# Demystifying Stem Cell Transplant for Multiple Myeloma Treatment

In 2017 stem cell transplants remains a key option for treatment of eligible multiple myeloma patients, and in majority of patients it is done as a part of frontline therapy. Research shows that stem cell transplants significantly increases the amount of time, for which a patient has their disease under control. How safe are transplants? Who is eligible to get one? What are the side effects and how can patients tackle them? The myeloma panel is talking to Dr. Rafael Fonseca for answers to these and more on the latest developments in stem cell transplant technology in multiple myeloma treatment.

**Full Transcript:**

**Priya Menon:** Good afternoon everyone and welcome to CureTalks. This is Priya Menon joining you from India and today we are talking about Multiple Myeloma. The myeloma panel is led by Gary Peterson, Myeloma survivor and editor of Myelomasurvival.com and co-host of today's show. Joining Gary on the panel are myeloma survivors and advocate Jack Aiello and Yelak Biru. The featured expert on the talk is Dr Rafael Fonseca, hematologist oncologist at Mayo Clinic, Dr Fonseca. Welcome to CureTalks, such a pleasure to have you with us again.

**Dr Rafael Fonseca:** Oh, pleasure's mine. Thank you.

**Priya:** In 2017, stem cell transplant remained a key option for treatment of eligible multiple myeloma patients and for a majority of patients, it is done as a part of frontline therapy. Research shows that stem cell transplants significantly increases the amount of time for which a patient has the disease under control. How safe are transplants, who is eligible to get one, what are the side effects and how can patients tackle them. In the coming hour, the panel will talk to Dr Fonseca for answers to these and more on the latest developments in stem cell transplant technology for multiple myeloma treatment. Gary will be leading the talk, but before I hand over to Gary, I would like to inform the audience that we will be addressing questions sent in to us the end of the discussion. If you have a question for Dr Fonseca, please email me at priya@trialx.com or post on CureTalks website. You can also press one on your keypad and we can bring you on air to ask your questions directly. With that it's over to Gary.

**Gary Petersen:** Well, thanks again Priya for bringing all the myeloma patients this forum for discussion and of course, thank you Dr Fonseca for all that you do, in my opinion, and I think in most people's opinion you are one of the premier Myeloma specialists in the world, so thank you so much for being here. Dr Fonseca received his medical degree from the University Anahuac, School of medicine in Mexico City. He continued his postgraduate studies with a residency in internal medicine at the University of Miami. A fellowship in clinical hematology and medical oncology at Mayo Clinic, Rochester, Minnesota. So, Dr Fonseca is currently Deputy Director Mayo Clinic Cancer Center, Professor of Cancer and Professor of Medicine, Mayo Clinic College of medicine as well as a site director for hematological malignancies at Mayo Clinic, Scottsdale, Arizona. Dr Fonseca is a fellow at the International Society of Hematology and is board certified in internal medicine and medical oncology and hematology in addition to professional memberships and the American Association of Cancer Research, American Society of Hematology and many other organizations. He also has written more than a hundred peer review articles, books and abstracts. He's reviewed numerous journals including the American Journal of Hematology, American Journal of Medicine, Blood and many other journals as well. So Dr Fonseca has developed an expertise in the measurement of plasma cell disorders, and he is definitely, was actually sent from Rochester to Scottsdale to develop a Myeloma program and obviously has done a great job of doing that. So, welcome, Dr. Fonseca

**Dr Rafael Fonseca:** Oh, thank you. It's my pleasure to be with you all here today.

**Gary:** Well thank you. You certainly have helped the Myeloma patient community tremendously. So first of all it's like to transplant or not to transplant. That is the question. What, which is correct. Can you discuss with a audience why there is this question and what is the evidence which has mounted up to favor transplant?

**Dr Rafael Fonseca:** Sure. Well thank you and thank you for the opportunity again. As we were discussing just briefly before the call, the question of transplant remains relevant now as it was 20 years ago. And for the first 20 years the myeloma community spent a lot of time and resources and a devoted itself to do the clinical trials to prove that transplant was superior to no transplant. And more recently with the advent of better therapeutics, the question is the exact opposite. So there's clinical trials that are wondering is transplant feel needed as care for patients with multiple myeloma. So we've spent the first 20 years proving that it was needed and then there's almost an interest now in proving that they may not be needed. So we'll try to cover this questions during this conversation. And I think part of the theme that we have here is to demystify stem cell transplant as a treatment option for patients with myeloma. So we can start with some general comments and then go down into the controversy.

