



## Bone Marrow Transplants for MDS

**Gainesville, FL February 25, 2017**

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Speakers:

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**Christopher R. Cogle, MD:** So, I'd like to next introduce Dr. Preeti Narayan. She's one of our fellows in our oncology and bone marrow transplant program. She's a second year fellow and she's going to present MDS and bone marrow transplant.

**Preeti Narayan, MD:** Thank you. Hi, everyone. Thanks again for... can everybody hear me okay? Okay. Good. So, as Dr. Cogle mentioned, I'm going to kind of go over with you guys what is the role of bone marrow transplant in MDS and some of you might already be very familiar with this and others may not. So, I'm going to kind of, you know, present this from sort of the basics and go on from there.

So, you know, I'm going to start off with sort of very basic thing what is our bone marrow and you know, you can think of this basically as our factory. So, all of us are born with bone marrow systems in our bones where we make these cells that go out into the blood that we get drawn when you go and get your phlebotomy done that's the blood in your vein. So, that's like your peripheral blood, but when we think about where do these cells comes from that make up this blood the factory is actually our bone marrow and it's responsible for making the cells such as our red blood cells and as you know from what Dr. Cogle is talking about these are the kind of cells that are taking around your oxygen and things like that and as many of you might know who've received transfusions before if you feel fatigued that could be because your red blood cells are low. In addition it also has... we have our white blood cells which are the cells that are responsible for keeping us protected from infections. So, these are important if we're really low on these you might be more susceptible to infections which are sort of around us all the time and these really act as the things that can protect us from these environmental infections that are all over the place and finally platelets which is another major component are the cells that if you notice when you cut yourself, you'll initially bleed a little bit, but then you'll put some pressure and really what's helping you stop that bleeding initially are the platelets. So, that's why we care if they go really low you could be at risk for having more frequent bleeding and whatnot. So, really the bone marrow what it contains extra that our blood may not contain as much of is what we call our stem cells and these are the cells that eventually will come out and make these eventual mature cells. So, this is why we call it our factory basically.

So, now if we go into what is the purpose of a bone marrow transplant and so as many of you know probably ideally if we have healthy levels of blood cells and good blood cell counts that's what in part keeps our bodies healthy and various diseases that we deal with here in the bone



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marrow transplant unit deal with diseases or disorders that are going to effect the cells either you just don't make enough of them or for some reason that you don't make them properly and that's what we kind of see in MDS as Dr. Cogle mentioned these sort of funny cells. That's what's happening here. So, for whatever reason these cells are not being made and sort of going from stem cell to then red blood cell or stem cell to white blood cells or to platelets we're sort of getting these immature funny looking cells. So, that's why we care about having a good supply of these and so as you know diseases as MDS effects this and the purpose of a transplant in the case of a Myelodysplastic Syndrome is to potentially cure. As Dr. Cogle mentioned right now bone marrow transplant offers a potential cure for MDS and so basically the whole idea behind a bone marrow transplant is we're going to try to take those unhealthy cells whatever they may be in your bone marrow and replace them with a healthy contingent of cells that can now go on and hopefully make all these mature cells and avoid all these things like low blood counts, infections, etc.

So, the two main types of transplants that you may of heard of is autologous and allogeneic and so the autologous is where basically you're using your own cells. So, the process will be that at some point we will collect your own blood cells, store them, isolate those factory blood forming stem cells and then we'll give it right back to you after cleaning them up a little bit and whatnot. The second kind which I'm going to highlight for you is the allogeneic transplant and is this the one used in MDS and this one uses cells that are often donated by 1) your family member who is a close match to you, 2) it could be a matched to unrelated donor meaning someone who matches your blood cell type, but is not related to you. So, it's from a blood bone marrow transplant registry or whatnot and finally you can even get cord blood donation. So, this is more common in children, but you can have a lot of places store cord blood. When a baby is born the blood in the cord can be stored after asking the parent can we use this and that can be banked and it's available in a registry that doctors can access and bone marrow units can access to see if that's a potential match for you, too. So, these are the sort of ways... these are the two big ones if you're kind of thinking in your head how do we get what kinds of transplants we do.

So, this slide really is just to show you some statistics and these are taken from 2010 and as you can see here this is breaking down the allogeneic versus autologous allogeneic transplants in the United States and if you see if you look at different disease here along the bottom you can see there's a different proportion of where we use the auto meaning cells from yourself versus the allo where it's cells from somebody else and if you can see here in the MDS and I'm just going to put my pointer over it here you can see it's all allogeneic. So, if you are going to go to transplant for this we will be looking at a donor for you to do the transplant with and some of you, like I said, may be familiar with this.

