



FA Connect: Question & Answer Transcript

Session Title: Haploidentical Stem Cell Transplantation

Invited Speaker: Dr. Alice Bertaina, MD, PhD; Associate Professor of Pediatrics; Stanford University

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Access a recording of Dr. Bertaina's presentation by visiting www.fanconi.org. The recording has been uploaded with Spanish subtitles.

FARF is not making recommendations for one transplant protocol over another. Each family should consult their clinician (and FA specialists) regarding the best possible treatment protocol for their child, as each individual's case is unique to them.

Have additional questions for the speaker? Email Dr. Bertaina directly at aliceb1@stanford.edu.

Q: What are the eligibility criteria for your donors? Is there a maximum age that you would consider?

A: Yes, there are eligibility criteria which we evaluated through a pretty comprehensive workup that we do to understand if the donor is healthy enough.

To be a stem cell donor and to make sure that for the donor themselves, there is no risk in terms of donation, the workup is based on blood draws, a chest x-ray, an EKG and then a very accurate evaluation of the clinical status. Any prior disease, for example, or the existence of autoimmune disorders, can be a contraindication, but we really evaluate case by case because even in the presence of some conditions, still there is no contraindication to the donation. In terms of age, the numbers are a little difficult to explain. We prefer to have younger donors and that's why sometimes we look for haploidentical siblings, and I'll explain why we prefer a younger haploidentical donor. As an age range, we like to have a donor below the age of 50. Having said that, I've had circumstances in which I used a 54- and 55-year-old mother and father, because I didn't have alternative, and that worked out as well.

There are two considerations about the age of the donor; we prefer younger donors, let's say in the 20s or the 30s because of their ability to mobilize the stem cells from the marrow is higher, and so in this case, we know that we'll have a better collection of stem cell when we mobilize those younger donors. And two, if the donor is older, there might be a higher risk of graft versus host disease, especially of chronic graft versus host disease so, particularly when we talk about Fanconi anemia, we are very sensitive to try to pick the best donor in this perspective.

Q: And was that specific to FA patients with the age consideration?

A: Yes.

Q: There is some confusion around how a half-matched parent could be considered a better match than a 10 out of 10 unrelated donor. Even with the factors that were mentioned which favor the use of a parent donor, can you explain that again, because you can use alpha/beta T cell depletion with a matched unrelated donor, so why wouldn't you do that, instead of using the parent?

A: Yes, thank you again, because I think that this is one of the most important points, and whenever I consult a family with Fanconi anemia especially in the U.S., this question frequently comes up. I think that you know this is related to historically the use of just a fully matched donor for Fanconi anemia even when we do a t-cell depleted approach, so let me, let me try to explain it. I would like you to walk out of this meeting with a clear understanding of this topic.

The rationale behind the alpha-beta T-cell depletion is to remove from the graft, only the T cells which are responsible for developing graft versus host disease (GvHD), which are the alpha-beta T cells. So, whenever we remove these alpha-beta T cells, we remove the risk of the GvHD, because it is those cells that are mediating GvHD, either from a 10 out of 10 or from a 5 out of 10 mismatched donor. The data that we publish clearly shows that even using a donor which is just matching 50%, the reduction of the of the GvHD is so important that the incidence of GvHD using a haploidentical alpha beta T-cell depleted transplant is lower than using an unmanipulated 10 out of 10 unrelated donor.

Now, if the question is why is not better using a 10 out of 10 alpha beta T cell depleted donor instead of a haploidentical donor, those are my considerations. I showed you the data that we just published on 23 patients, where the incidence of actual GvHD is less than 20% (more specifically 17%) and we are talking about Grade II GvHD. There is no way we can further reduce these incidents just because we are using a 10 out of 10 unrelated donor, and if, instead of having 17% we have a 10%, that doesn't change anything.

My point is that, using a 10 out of 10 is not going to be beneficial in reducing the risk of GvHD, however, using a 10 out of 10 donor might be detrimental for other reasons. The most important thing about this transplant at ease and being able to infuse patients with the exact number of cells that we want. And there are two numbers that we look at, specifically the number of the stem cells, the CD 34, and the number of the alpha beta T cells.