**Gary:** Please do.

**Dr Rafael Fonseca:** The first one is transplant is just, and I say just with caution because I know it implies so many, many things, but it's just one more line of treatment in the care of a myeloma patient and, and it's an important treatment is a big deal of course, but it's a treatment that has allowed us to provide an option for patients that can result in durable responses. That's probably the most important concept behind the idea of a stem cell transplant is that patients can have the treatment that will lead to a durable response. Now, the reason it is durable is, it's twofold. First of all, the responses of a transplant can be very deep. For those members in the audience who may not be familiar with terminology, you should know that the words response and remission mean exactly the same in medical terminology. So, we classify that will say a patient has a partial remission or partial response or if there is no longer our ability to measure that the disease we will say maybe the patient is not completed response. So that's one feature why transplant works. It produces very deep responses. But the second one, which is very important, is that some of those responses are quite durable and that's independent of one, what the one does after transplant. So much so that just in 2011, a Spanish group, reported them very long term outcomes of patients treated with stem cell transplants. And they were able to show that if you look at patients who achieved a complete response based on the criteria that they had at the time and based on the measurements they had for the disease at the time, about a third of those patients have no disease recurrence. And that was with the follow-up of up to 20 years. So the question is, is it durable? Yes, it can be and it can be very deep. And for those two reasons, transplant has traditionally enjoyed an advantage when people ask the question, well, so it's better to go through a transplant or not and the clinical trials have compared transplant or no transplant in the past as I mentioned, and most of them show an advantage for using transplant fairly young. So that is a reason why we do stem cell transplants in myeloma. That would be kind of a first opening statement and then I'm sure we'll, we'll delve into some of the controversies.

**Gary:** Well thank you. One of the things I've noticed in talking to people is there is just a fear of transplant, whether it's founded or not, you know, what are the reasons that they have this fear and why do people choose not to transplant and what are valid reasons and which are, which are myths, for one, I heard more than once that people saying that I'm going to get leukemia if I have a transplant, but I did some research myself and I found little evidence online. What's your take on this, it's a fear?

**Dr Rafael Fonseca:** Sure. Yeah. It's the one treatment that's probably feared the most. And when we talk to our patients, some of them have heard about transplant and come with a natural fear of,that anyone of us would have when we face a larger medical treatment as opposed to say, taking pills and injections, which ended up themselves can sometimes be just as risky as a transplant itself. I always tell my patients the following, if we're going to go through the transplant, I know that we know what we're doing and our nursing

staff and our medical staff knows exactly what we're doing to the point that for a medical team that those transplant on a regular basis. It is a routine procedure and I always follow that with my statement. I know it will never be routine to you because you're, this is a big deal for the individual, but for the medical teams that care for patients who are going through a stem cell transplant, this is a procedure that we're very familiar with. We know what to expect and we know how to react. In fact, the safety of a stem cell transplant is as high or if not higher than that of all other combination chemotherapy. When you look at large series of patients, we say that a transplant center of excellence should have a mortality rate of approximately 1% or less, and if you actually start digging down into those numbers, we sometimes run into more serious complications. If someone has pre-existing heart condition or a pulmonary condition and there may be other risk factors, but for the average patient, it should be a very safe procedure. The big downside is that it's almost like you compress everything into just a few days instead of getting, people get chemotherapy and for those who have received, as you might think, oh well the chemo, you get before the transplant, you cannot spread it out over 4 months. So you kind of play it into 16 installments to some degree and transplant on the other hand it's like buying your house cash, you have to deal with everything all at once. So you go through the treatment. The treatment is one infusion and one period of recovery. So we concentrate a lot of that toxicity, a lot of that recovery in a short period of time. But with the hope of achieving what I previously mentioned, which was a durable response. But if you look at the numbers is really important to remember that transplant is actually a very, very safe procedure. And the other word I sometimes hear, sometimes patients might tell me, well this is like a hail Mary pass situation where we're only gonna use transplant where really need to. And my answer to that is no actually for the suitable candidate and we can expand on that a little bit later, but for the suitable candidate, transplant should be considered as frontline therapy as your primary approach, your initial strategy against the disease. And again, it's fair to say it's a very safe procedure. Now. I don't ever pretend to minimize the toxicity that comes with going through a transplant. And some of you in the audience who have been through this, you know, that there's some significant problems with appetite, with ability to tolerate foods associated weakness and recovery time. And that's something we have to be quite mindful, but it can be done from medical perspective in a very safe way.

**Gary:** All right, well, I think the 1% that you're talking about is that when I talk to people, it almost seems like they've got 50% stuck in their brain for some reason. You know that the fear of death from stem cell transplant is far, far, far greater than what the reality is. So know it just seems to be a very, very big misconception,

**Dr Rafael Fonseca:** That's a very important, I would say getting someone else in the audience who may be dealing with a related condition, amyloidosis, we actually have these numbers quite precise enough doses. For amyloidosis the number goes up substantially. The number goes up to about 2-3%, maybe 4%, but even then it's far from that 50%. So I think it's important to remind people that it's is really a safe procedure.

**Gary:** Oh, the other thing too is that based on the SEER data from the National Cancer Institute, the 20% of patients die within the first year. So more likely to die from the myeloma than you are from the stem cell transplant.

**Dr Rafael Fonseca:** Yeah. And if I could build on that comment, then of course, that's something that we don't like to talk a lot about, but the biggest threats for the person and usually more so than the side effect always remains to myeloma. So that's why our efforts have always been that in a safe and tolerable way. We need to keep an eye on the biggest enemy and that's myeloma itself, not the transplant, not the side effects from the medication.

**Gary:** Very good point. Thank you doctor, another point, that, people talk about is quality of life. You mentioned something about that and that there's a significant difference of quality of life with transplant versus normal chemotherapy. Can you comment on, on that as well?