So, where do we get or how do we get your stem cells out of your bone marrow? That's the next big question. Let's say now you've decided you're going to proceed with the bone marrow



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transplant how are doctors going to collect this from your potential donor. So, we have three common ways, again, that I sort of alluded to, but we'll go into more detail about. The first one as you can see is the bone marrow itself, the factory itself and where do we make the bone marrow? In children we make it in our bones. So, when we're born our bones inside if you look inside there's a soft spongy area and that's where our factories of all these stem cells, blood forming cells, etc. So, as we get older these areas tend to reduce down. More of our marrow is replaced by fat and what we call yellow marrow which is not as useful, but in an adult we can still get in a couple places and our hip bones are most common 1) because it's pretty easy accessible without causing too many risking other harm or damage to your body and so we can do this under anesthesia. In the case of your donor they usually will go under anesthesia in a day procedure and then in the OR the doctor will be able to go into the hips and through multiple passes collect these cells. For the patient itself who's donating this marrow they might feel a little sore afterward and then they'll usually spend a couple hours in recovery as per any surgery where there's any kind of anesthesia involved, but usually they're able to go home the same day and they'll be sore for a couple of days but usually people, the donor, for the donor this is only... this doesn't cause too much discomfort which is good. The other way we can use is called peripheral blood and, again, we're all familiar with this. We've all been to the doctor's office where we've gotten our blood drawn. In this case what we do is because we don't have on average as many stem cells floating around in our peripheral blood what you're going to get is your donor is going to get a five days of a special injection that's going to sort of gear up their bone marrow and is going to make them put out a lot of these sort of blood forming cells into the peripheral blood so that when they go to draw this from that donor that blood is going to be very rich in stem cells. So, that's the idea and so your donor will donate the blood and then that will be processed, again, into your transplant blood and as I kind of mentioned before we have cord blood, which is, again, can be collected at birth basically and, again, as far as at least I'm more familiar with this is used more because of the amount... you can imagine the amount of blood in the cord is limited. So, often this is more used for children in transplant, but there's... I think there's possibilities of pooling cord blood donors if you have multiple matches that you can then give to a patient.

So, this schematic is kind of trying to give you guys an idea of how we go through this process. So, the way we do it is the collection which I mentioned to you. Once we've identified your donor they will go and get their blood collected and usually this can even be done even a couple of days before you have your transplant. This process, again, of finding the donor can take a couple of months. So, as Dr. Cogle had mentioned oftentimes you may in the meantime between you and your doctor depending how your disease is doing you may be getting some treatment either Vidaza or some other treatment in the meantime to kind of while we're getting this process together and usually that's finding your donor, matching somebody, getting you through all the necessary tests and everything to make sure you are ready for the transplant that it's safe to transplant you and then finally when everything is sort of ready with our coordinators and



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everything your donor will go and get these cells collected. At that point that blood from the donor will go to a processing center and that's here at Shands we have it right there in-house. So, it'll go right here and people will work on sort of cleaning it up as I said, concentrating those stem cells and making it into a nice transfusion unit and the transplant when you think of organ transplants that's like a big surgery. You'll go in, you'll get an operation, but this the bag oftentimes some people are surprised. It just looks like a blood transfusion bag at the end of it after all that even though we call it the official bone marrow transplant, it's what's in the bag that's different than your typical red blood cells or platelets that you may have been getting used to being transfused with. Then we go into step three is when the cryo preservation. This could be used in cases this is where we freeze the cells to store it and this can occur in a couple of cases, 1) if your donor donates the cells well before you're getting the transplant they'll have to be preserved. We don't want those cells to break down. Obviously, all this hard work has been done to get you these cells. The last thing we want to do is have them break down. So, they could be frozen or if you have extra cells because the donor was able to donate so many cells that they had a lot more than they needed even for your transplant. They may freeze those extra cells for you for banking for later.

So, next if we go to step four, this is the part for the patient now. So, basically the patient is going to be admitted to the hospital. This is going to be when the real transplant process gets started where you're going to get then high doses of chemotherapy and this is a bit different from the chemo that you might think of if you're just receiving chemotherapy to treat your disease. The idea here is that this chemotherapy is strong enough that it's going to kill your bone marrow. So, that's why you're admitted to the hospital and then you're going to get basically get this chemotherapy to take out hopefully all the bad cells in the bone marrow and then we're going to give you these new stem cells to sort of repopulate everything. So, and that's where we see step five as you can see that the stem cells are infused and like I said it could be in the style of like a transfusion where it feels like you're being hooked up to this bag of cells and it's just (inaudible 13:29). So, that's kind of the basic steps here.

