once the donor has been identified, the process of donating stem cells is rather simple. Its similar to the way we mobilize stem cells from patients. Donors receive five to seven days of shots with GCSF, which is granulocyte colony-stimulating factor. GCSF is a hormone that stimulates white blood cells, mostly neutrophils, in the bone marrow, but its been…, it was learned almost 20 years ago that by successive daily

administration of GCSF to…, to patients and donors, you could get the stem cells which normally reside in the bone marrow and don't circulate in the blood. You could get these stem cells to leave the bone marrow and circulate in the blood stream for a period of several days and then its possible to collect those cells. The donor cells are collected on an aphoresis machine. This is a blood cell separator. Basically, its a fancy-looking centrifuge, sort of looks like a washing machine with a lots of bells and whistles and the patients donate by venopuncture… The donor donates by venopuncture, which means a needle is inserted into the veins in the arm on each side. Blood is withdrawn from one side, mixed with a blood thinner so it doesn't clot and run through the centrifuge where its fractionated into the liquid and cellular portions. That white… The white blood cell cellular portion is then collected, while the rest of the blood is returned to the patient. The patient or the… Excuse me… The donor…, the donor lies in a bed next to the machine for somewhere in the neighborhood of 2-1/2 to 3 hours. These isn't any real pain or discomfort involved other than the discomfort associated with the needlesticks and at the end of that 2-1/2 to 3 hours, they often have enough cells to do the transplant. The GCSF in the donor generally can cause some kind of bone achiness that lasts during the administration. Rarely patients can get headaches or low-grade fevers or nausea, but generally these effects are…, are mild and short lived and associated just with the time period when they are receiving the shots of GCSF, but its pretty simple for the donor to be a donor and not really associated with any serious consequences.

Priya Menon : Thank you, doctor. That was very helpful. We just have a last question. Dr. Bensinger, how many people have been 100% cured, asks our listener.

Dr. William Bensinger : I am sorry, how many people what?

Priya Menon : Have been 100% cured.

Dr. William Bensinger : Well, I would say that's a difficult question and I don't know the answer to that. I would say that probably a couple thousand patients worldwide have been cured with donor transplants for myeloma, but that's really a guesstimate based on my view of how many publications have been and the numbers of patients that have been reported in various trials. Its probably a couple of thousand.

Priya Menon : Thank you, doctor. Pat, if the panelists have any more questions, maybe we can just get to them.

Pat Killingsworth : Sure. Gary, do you have a followup? (Pause) Cindy, Jack?

Jack Aiello : I don't, Pat.

Pat Killingsworth : Okay.

Priya Menon : Thank you, Dr. Bensinger. I think we will bring on our next guest. We have with us a special guest today, Sarah Kaufmann-Fink of MMore. She is… Sarah is a multiple myeloma patient who was diagnosed in 2005 at the age of 22. Sarah remains in remission since an autologous stem cell transplant in 2005. She is actively involved in fundraising for…, and raising awareness of multiple myeloma research. Sarah is a Board Member with the non-profit myeloma organization, MMore, Multiple Myeloma Opportunities for Research & Education. To recognize the month of March, which is Myeloma Awareness Month, MMore is conducting an End Myeloma Campaign. I invite Sarah to tell us a little bit more about the same. Sarah, you are on air.

Sarah Kaufmann-Fink : Hi! Can you hear me?

Pat Killingsworth : Hi, Sarah! You sound great! How are you doing? How is the new baby?

Sarah Kaufmann-Fink : Its good. Thank you. I was going to apologize if there is some crying in the background. Hopefully, there won't be, but, yep, she is 6 weeks old, so we are doing great. Thank you so

much for having me on the show. I am so excited to talk with all of you and a little bit intimidated since you all are such experts, but I wanted to talk a little about a crowd funding campaign that we are doing for some pretty exciting research to commemorate Multiple Myeloma Awareness Month, which is this month, the month of March, and as…, as Priya was saying, I am… I am not a researcher, I am a patient and I am…, I am part of a non-profit organization called MMore. It stands for Multiple Myeloma Opportunities for Research & Education and its a…, its a small grassroots non-profit that was started in 2008 after I was diagnosed by some of my family and friends and the goal is to raise funds to support early-stage innovative new myeloma treatment with the hopes of bringing us closer to finding a cure for this disease. Since 2008, MMore has donated 2.4 million dollars to myeloma research. We have a scientific advisory board that _____**INAUDIBLE [00:54:19]**_____ and we support and we have built pretty great relationships with some researchers around the country and I don't know, I am sure you all on the panel have known, have realized this too, but it seems like myeloma specialists are a really great group, like a special breed of people. I haven't… I have yet to meet a myeloma specialist who hasn't just been a wonderful person. So, its been really wonderful to get to know some of them. So, what we are doing this…, this month for the Myeloma Awareness Month, is we have a…, what's called a crowd funding campaign and that just means an online fundraiser and we are calling it #EndMyeloma or the End Myeloma Campaign and the goal of this campaign is to raise 200,000 dollars and those funds will support a specific research therapy for myeloma research and that those funds will act as a bridge into the… The researchers working on this have been granted large sums of money, I think 800,000-dollar grant and working on a 1 million-dollar grant, but those funds take time to come in. So, the…, this 200,000 dollars is the way for the myeloma community, those of us that are directly affected, to actively participate in making sure that there are no hold backs, no waste of time, that this research can continue to move forward because it is so promising and the research is…, is also an immuno…, immunotherapy option which maybe people have heard of, its called…, it uses CAR T cell research. CAR stands for chimeric antigen receptor therapy or the CAR T cells, so just like Dr. Bensinger earlier was saying that the transplant is the.., maybe the oldest form of immunotherapy, this CAR research may very well be the newest form of immunotherapy, the newest promising area of research at least.