**Dr Rafael Fonseca:** Yes. And that's another very, very common statement we get. And I appreciate the question. I think we've all heard and not in myeloma, but in all cancers, patients come in with their families and their loved ones and they might say for me, quality of life is very important. Then we all recognize that

uncertainly there's an increased awareness of the importance of quality of life in this survivor aspect of the only with one of those disorders. The good news is that in myeloma quality of life usually not always, but usually goes hand in hand with quantity of life and what I mean by that, effective treatments that can keep the disease under control and in consequence can prevent bone lesions or pain associated with the bone lesions or it can prevent problems in the kidneys or could fix even if partially could fix anemia. All of those things we sought to improve quality of life. Now sometimes, and I use that analogy again of like paying your house with cash. In transplant you do concentrate a lot of the toxicity, so in a short period of time. So there is no question that while you're going through the transplant and during the early phase of the recovery, there will be a decrease in the quality of life. I mean, just being in the hospital alone and just being bedridden and not being able to eat your usual foods. And then even after leaving the hospital for a few weeks, they're superior to where someone, you know has to re-incorporate slowly into their normal life, their normal activities. But you do so knowing that for many patients who complete this, they can go back to quite decent level of quality of life. In fact, when I'm talking about transplant to my patients, I'll say, I bet you there's several people out there in the waiting area that you saw and are looking quite healthy who already went through their transplant and I like to give them a little bit of what to expect.

So I mentioned that Spanish study, the very durable responses, but there is a possibility and still for a lot of patients, myeloma will remain a threat and will come back later. But with transplant and now with the advent of maintenance approaches, which we do for the majority of our patients. If you take 100 patients, you can tell them that somewhere between four and five years after the transplant, there won't be a need to intensify treatment, meaning there won't be a need to think about changing treatments or including new injections or anything else because the disease will be well controlled without maintenance and we can talk more about that and even though there can be some side effects, a lot of people who have recovered from the transplant, particularly somewhere between the 3-6 month period after transplant can go back to again, a quite reasonable level of quality of flights going back to work, traveling, enjoying your leisure activities, sports, etc. So we do think it's a good thing in the long term for the quality of life for patients.

**Gary:** Well, thank you. I appreciate that. I think from my perspective I had to stem cell transplant plants, but more recently I had a part of my kidney removed from because I had a malignancy on it and I gotta tell ya, gimme a transplant any day.

**Dr Rafael Fonseca:** Oh really. We're not gone through either, but I sometimes say it's like recovering from a surgery and you know that it's going to take some time and…

**Gary:** … with the transplant and they tend to put a bunch of holes in you even if you use the robotic surgery and if they don't then you've got a huge incision which takes a long time and a lot of pain medication to get through.

**Dr Rafael Fonseca:** Sure, sure, sure. Well, speaking of that, we, we are trying and I think most centers are trying to do things that would improve the quality of life both before and then after the transplant. So let me just use a few simple examples, things that are not necessarily that innovative but that can greatly enhance the quality of life of patients. So even during the transplant, we tend to use far less of the more invasive catheters, we tend to use the larger catheter used for the stem cell collection, but then we would use a thinner catheter, what's called a PICC line or many of you I presume are familiar with that which goes into the arm. So we don't have to be poking the person for blood draws every morning. We can give them medications through that we've done quite routinely the use of the ice chips to prevent the mouth ulcers and then the irritation and inflammation that could happen in the throat in our patients. So that helps tremendously in preventing that from happening. We actually use some prophylactic medications to prevent infection. We worked very closely with patients with providing them some dietary advice when they're going through the transplant, even simple things like saying, you know what, if you don't have an appetizer, if you're nauseous, let's focus on a few things. Let's use smaller meals. Let's try to concentrate, for instance, in foods that won't emit an odor or smell. So maybe colder foods that are a little bit easier, let's break the amount of food you eat into smaller portion. So all of those things make a big difference in how we work towards enhancing the quality of life of patients. Then providing them with support once they leave the

hospital for their continued recovery.

**Gary:** I understand now you can also not lose your hair by using cold flow through head apparatus.

**Dr Rafael Fonseca:** Yeah, there's some efforts in that regard as well too. And I think all of those things are very, very important. Even for sometimes we tend to think and half joke people will say, well, you know, but you're "a guy or a man" and it turns out we all care. That's our, our appearance. And it's a very public display of having, been coming to be dealing with a disease. So all of those things are very, very important.

**Gary:** There's some doctors believe that MRD minimal residual disease testing will be the new endpoint for treatment. So if MRD negative patients can discontinue their treatment, are we there yet or how long before we get to that point in your opinion?