So, again, as far as what is the timing of all these things? So, as you can see step one is our conditioning which is giving you either the chemotherapy or other treatment to wipe out that bone marrow so that we can get you ready for your new infusion of cells and basically, again, it's doing a couple of things. It's removing your marrow, but it's also suppressing your immune system from rejecting your donor stem cells because we want to make sure you get your stem cells and they can start up again in your system and create new healthy cells. The stem cell infusion itself only takes a couple of hours and it's done in the hospital. Then we go into sort of a waiting phase which is basically now that you've been given these new stem cells what's going to happen to your blood counts? Initially actually after your transplant your blood counts are going to go down and that may seem odd, but what's actually happening here is this is the effect of the chemotherapy or treatment we've given to you. So, your counts will go from whatever



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they were at and they're going to go down, down, down and they're going to eventually hit a point where they're almost zero and very low and you may potentially need some transfusions to support you through that phase. Then we have a period... so, that's what you see is called the neutropenic phase meaning your white count can be low at this time and the reason why we watch you in the hospital is because, again, you're more prone to infection and whatnot. So, we want to make sure that we're able to treat you for any potential infections you may have or anything else. If your blood counts go low you might need a transfusion to support you and really this phase is just waiting on those new fresh stem cells to engraft and sort of start to grow and as you can see this can take up to 20 days and then you have what we call our engraftment phase. At some point that zero count is going to start creeping up slowly and this is where we're hoping that your new fresh stem cells that you've been given are going to now be taking over and that can take anywhere from two to three weeks to happen to get to the point where your counts, again, are healthy enough that you can go home and sort of continue your recovery at that point and then we have our post engraftment period which can kind of it goes beyond that. It's sort of the indefinite period beyond that where you're going to be following up with your doctor, you're going to be checking your blood counts, you're going to be monitored for any symptoms or anything like that, but that's basically the idea here.

So, Dr. Cogle touched on this so I'm not going to spend too, too much time, but again we had how did we prognosticate people to take them to bone marrow because as you can see hopefully from my description bone marrow is a pretty involved process. It takes not only a number of months but keeps you in the hospital for a long time and potentially there are some complications which we work hard to minimize, but we want to ideally choose patients who we think 1) are going to do well with this and also who are going to benefit from this. So, as you can see here we have what patients when we prognosticate you here based on as Dr. Cogle had mentioned how many blasts are in your bone marrow, your genetic make up, your blood counts which are those cytopenias here and as you can see I've highlighted here this high risk section and you can see there's two sections called Intermediate 2 and high risk and if we put you into those two boxes so to speak then you are a candidate for a bone marrow transplant potentially and if here this is just to show you kind of on average and this is taken from 1997, but at that time this group of patients they looked at these were how the patients fell into these groups. So, as you can see the majority of patients fell into the low and the Intermediate 1, but you can see there's a significant number of patients, about 30 percent who are potentially bone marrow transplant candidates that then we would consider to do a transplant because as I mentioned this is offering now potentially curative treatment for this disease and, again, I put this revised one up. I know you guys have already seen it, but this just now... this was revised from that original IPSS score to include more of these cytogenetic groups that we've been talking about, again, because we're realizing how important this is to your treatment to know what is your chromosomal make up that makes up your specific MDS. As you can tell MDS is not one catchall thing. Everybody's MDS is a little different. So, again, we're looking into ways to trying to figure out more and more who are the





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people that benefit the most from these treatments and, again, we stratify it pretty much the same way and the graphs here at the bottom are just showing you, again, your risks. So, very high, obviously, is the red line closer to the bottom here, which those patients don't tend to do as well versus patients with very low MDS tend to do better left on their own before we treat them.

So, again, now we've sort of established that we do these bone marrow transplants for our high risk patients and so what are the other things we look at now that we determined you're a high risk patient. What else can we look at now to determine is this the right thing to do? Is it right to go through this transplant process? So, to be considered there's some general guidelines we try to look at or think about and basically you want somebody in relatively good health otherwise other than their MDS. If you have a patient who has maybe a lot of other medical problems cardiac issues or other very significant diseases you have to take that into account because the bone marrow process can be a stress on your system and you want to make sure that the body has enough reserve to sort of get through that tough process. So, again, we don't want an acute severe illness. So, something new, a poorly controlled infection. We want to get those all under control because, again, we're going to be putting these patients in a state where potentially they could pick up other infections. So, we want to get them as healthy as possible before they go through this process.