We want to have a stem cell, the CD-34, higher than 10 million per kg and, ideally, we want to have them higher than 15 million per kg. Why? Because with this dose the risk of failure is incredibly low and the time of neutropenia is extremely short, then, because these patients engraft very, very soon. And that means that the risk of infection is lower, and the number of transfusions that they require is lower. And then, the number of alpha-beta T-cells that we want to have is low. When we collect a donor apheresis what happens? We give them medication, the GCSF to the donor we check after four days and we looked to see how the cells are actually mobilizing in the peripheral blood. Then on day five, we actually collect the cells. What can happen when we collect the cells? Either we are very lucky, and we have right away, the number of cells that we want, or we are not lucky and we don't get there. So, if we are lucky, fine. If we are not, what do we do? And that's exactly why having a donor, which is the mother or the father, in your hospital at that moment, versus having a donor which is on the other side of the country where you cannot do anything, makes a huge difference.

For example, if a clinician collected the cells from a donor, whatever they received is what they have to work with. If they get less than 10 million per kg of stem cells, and have to manipulate them, but during the manipulation they lose more cells, they'd end up infusing just 5 million per kg of stem cells. That's all they'd have to work with, which is why I feel an unrelated donor from a registry may not be the best method, and why I strongly recommended to have the related donor available. If the first collection is not optimal, I have the ability to request a second collection. This process is not established with donors from a registry.

So, to summarize, from my perspective, there is no evidence that using 10 out of 10 unrelated donors will significantly reduce the incidence of GvHD over a haploidentical donor with these graph manipulation strategies, because the incidence rate of GvHD is extremely low when using these methods. That said, there is the risk that the transplant is not successful for other reasons. Please contact me if you need more clarity around this.

Q: Can a second haploidentical transplant be done if the first one fails?

A: It really depends right? I mean it depends on the reason why you fail the first T-cell depleted haplo transplant. In general, when you have a graft failure after a first haplo transplant, our strategy is to repeat a second transplant, again, haplo, using the other donor. Most especially in Fanconi anemia, we learned that it happened either because the patient received too many transfusions before the transplant, and so they got sensitized. Therefore, they use a conditioning regimen back-to-back, and then the haplo transplant is helpful, it is enough. But there might be other reasons for the for the rejection and so in this case, it might be helpful to use another type of donor instead of a second haploidentical transplant, but this is really difficult

to generalize. It really depends on the on the single situation. It is absolutely possible to do a second haploidentical transplant, but it needs to be very well evaluated if that's the best choice.

Q: Can a sibling donor be used?

A: Yes, if a sibling donor is a haplo match, so that means they'd be a 50% match, they can be used. In general, we like to use a sibling only if they are greater than 16 years old, just because it's minor surgery and we don't want them to undergo such a procedure if not necessary. Again, different situations can call for different circumstances, such as a family going through this where the parents are not eligible as donors for whatever reason, in which we had to use someone else like a sibling as young as 12-years-old; however, we didn't have problems with that.

Q: Are their potential health risks to sibling donors that are younger than 16-years-old?

A: Not really health risks, although the only consideration is always the IRB requires a line to be put in for collection. That sometimes cannot be a peripheral line, but instead needs to be a temporary central line. Regardless, there is consistently a procedure and so they always want us to be extremely thorough in evaluating the need of this procedure to collect. But there are no risks in terms of health issues or for the donors.

Q: Can you talk a little bit more about why parents should consider this protocol if the patient has a 10 out of 10 unrelated match?

A: There are a number of new protocols, such as T-cell receptor or alpha-beta, so let me try to address the first question. If I need to choose between a 10 out of 10 unrelated donor and a haploidentical donor, with both alpha-beta depletion for the reasons I explained before, I will definitely use a haploidentical donor. One more time, the reason being, is there is no increased risk of graft versus host disease using a haploidentical donor. This has been shown in the data that we've published. And there is a risk with the unrelated donor that we don't collect enough cells, which leads to a less than ideal graft composition for the patient.

I am not sure which protocol you are referring to in terms of other T-cell depleted approach. For Fanconi anemia, and to the best of my knowledge, the approach that is very widely used is the CD-34 positive selection. We developed the alpha-beta T-cell depletion to overcome the limitations related to CD-34 positive selection. In my opinion, the CD-34 positive selection is dated, considering we have a strategy which I feel has been proven to be superior. The reason why I feel it is superior is the reduced risk of graft failure. The graft contains not only stem cells, but also effector cells, which facilitate engraftment. Most importantly, there are cells that promote the prevention against infection in the very early phase after the transplant, during the first two to three months, which is the most delicate phase after the transplant.