**Dr Rafael Fonseca:** If I could explain for the audience too as well. So MRD stands for Minimal Residual Disease and then we say MRD negative or positive meaning we can detect or not very, very small amounts of remaining cells in the person's body. There are two methods, one of which uses something called flow cytometry that can be done by standard clinical laboratories and there's one that it's called Next Generation Sequencing and that is actually something that we send out. This one, the last one has a sensitivity of detecting one abnormal cell out of a million cells. The flow cytometry is thought to be somewhere around 1 in 100,000 cells. So what it really tells you is that it goes much deeper than what we can currently do with standard laboratory testing. This laboratory testing that we do, what would really take you maybe two, one to the minus three, rarely wanted to minus four, I would say. So that when, when in the old days we used to tell someone, you have a complete response, what you're really saying is up to my level of detection, I don't see any residual myeloma cells, but now with the MRD testing, we're taking that to a much deeper level. So it's a very, very deep way of testing for residual myeloma. Now it's still in evolution. It's available. In fact, in our center, we do it as a matter of routine. We are hearing that the FDA is in the process of hearing and considering this perhaps as an endpoint for clinical trials and there's some technicalities and nuances of how that may apply or not but we don't have a full set of clinical trials or information that could guide us precisely about the specific question of discontinuing the disease. But let me give you a couple of examples if you, if you'd go through a transplant most of the time, we'd have patients come back three months after the transplant, what is commonly referred to as a Day 100 visit.

Then we repeat a bone marrow and now we're doing MRD and the information there is used to say, well, if you're MRD negative, it's important prognostic information to share with a patient and their family because achieving that it's a very high prognostic significance, a greater likelihood that one would not require additional therapy or be many years out from the transplant. It is not an absolute warranty, but it can help in that regard. The second situation is we're using this and and trying to understand, for instance, in patients who are on chronic therapy, I have patients and my colleagues may have some patients that for instance, having on let's say Revlimid and have been on that for eight years and then we sometimes will go through the discussion now you would you like to know your MRD status? Now that we have it, we don't have strong clinical information, but if a person told me, you know what, I am having some side effects. I'm having more fatigue. I would like to consider discontinuing the medication, I think that would be a reasonable thing to do and to consider because likewise, there's no data to suggest that you can be on Revlimid for that long, a lot of this is largely empirical. We do find sometimes that some patients will say, you know what, I know what you're telling me, but I'm not so sure I would like to start my medicine no matter what the results are. So there's a human aspect of that question too as well, but the good news is that we're even having the conversation. We're having a conversation of having to develop better tools to go deeper to understand if there's any residual myeloma and that's only because we have better treatments.

**Gary:** So now we've got a bunch of clinical trials yet to be developed to answer that question.

**Dr Rafael Fonseca:** That is correct.

**Gary:** All right, well thank you so much Jack, are you on the line?

**Jack Aiello:** Hi. I want to clarify for the audience up to now and after my talk and my questions. The definition of transplants for myeloma patients means using your own stem cells. So I wanna for many, many years. I've heard the following statements pertaining to allogeneic transplants or specifically using donor stem cells. One statement I've heard since I was diagnosed 23 years ago is that an allo transplant can result in a cure and the other statement I've heard is that if you have an allo transplant or if you're considering doing an allo transplant, it should be done within a clinical trial. So I have three questions. The first of which is, are there actually allo transplant trials available for newly diagnosed myeloma patients?

**Dr Rafael Fonseca:** Okay. Do you want me to answer one at a time?

**Jack:** Yeah, sure. I'll ask all three. So maybe you want to just combine the answer. So are there allo transplant trials for newly diagnosed patients. The second one is one type of a newer type of allo transplant is referred to as reduced intensity conditioning transplant. And I'm wondering why haven't they been more successful if they ultimately replace the patient's immune system with a donor's immune system? And then I'm kind of wondering, do you ever prescribe an allo transplant to newly diagnosed patients or is it only for patients who have run out of options?

**Dr Rafael Fonseca:** Okay. Well, thank you, thank you for the question. Let me start by the first statement you made regarding the plateau in the cure. That has been always the argument for allotransplant in the idea that you incur very high risks initially because of higher toxicity associated with the transplant and the possibility of the development of this condition of graft versus host disease, but the exchange or the trade off is that you are hoping when you embark in a treatment like this that might end up in that curve of patients who ultimately are considered cured from their myeloma because of the allo transplant. Now a couple of comments there. One is it's true that there's a fraction of patients that remain in that plateau. However we know now and including the study of previously mentioned, that's also possible with autologous stem cell transplant. So the one when you use your own cells. So I think that argument does not carry as much weight as it could have done in the past because there is a possibility that myeloma patients who achieve great response and receive optimal induction could be potentially cured with the disease with non allogeneic approaches. So that's the argument. I think for allo transplants the data has shown that this studies show benefit when they're done very early and they are not as useful when they're done for a rescue. And there's some data from the european groups, particularly Dr Garten Sweden that is not very promising. And so when we're going to compare now an allo transplant again cells from someone else versus the very best of our lineup that we have for initial therapy, including, an induction with VRD stem cell transplant and maintenance and standard maintenance.