Sarah Kaufmann-Fink : So, CAR research has been used or has started to be used in the last few years with several different kinds of cancer, so with the research study done at the University of Pennsylvania, I believe, by Dr. June several years ago for acute lymphocytic leukemia or ALL that showed amazing initial results, very, very promising study and since then researchers all over the country and all different areas of cancer research have kind of taken this idea and tried to use it with.., with a variety of different cancers and again, I am…, I am a patient, not a researcher, but I do believe that one of the researchers working on this CAR T cell research for myeloma will be able to come on Cure Talk next month. So, they can talk more specifically about some of the details. So, my understanding is that this research or this therapy option would take a patient's cells via a blood draw, separate out their T cells, a type of immune cell and modify, genetically modify those cells to target, specifically target myeloma cells and, of course, the…, the difficult part is how do we…, how do we target them. So, that's what the researchers are working on, finding the right markers and enter target and then once the targets have been added to the patient's T cells, the T cells are given back to the patient via an infusion and then those cells are in your body for ever and so those cells ideally will go out and not only kill the myeloma cells but stay present in your body so that if you were to have a relapse, you know, if the cells…, if the myeloma cells would begin to proliferate again, then these modified T cells that you already have in your body, would jump into action again and be able to tamp down those and attack those myeloma cells before a full-blown remission happened.

Sarah Kaufmann-Fink : So, this research is currently in laboratory stages and has been for myeloma. The researchers have been working on it for over a year now and they have gotten patents, they have got initial FDA approval. Things seem to be going really swimmingly, but again for Myeloma Awareness Month, we still like…, there is a place for us as the myeloma community, as people who are directly affected and directly impacted by…, by new treatment options. This is the way that we can help participate to help speed up the process of bringing this to patients. So, if we are able to get all required funding in and if everything, you know, if we are able to raise this 200,000 dollars, then researchers are confident that the…, the first clinical trials for myeloma using this therapy may be available to patients in as early as 18 months from now, which would be sometime mid 2016, which in the scheme of medical research and science innovation is

extraordinarily fast. So, I am…, I am really… Personally, I am…, I am really excited about this. I think, you know, a lot of… As many of us patients know, a lot of the current therapy options have a huge amount of side effects. You know, Dr. Bensinger has highlighted today some of the…, the side effects associated with an allo transplant and that's just, you know, that's just one treatment option. So, if we were able to… If this…, if this works as well as…, as we hope it will, then this would have so many fewer side effects. So, it would be much easier on a patient's body and…, and then ideally it would stick around, so relapses would become less of a concern. So, I think that's about all I have to say about that. I don't know if there are questions, but I would encourage everyone to go check out our campaign. We have a lot of information online. You can see the campaign at endmyeloma.org, spelled exactly how it sounds, that's our campaign fundraising site and if you visit MMore's website which is mmore.org, we have a big link to our End Myeloma campaign and there is a special link to some more research information on that page as well. So, a lot more information about…, about that and we have some videos. We have a video from one of the researchers, which is on our Facebook page. You can find us at facebook/beMMORE and…, and of course, you can always contact me and my email adddress is sarah@mmore.org.

Pat Killingsworth : Hey, Sarah, was Dr. Bensinger your…, your doctor when you transplanted?

Sarah Kaufmann-Fink : So, I…, I am out here in Seattle and I do know Dr. Bensinger well. I have a lot of respect for him. He… So, out here at the Seattle Cancer Care Alliance, when you transplant you don't stick with one physician. You have…They rotate you. He was… Yep. He was on my transplant team for sure, uhmm…, and I was…

Pat Killingsworth : Awesome! Well, the guy has a magic touch. I mean, what's more inspiring than a…, a young woman that responds as well as you did and…, and now has a…, has a…, has a baby, a new baby, and its…, its amazing! Its so great to hear your voice.

Sarah Kaufmann-Fink : You too, Pat. Yep. Life is good.

Priya Menon : Sarah, thank you very much for sharing this information with us and we will be talking to one of MMore researchers and talking about the therapy that Sarah just mentioned in our April talk on myeloma. Dr. Bensinger, it was amazing and great listening to you. Thank you very much for having taken time out to be with us and our panel. Pat, Gary, Jack, and Cindy, thank you so much for your active participation. Today's talk and transcript will be made available on Cure Talk's website. Please visit curetalk.com for details on our upcoming talks. Until then, thank you so much.

Pat Killingsworth : Thank you, Priya. Thank you, doctor.