There are protocols with another strategy of depletion, called the CD-45RA depletion. To the best of my knowledge, this data is yet to be published for Fanconi anemia patients. In general, the risk of graft versus host disease in the cohorts that have been published with that approach are higher than the one obtained with alpha-beta depletion. So, I would be a little skeptical in using that approach for Fanconi anemia patients. There is definitely an explosion of interest in T-cell depletion, because the haploidentical transplant is now the main approach used, and so, we are trying to optimize this approach as much as possible.

Q: Regarding patients being treated outside of the U.S. where the transplant protocol is chemo only versus radiation, would you still recommend the alpha-beta depletion protocol or the CD-34 depletion?

A: I would recommend the TBI with either of the two. The risk of graft failure is lower with the alpha-beta depletion than with the CD-34 selection, so in my opinion, these 200 centi-gray of TBI dramatically reduce the risk of graft rejection and are proven to not be toxic on a long-term basis for Fanconi anemia. If the center that is using these approaches are using only Busulfan or any chemotherapy-based approach, if that works for the CD-34 positive selection, there is no reason to think that it works less for alpha-beta depletion. Although all our data produced with alpha-beta depletion have been produced with the 200 centi-gray of TBI.

Q: Is this kind of alpha-beta T-cell depletion in haploidentical transplants also available in Italy?

A: Yes, this is available in Italy. In Italy, we have a totally different health system than in the U.S., and everything is covered financially from the State. Nothing is charged to the family. It's not available in all centers, as it's an expertise in the lab, but now many more centers in Italy are doing that.

Q: In the U.S., what would be the approximate cost for this transplant once the clinical trials are concluded? If the transplant is done in a trial, what is the cost to the patient/family?

A: In U.S., even if we do the transplant under the clinical trial, the insurance pays for this transplant so it's not a cost which is an out-of-pocket cost. It is paid by the insurance exactly like the CD-34 positive selection is paid. We work with the insurances and with all the administration to make it possible, so is not extra cost for the families. When it is part of a clinical trial, there are other costs that are usually a part of the transplant which instead are paid by the research. But the transplant itself is reimbursed by the insurance. I am working hard with the company producing the kit for the depletion to have the alpha-beta deletion approved by FDA so that it can become considered standard of care, and there is a lot of work behind that but I'm optimistic that in the next couple of years, this is going to happen.

Q: Can a transplanted child be the donor of a sibling?

A: No, we cannot use a transplanted sibling. I mean hypothetically, I wouldn't say that you know scientifically it isn't possible, but in reality, I'm not going to allow us to do that.

Q: How many FA transplants have been done with alpha-beta depletion, what is the typical treatment recovery time and how does that compare with the T-cell depletion?

A: It's difficult to say how many of these transplants have been done. We published 27 patients; I would tell you that outside of that clinical trial, that we have done at least probably 25 more patients in another clinical trial, and I'm sure, in Europe there is another number, but we need to talk about what is published and what is realistic.

As for the length of the stay and the overall package of the transplant, we always say that the length of stay for the admission is around 30 days. And we are trying to be cautious, but we typically say 30 to 40 days. Seven days is, overall, the conditioning regimen, then there is the day zero, and so we aim to discharge the patient between day 20 and day 30 based on how the transplant goes. We discharge the patient when they are engrafted, they can eat by themselves and they can take a medication by mouth. The engraftment with this approach is extremely fast. Usually, you have seen the engraftment of both neutrophils and platelets by day 10-15 which is much, much faster than what we saw before when we do unmanipulated transplant or CD-34 positive selection.

After that, the most delicate time is really the first three months after the transplant, so when the patients are transplanted at Stanford, I always ask the family to stick around Stanford for at least two months after the transplant. Let's say that I asked for two to three months, and then that's usually my policy is that if by two months the patient is doing really, really well, I'm happy for them to go back to their home. My team and I see them monthly and then I'd like canonical time points; if there is any infection and GvHD, any complication which can arise, I then prefer to have them under my watch the first three months, and then send them back.

We don't do surveillance of bone marrow aspirate after the transplant if the patient didn't have any MDS or AML before the transplant, so it is just deep investigation of the immune reconstitution. The patients have a central line placed before starting the conditioning arrangement, and we keep the central line in place for again two to three months or so, depending on the age of the patient and the progress of the patients. Usually, the patients have preferred to have the central line because they then won't need to be poked every time we need to do labs. But there are other patients who are maybe young adults or teenagers that eventually just prefer to come and have the peripheral vein used, so we are flexible on that, based on the needs of the of the single individual.