I think it's a hard proposition for us, think of that as a potentially superior a management strategy for patients. So for that reason alone, I myself have not recommended allo transplant in greater than 15 years on any patient. Now that is not to say that one holds the truth, of course, and I know very seasoned and wise clinicians and clinical investigators who would do that and who have offered that to their patients and people that I respect their opinion, but I just haven't really found a good rationale to make this part of our standard recommendation for our patients. And again, I could mention, you know, very, very smart and wise people like maybe Dr Giralt or Dr Maloney, or Dr Benzinger who would consider this as a potential option for their patients. I do remain unconvinced and that's why we, I work like that in my practice. However, in 2017, I am a firm believer in our autologous transplant, itself. I always joke when I give my talks that I'm not a transplanter. So I do participate in the trust fund team, but I don't attend the transplant meetings, what they call tandem meetings. And I promise not to shed a tear for disappears. In fact, I probably will be rejoice if it disappears, but I do believe it adds to the care of patients with a possibility of keeping the disease in their control for longer. So that's what we have for now. Now the mortality is much higher with an allo transplant because of their risk of more serious complications. And even if it doesn't happen right away, one of the most difficult things we've seen, hematology is graft versus host disease. Now there's better treatments, there's ways to reduce that. But all of us who were in training in hematology don't really like to see that. That's really a dreaded complication from one of these procedures. That actually doesn't go away with a mini allo, which was your second question because the risk is not how much chemo you give. The risk is the other cells not recognizing now the patient's body itself and mounting this very aggressive autoimmune type

response. And they are trials. I think I can't recall if there's one open in the states. , there's several that have been looked for it in Europe, and I'll just finish with a humorous note, which is that the last time an allo transplant clinical trial was reported in the journal Blood, which was the BMT CTN 0102 clinical trial. My good friend and colleague Keith Stewart said that pursuing knowledge in egg stem cell transplants in myeloma was like second marriages, the triumph of hope over experience. And that's just summarized a lot of what we're thinking about this.

**Jack:** I appreciate that. I think you're right and I'm not recommending allos, but I, in fact, I guess what I'm taking away from your comments other than you mentioned a couple of doctors who might recommend allo is that, it's kind of heading either towards not doing allos at all anymore or again, is it considered. I mean, some doctors might consider it as a for patients who have run out of other treatment options?

**Dr Rafael Fonseca:** Yeah. No. So some doctors would consider it and they will do it even outside of a clinical trial. And again, I think there's a, it's a defendable clinical stance and in medicine, not everything is black and white sometimes as we would want it to be. So it's a defendable stance. Now, one of the things I meant to say, and I forgot, I'm sure the audience knows about the CAR T cells. Well the CAR T cells are a smart allo transplant in many ways, except you're using your own cells, but now they have that drive to go back and kill the myeloma cells without having the risk of cells recognizing your body itself because they're your own cells. In fact, you can take that one step further. People are thinking, and this is almost like science fiction, but it's just absolutely incredible. People are thinking of strategies that are called allogeneic CAR T cells. So could you take T cells from other patients? You could genetically engineer them so that they would not recognize the recipient as something foreign. So you could eliminate altogether the risk of graft versus host disease and still prime them to go on kill myeloma cells. So you would have them ready on our shelf so to speak, so that if someone needed CAR T cells, they could be used for that. So I do think CAR T cells will at some point over the next several years totally displace the idea of allogeneic transplant for myeloma.

**Jack:** Thank you. That's really informative. That's it for me.

**Gary:** Great. Okay. Well thank you so much. I appreciate it. Yelak, your questions.

**Yelak Biru:** Thanks, Gary. Thanks for taking the time from your always busy schedule Dr Fonseca to educate the patients. But I think most importantly for the work you do tirelessly advocating on behalf of myeloma patients. So thanks for that.

**Dr Rafael Fonseca:** Oh my pleasure.

**Yelak:** The three of us on this call, have different experiences from transplant. One has tandem transplant, one has allo transplant and the third has not yet had the transplant. All of us have thankfully over a decade and a couple of us for 2 decades. So is that question. I think most patients struggle with ease with be the one who benefits the most out of the transplant or would I be the one who will relapsed months after having gone through one? How do you answer or address this question?

**Dr Rafael Fonseca:** That's a very good question and it's a very hard one to answer in a precise way to the patient that's sitting right in front of us, in the office in the clinical scenario. We like to think that as one embarks on treatment, you start getting a flavor as you go through the various treatment stages of what kind of disease you're dealing with him. Pretty early on, you started getting some readings that would be indicative of a more favorable or perhaps a more challenging situation. I would say even that we don't have absolute predictors of how outcomes will be after transplant for the suitable candidate for the auto transplant today in 2017, I try to steer most of my patients to consider it seriously. It should say I don't think transplant is a must have because it was just one of many other treatments. I will say that there's no one that can look at the patient and say, this is something you must have, at least in my opinion, but I am of the idea that it adds significantly to the time that the disease can be controlled, so I like to put a lot of emphasis on the transplant with the caveats again and we'll be happy if it goes away. In fact, I already said that I do believe, and I think this is quite likely that the CAR T cells will displace allo. It is possible that the CAR T cells will also

displace auto and if you can just start thinking of a future where instead of having someone having to spend two and a half weeks in the hospital and have a recovery period then afterwards, that is where we are getting better and we have better understanding of how to manage the CAR T cells.