Where we say preferably have a well matched HLA done. So, what is HLA? HLA is when we're looking for your donor we're going to look at these markers that are on cells that kind of tell our immune system... when our immune system fights an infection you might ask how does it know this is an infection and this is not an infected cell and the way it does that is looking at these HLA markers. So, these are markers are kind of like a team jacket like I'm part of the team. I don't know if you follow football, like I'm a Patriot or whatever and the bad team is the opposing team and so your body will use this to decide is this a cell that belongs to us, part of our team that I don't want to attack and I don't want to kill versus is this a cell that I need to get rid of. So, we want to find your donor who matches you as closely as possible because you can imagine if we give you donor cells that are so different from yours, you're going to try... the donor actually is going to come and try to attack your body because it's going to think what is this? This doesn't belong to me. So, that's important, of course, and then we want to also make sure that your MDS is relatively well controlled in the sense that if it's progressing at such a rapid rate that before we even think we can get your to transplant that you're going to be a lot sicker than you were when we evaluated you that's going to affect how well you do with this and also this can't be said enough. The caregiver's role is so important in this. You need somebody who can really support you through the process and help you get through it, get to your appointments and help you with the things that might come up throughout this process.

So, how effective are these bone marrow transplants? So, there's a couple of studies quoted here, but generally speaking there's maybe about a 20 to 30 percent progression, free survival



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progression free meaning like how long can we sort of hold your MDS where it is before it starts to get worse again and this was done in older patients. So, patients above, I believe, 65. So, 20 to 30 percent. So, there's a benefit in older patients and even in the Center for International Blood and Marrow, they had a 30 to 40 percent progression free survival and these included some younger patients as well and the more important thing is if we're going to put you through a bone marrow transplant, we want to make sure you come out the other side with hopefully a better quality of life than you had before. That's the whole goal of it is to help you feel better. Could quality of life mean reducing your number of transfusions because that affects how well you feel if you don't have to keep coming back as often to the doctor to get a transfusion.

So, the risks and this is an important thing we should talk about. So, bone marrow transplants even though the transfusion part of it seems simple enough, it is a complicated procedure and it's still a very high risk procedure. So, we want to, again, make sure we're taking patients that we think will do okay with this. Again, a higher that risk score that we talked about could increase your relapse risk and transplant related mortality and so that just means your risk of just having a complication from the transplant in a way is affected by your score to start off even though we're picking people already with high scores and also we have to think about age. There's no done age cut off for a transplant, but generally speaking as you get older above 65 – 70 years old the risk is going to increase, so we have to look into that.

So, here I've tried to show you a slide that kind of summarizes the main risks that we worry about after a transplant. So, here basically the majority the majority, the major complication could be just the progression of disease, unfortunately. So, that is the majority of the pie here, but we do have some other things which I'm going to touch upon. One is called graft versus host disease which I'm going to talk about a little more, but that's an unusual case. Like I said the goal of a transplant here is by putting in these new donor cells what we're hoping is that immune system, that donor's T cells and B cells are going to come and look at your disease and start killing it. So, we call that a graft versus cancer effect meaning... and that's a positive thing we're looking for, but the flip side of this coin it's a very fine balance is a graft versus host disease meaning that are these cells going to then turn on your own tissues and organs and start thinking of them also as things that are foreign and start attacking those. So, that's the balance we're trying to look for. We want the effect against your MDS, but not against your other tissues and organs and then, of course, we have infection, a small risk of other cancers and any other complications basically when we go down the list.

So, if we focus, again, on graft versus host disease this is the one whereas I mentioned this is when your donor... the donor cells from your donor are going to at some point maybe look at maybe your liver or look at your skin or look at some other part of your body and suddenly think is that a bad cell and they might start attacking that and that's what happens here and so you can get symptoms because of that. You can get skin issues, you can get organ damage and we have