There is no pharmacological prophylaxis after the alpha-beta T-cell depleted transplant. I didn't mention that. There is no cyclosporin, there is no mycophenolate, there is no tacrolimus, anymore, so these incidents of graft versus host disease are without any pharmacological immunosuppression, which of course favor immune reconstitution, and so the ability of these T-cells to be able to respond to viral antigens that can be very dangerous in the first month after the transplant. And that's an important difference with the CD-34 positive selection.

When you get the CD-34 positive selection, for two months you basically don't have any cells that can fight any viruses. Therefore, if you get any infection at that point, there is just the medication that we can give. With the alpha-beta depletion at least you have the NK cells and the gamma-delta T cells and starting 40 to 45 days after the transplant, you have a more mature T cells, which are coming up. In the normal cohort, 80% of our patients achieved a completely normal T-cell function six months after the transplant, which is amazing, because it means that, after that point that they don't require that a full prophylaxis for fungal infection viral infection and bacterial infection.

Q: For foreign patients not covered by local insurance, what would be an approximate cost for an alpha-beta T-cell depletion haploidentical transplant?

A: I have to say that it really very much depends on the institution because it is not the cost of the of the T-cell depletion itself, which is the cost of the manufacturing. The real cost of the transplant is the stay in the hospital. It's not about one given number, but it can be really very, very variable. What I can say is, if there is any case like this, what I have done so far is working with the international medicine (department) in in our institution to find the right approach. Unfortunately, I'm coming from a health system where I didn't have to think about the money, and I have to tell you it is extremely hard for me when it's about money, because I just feel that's not fair, but it is what it is. There are places in the world, especially in Europe, where you can have these transplants for free and of course, I recommend the families who are in need of this approach. I'm happy to give you the name of the doctors that work with me in Italy or other places in Europe. If you are in the U.S. and you are interested to have this kind of approach at Stanford, I will be happy to get in touch with our international medicine which can evaluate the single situation. We are trying to make discount packages for patients coming from other countries, exactly to broaden the access. I'm doing my best to work on that, but in the end, I'm not the person who really decides how much it costs, but again, I'm absolutely willing to intercede in any way that can be helpful.

Q: Is this procedure available in countries other than Italy, so other European countries?

A: I know for sure that Germany, the UK, France and Spain are all doing that and I think also East Europe. If I am correct, Prague is now up to speed the with the alpha-beta depletion. Austria for sure also and probably a number of other places.

Q: How much TBI is used in this protocol?

A: The amount of TBI is extremely minimal (200 centi-gray). To give you an idea when we transplant the patient with the leukemia, we give him between 1200 and 1320 centi-gray, so it's a very tiny dose. Plus, when we do this radiation, which is a total body radiation, there are a lot of measurements which occur before for shielding the vital organs, especially the lungs, the heart, the thymus itself, so that we are not too toxic on these areas. Our radiation oncologist is particularly good, because they really have a lot of experience and we are developing the new way to really deliver the TBI. When it's such a little amount, it is most important recognizing how you deliver the number of radiation so that it's less toxic on your other organs.

Q: Do you have information on the new clinical trial at Stanford using JSP-191 for conditioning and a timeline as to when recruitment might start for that?

A: Yes, for sure. As some of you know, this trial is basically going to explore the possibility of substituting the TBI with a monoclonal antibody and CD-117 as part of the conditioning arrangement. The transplant in this case will be a transplant from alpha-beta T-cell depleted graft condition where the fludarabine, cyclophosphamide ATG are part already of the base condition engagement; however, instead of using the TBI, there will be the use of the monoclonal antibody. In terms of timeline, I think we would probably be ready to start enrolling around the Summer or the early Fall. We have the trial already approved from the FDA and we are finalizing a number of things with our IRB; it's a very innovative and complex trial, so we want to make sure that everything is perfectly in place before treating patients, but we are getting very close to that.

Q: Is University of Minnesota using this process?

A: Yes, I believe MN is using alpha-beta T-cell depletion with their 10/10 unrelated matches. Their data is yet to be published. If I can say one thing that really makes the difference in the outcome of patients, is do not transplant them too late. With this approach, and for those who have access to it, we very rarely have problems finding a donor. We are however, in trouble if we transplant these patients too late, either because they develop MDS, or because they become very sensitized from the transfusions. So please be very mindful of that whenever you consider what to do for your children.