Maybe that CAR T cells will be applicable to not only younger individuals but patients of any age and patients with other comorbid conditions that normally would preclude them from going through the stem cell transplant. So it's a very long winded way of answering your question because you're asking me how do I know I am the one and and we don't really have the ability and I don't foresee at least in the near future that will have that ability to predict individually, but if you were presented with a similar set of context, say in an investment scenario, I think any wise person would say, I have to consider that if this was an investment given the overall probabilities, I don't know individually what my outcome will be. Now there's another important layer that one must consider and myself and others think it's critically important. The matter is that as we plan for transplant, we really need to try to get as much information about the biology of the disease of the individual patient, because that is coming to be a very important marker of what to do after transplant. Very specifically, and I know many of the audience are familiar with this, we talked about the risk stratification and this can be done in multiple ways. You can do the FISH analysis, you can do the gene expression which is commercially available as you know.

But it's important to do that because what do you do after transplant appears to matter and matters of lot. For patients who have high risk disease markers, it seems that standard maintenance is just not enough. We need to give them a bit more. Now we recognize a lot of our patients have been already through a lot than driving back and forth to the treatment center and getting infusions and getting injections. But we've been able to get away with ADL of using not only the combination of Lenalidomide Revlimid, which is a standard maintenance for most patients, but we actually have combined this with Ixazomib and the commercial name for this is Ninlaro pills, if you're familiar with this and we've known this for high risk patients and I can tell you the experience is still pretty short. We've known this for a couple of years, but patients with high risk markers including I have three that I can think of my practice who had deletions of chromosome 17, who are 2/3 and 3+ years out from their transplant doing very well because of a strategy that includes this types of combinations. The reason we're doing that is because a number of clinical trials have shown that using these types of drugs globally we call them, which is a mouthful, but it's a Proteasome inhibitors and that includes the VELCADE, the Carfilzomib, KYPROLIS and now this one Ninlaro Ixazomib appears to be of importance for the high risk genetic markers. So again, second time, I'm going to say it's a long winded way of answering, we don't know, but we try to adjust for the individual patient.

**Yelak:** That's absolutely correct. So you mentioned maintenance, increasingly trials are being developed or doctors are advising patients on study or off study to go on maintenance therapies until progression or a until relapse, right? If you opted not to do a transplant from the gate go or you are the ones that have to do a second transplant for whatever reason are some of the drugs more prone to suppressing stem cell collections than others? Like you mentioned, like a Imm-meds or monocular antibodies or proteasome inhibitors?

**Dr Rafael Fonseca:** Sure. That's a very, very important question. So I think the first point is just to affirm what you were saying that patients who are not going to proceed to transplant after induction, they really should be on some form of chronic therapy. Again, this may change in the future, but in 2017, I do believe that chronicity of therapy so that is long term use of medications still seems to be important. And part of this has to do with the fact that the myeloma cells are not as fast dividing. So the opportunity for us to expose them to this drug is a little bit diminished because of that. So, our patients, most of them, we would put them on some form of maintenance and if you put that in context and the question comes, okay, how does that relate to the ability to collect stem cells because maybe there's a life situation that would maybe just preclude me from having a transplant now, but I don't know if in a year from now I could do it or in the summertime and one has to consider two things. First of all, if someone has completed induction therapy, that's an ideal time to collect stem cells. So if someone could, I would recommend that they collect stem cells before they embark on maintenance treatment. Now, if that's not possible, or if the patient has to proceed to maintenance, we do have the possibility that some of the drugs could interfere with,stem cell

collection. We've learned a lot about that too as well, I have to say because we were more concerned in the past. Obviously with Revlimid, we have learned since that most patients can't collect for at least one transplant. And with the advent of this new drugs that helps move the stem cells into the circulation, the Plerixafor, we are able to actually do that in the majority of patients. This Plerixafor drug is actually quite interesting if I may for a second that, the stem cells, it's funny because they like to live inside the bones and the space inside the bones is almost one and the same with the one in our circulation in our blood. So you would ask a question, how would they stay there? How come they don't come out, how come we have to give them medication so they come out? Well, it turns out they have certain markers on their surface that make them attach to receptors that are inside the bones. So I described this to my patients and so they have matched velcro straps so they have matching velcro straps and making states and this Plerixafor, it's like comes in between the velcro and that's what makes them come into circulation and that's why we can collect it in most patients. So I would say most patients can. The other class of drugs started what we call Alkylators and that includes Cytoxan or cyclophosphamide or the Melphalan. We don't use as much Melphalan anymore, but in the olden days that was a big concern with regards to stem cell collection. But I would tell most patients can actually successfully complete. If I may, let me give you some example. I have patients who for unrelated reasons to their disease, I have a patient, I can think of a person who's on a high level professional who just told me I just simply cannot get out of my professional life right now. I'm in one of the best moments in my career. I understand what you're telling me about transplant. Can I transition to maintenance post induction and the patient now has been about seven years on Revlimid and doing very well.

**Yelak:** Okay, so my last question relates to that Dr Fonseca is how long can you store a stem cell, mine for example, they stored for almost a little over 20 years, is the time correct and how long is a viable time span for storage of stem cell?

**Dr Rafael Fonseca:** Okay, great question. For those of the audience who don't know that this cells when they're collected, they are frozen immediately and the way in which they're frozen is the cells are put in a medium that contains a substance called the DMSO, and the purpose for the DMSO is that it actually prevents ice crystals from forming. If you can imagine, if you free cells and you don't put the ice crystals form and the cells will die. They would old burst out, but by putting these DMSO the cells freeze, but they retain their structure and when they are thawed they're viable and that's what gives that smell that comes out, sometimes described as cornmeal when people get your stem cells back during transplant. Now most centers would tell patients or think about seven years that the cells were going to be stored, but this is more of an administrative comment, I believe given what we know about cryopreservation and freezing, that it is quite likely that cells that have been collected and stored for 20 years, will still be actually good. Now on top of this, we always have a human factor. If someone is doing really well and he's been 20 years, every doctor that I know would ask the question, well yeah, but they've been around for 20 years. What if we tried to get "fresh cells"? So a lot of the patients will have sales recollected, which you can do always after treatment, but the very specific answer, I think 20 year old cells probably will be good, if you're one who could not recollect cells again.

**Yelak:** Perfect. That's all the questions I had Gary. Thank you for the time.

**Gary:** Alright, well thank you. But just think how much more energy you would have with those young cells back in you. Priya some questions from the people who are listening?

**Priya:** Yes Gary. We have some questions Dr Fonseca coming in from our website. I'll just go through them with you. The first one is today is the eighth anniversary of going in for my Stem Cell Transplant. That along with maintenance dosages kept me almost cancer free for 6+ years. If transplant was so successful, should I consider another one if needed? He turns 62 in a month.

**Dr Rafael Fonseca:** Yeah, sure. My short answer would be yes. If someone had a transplant and they had, six, eight, 10 years of duration of disease control, I would strongly suggest that that's considered again. When we would face a situation like this, we usually will do some treatments again, some reduction if you

may, to be followed by a repeat stem cell transplant. They want us to do that. It's hard to give precise estimates for the person as far as how long the treatment will be effective. In general, in oncology and in cancer, you think that, as you go along through the treatments, historically we have perhaps not gotten as much benefit from a repeat treatment than when we did the first time. But if someone comes with a disease that comes out several years later, I think all bets are off and it could be that one could control the disease, maybe a person like that could have been receiving VAD treatment and then a simple transplant and now they're going to get the VRD or KLD or a transplant that it maybe some Rev maintenance and the outcomes could be as good or if not better than they were the first time around. And I cannot say they will be, but I would go with some hope and enthusiasm for that second transplant.

**Priya:** Thank you doctor. We have another question. Is it best to be at a point where you are in some form of remission before transplanting? I have also seen where many centers look for to be at least a 90 percent decrease in the M spike number. Do you agree with that?

**Dr Rafael Fonseca:** We like to see our patients be on their good state of control before they go to transplant. And this varies by center. We don't really have a strict cut off of 90%, but given what we know about the current treatments that can be used for induction, we like to have patients at least 75% reduction in their protein before doing the transplant. So oftentimes, we treated a patient and say, we would see a patient, I get so regimen one and they only have 50% reduction. We sometimes will switch to another regimen, we don't require or actually do a bone marrow biopsy and aspirate before the transplant because as long as we have the protein markers, we'd like to proceed. Now, part of the reason for doing this, it's the following: Transplant is just one treatment is the one dose of Melphalan. In fact, the credit should all go to the Melphalan. You know, everyone brings their cameras to take pictures of the stem cells and all of the stem cells with the credit really for the Melphalan. That's what takes care of the myeloma that stem cells are the rescue, but there's significant periods of time when a person is going to be without treatment before the transplant and then after the transplant, that's one recallers. So if you don't start with a right foot, meaning you don't have a very good level of response and let's say the transplant for that person didn't work as well, then you have a significant exposure there for still having a large amount of myeloma cells be residual and that's why we like to see better responses.

**Priya:** Our next question is, I live in an area where one hospital does transplant as inpatient and the other hospital does it as outpatient. Is that reason to prefer one over the other?

**Dr Rafael Fonseca:** Okay. I'm glad they didn't give me the names of that hospital, but I will tell you what I would do. Usually if, if a transplant center can do it as an outpatient in general, it implies a certain level of comfort with the transplant procedure because most centers start with inpatient and they move to the outpatient. I personally have always thought that if I was to do it, I probably would do it as an outpatient. I just like better being in my bed then being asked my birthday at four in the morning before they blow up, troll my blood. so I probably would do it as an outpatient. You have to do your research about the center and the specifics, but more centres who offer outpatient will have quite a bit of experience with the procedure and then you don't have to be dealing again with it. Well, the things that we normally have to do in the hospitals, I mean a hospital bed and be exposed to the bacteria that are in the hospital and all those things. And, that's why I would be inclined to do that. But the reality is mostly a preference. And then that's how I sell it to my patients when they're thinking about transplant. I say, well, you can do it as an inpatient and you can do it as an outpatient. Some people would be much more comfortable knowing that they're in the hospital, they're there just a few steps away from a nursing station and that may be very important for them. Some people might say, I'd rather be at my home and just drive to the center. And so the key factor is convenience because the safety for centres that have established both in safety sense seems to be quite similar.

**Priya:** Thank you doctor next question is, how is the decision to do a donor transplant made? Why donor transplants more risky for myeloma patients and other cancers and are strides being made to achieve better survival statistics?

**Dr Rafael Fonseca:** Yeah, I think it's fair to say that things have improved substantially with an allo

transplant, which I presume that's what's referred to here, by the donor transplants. The outcomes are better for patients. You do still have the risk of I mean, the major risk is, as I mentioned, not actually the drugs, the concept of graft versus host disease. What our transplanters like who to do is that they give the cells and they know the cells, there's going to be innocent bystanders that's the graft versus host disease, but they hope the cells also will attack the tumor cells and that's the graft versus myeloma effect. This graft versus myeloma effect is not as strong as it is for some forms of leukemia. So, the allotransplant is pretty standard treatment for many leukemia forms and also myeloma patients coming to this treatment sometimes with not as good at kidney function or inability to move because of the pain. So that also heightened the risk for complications and therefore there's been that great focus on allo transplant.

**Priya:** Okay. Thank you. Doctor. I know we touched up on maintenance, but we have another question on this, after transplant maintenance or not?

**Dr Rafael Fonseca:** After transplant maintenance or not. I will tell you that I think we're at the point now that even the most conservative of my colleagues now accepts that maintenance is an essential component of treatment after stem cell transplant. If you had your transplant in the past, and I have many patients like this who maybe many years out, who are not on maintenance, I don't start maintenance, but if I don't know any different, if I take 100 patients today and I were to put them on maintenance, the data is showing us as follows. The data is showing us that in general, maintenance will keep the disease away for about two years longer than if you don't take maintenance. And there's some early data that still needs to be validated by larger studies with there's early data that by as much time or there might be a difference in total survival time. So the answer to that, it's a very simple, I would say yes. Now again, the situations where an individual patient condition may preclude this, but if possible we put our patients on maintenance.

**Priya:** Thank you. Dr. We have a caller online who wants to ask a question. Person calling in from 6051816. Please ask your question.

**Caller 1:** Yes. My name is Janet and my question has to do, and I apologize I came into this call late, so if you've already covered this, just let me know, but it has to do with the mechanism of action of the Melphalan to choose prior to the transplant. My understanding is that it relies on a functioning p53, the signal cell death. What about those with 17 p deletion that are missing at least one p53 off of one allele. Does that make the transplant maybe potentially less effective or as long as you have one functioning allele with p53 you're good?

**Dr Rafael Fonseca:** Great question. That's a fantastic question. You're absolutely right. It not only applies to Melphalan, but almost all drugs, even the Velcade and the Revlimid, they'll produce certain things to the cells that make them be in an uncomfortable or toxic state if you may, but ultimately the cell dies if that level of distress reaches a point that the cell goes through a signaling process that leads to cell death or apoptosis. A lot of that is mediated through things as you mentioned like p53 and there's a number of other genes that are involved in this. So the whole thought process is that for patients who have some of this abnormalities, you can create as much stress on the cells, but they will have a weaker signal to go ahead and die and that has been the biggest challenge. I think we see that with transplant, but we see that with most other treatments because again, the, the other drugs I mentioned they do depend on that signaling. Now, one of the things, there's a couple of things that we're excited about. one is that there's groups that are trying to work towards being able to overcome some of those blocks by the lack of p53. This is very early. This is not quite ready for clinical trials, but it's been looked at quite carefully. But the other one is the immune approaches. So one of the hope is that through immune approaches you can attack the cells independent of what they're going to do inside the cell. So what signaling may occur. Let's take it to an extreme. One example would be the CAR T cells. I encourage anyone who has the time go to the web and look for a video of T cells attacking the tumor cells. They are vicious cells. They go off to the cells and inject their poisons and they kill the cells and they will depend on that p53.

So the answer is we're hoping that immunotherapies will overcome some of this for p53 situations, but p53 can be improved, as I mentioned with proteasome inhibitors. And I should have mentioned earlier, I'm sorry

I didn’t do it for those still on the line, a few months back, I actually recorded a video which available in youtube that was made for my patients, that I call stem cell transplant for patients. So it actually explained the logistics and the what to expect through the transplant, so about a 20 minute video, but I have all my patients see that before they come for their final appointment before they go into the hospital, as I tried to put it as best as I understand it without my cell being through a stem cell transplant, what transplant is like.

**Caller 1:** So would you still recommend a transplant for someone that had 17 p deletion?

**Dr Rafael Fonseca:** Yes. And followed by many induction with a combination of a Revlimid usually plus Ixazomib. And, we’ve had some, some good outcomes with that. Emory university has a good series on that as well too.

**Caller 1:** Okay. Thank you very much Dr Fonseca for answering that question. Thank you.

**Priya:** Thank you Dr, thank you Janet. We’re almost to the end of time here. And Dr Fonseca thank you so very much for sharing so much information and being so patient with the questions and all the information that you shared with us. Gary, Jack and Yelak thank you so much for your participation. Today’s talk will be made available on CureTalks website, please visit curetalks.com for details on upcoming talks. Thank you everyone. Have a great evening.