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two types of GVHD that we think about. One is acute which happens in the first, usually, 100 days after your transplant which can occur as a skin rash as you could have GI symptoms, nausea, vomiting or you could have issues on your blood counts. You could have effects to your liver and this often occurs as you have a less matched transplant. So, if your transplant was unrelated matched donor, not related one that risk is increased as you were less matched for the transplant. The treatment for this is us all things that suppress the immune system. So, what we're trying to do is tamp down that immune system so we might use steroids, we might use some of our immunosuppressive medications that you might see people who get solid organ transplants on such as Tacrolimus and generally speaking this often can affect older individuals more than younger individuals, but it can happen to anyone and then we have the phase after that 100 days called chronic GVHD. So, you may do totally fine after your transplant but then somewhere down the road you might have some of these symptoms again and they tend to initially mimic autoimmune disorder sometimes because it's a decent distance from your transplant so they may be working up other things and, again, you can have rash, you can have other issues. It tends to be maybe sometimes a little less severe than the acute GVHD and we often treat it the same way and so this is a major thing that if you've had a transplant especially an allogeneic transplant which this happens in this is what your doctor will be following with you and your doctor will be asking you about these things. Have you been noticing any rashes? Have you been having any nausea or vomiting. So, it's important to share these things with your doctor if you're having anything, any concerns you should share these openly with your doctor. In many people we can kind of control this, but I think this still remains an area where we're always trying to find that balance. We don't want to suppress immune system so much that we take away that effect of your new immune system because want it still to fight off infections and do the good work that it does, but at the same time we don't want it to be overactive. So, it's like a seesaw.

So, other risks that we think about is due to low counts which you could have they're very uncommon usually after transplant, but they can happen and, again, the idea behind this would be to support your counts and to keep them as high as possible and also a very rare thing that could happen is what failure to engraft. So, what I talked about initially that period where you're going to be neutropenic meaning your counts are going to be pretty much zero or close to zero in some rare, rare cases for whatever reason the transplant does not take. For whatever reason those cells are not able to sort of grow and sort of takeover that job of being your new bone marrow. So, again, this is very, very rare, but it's something to just be aware of and of course, always we worry about anything like organ failure, but again these are very rare side effects but we look at you'll see that you will get monitored constantly for changes in your lab work, changes in your clinical condition and that's why we have patients spend such a long time with us after their transplant to watch these things very closely.





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So, I wanted to touch upon this to kind of go back to what Dr. Cogle had earlier been talking about. How do we understand a little more given what we know now about how big a process a bone marrow transplant is? What can we use to kind of figure out who's going to benefit from a transplant? Can we use these new gene mutations that we're discovering or that we're now more regularly looking at in patients to decide who might benefit more than someone else going into a transplant or who might do better after a transplant? So, this study here that was taken 2014. It took 87 patients and basically they looked at... they did the gene mutation panel on them and I've picked out three here that they picked out specifically the TP53 that you heard from Dr. Cogle. There's another one that they found that in about 21 percent of the patients that they tested here out of the 87. The DNMT3A which was found in about 18 percent and something called TET2 which I believe also Dr. Cogle had touched upon in 13 percent of patients. So and they found that actually patients who carry these mutations represented more of the death eventually after the bone marrow transplant compared to patients who did not have these mutations. So, what can this tell us? Perhaps if we have patients with these mutations we need to maybe keep a closer eye on them or we need to also figure out why is that these mutations confer... at least in this study why were they conferring worse survival than the others. They also found the three year overall survival meaning after three years how many of these patients were still alive was 59 percent for the patients without these mutations meaning 59 percent of those patients were still alive versus 19 percent with those three mutations. So, there is a difference here that we want to look into why we have this and the graph here what I'm trying to show basically here is as you can see the sort of brown reddish line is the ones with none of these mutations and as you can see their survival is the highest. Their line is the highest on the graph which means a higher survival and then these other ones represent either just having one mutated or multiple mutations and as you can see the yellow line which is the worst one there is actually the TP53.

So, I'm going to also mention one other study for you guys which actually came out very recently in the *New England Journal of Medicine* in 2017. I believe it just came out in February actually and, again, this took in a lot more patients; 1,500 patients with MDS were enrolled in this study and they were looking at how many of these patients had one as you can see at the top here, again, it looked at all the mutations people have. So, this just shows you the higher the bar was how many more patients had that mutation and what they were looking at specifically, again, do any of these mutations affect your outcome and what I pulled out here for you is that the TP53, again, the one that we saw was kind of negative in the previous study were present in 19 percent of patients. So, somewhere here more in the middle I would say down here and they had, again, a shorter survival and a shorter time to relapse meaning they relapsed quicker also and you can see that in the graph here in the first B graph here we have with no mutation on the top, no P53 mutation, I'll highlight it with my pointer here. They have a higher survival than those with the TP53 and then they also broke it down by age and as you can see here, again, no TP53 mutation, but they were less than 40 years of age. They did the best and, again, that could

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be because, again, age as we were talking about you may have less other diseases as when you're younger as opposed to when you're older and your health is just generally better at that time, too, and as you go down you can see no TP53, but greater than 40 years of age that affected it, too, and then we go into the TP53 mutations which were the worst. So, this is just to give you guys an idea of sort of what researchers are looking into now to try to really break down these grips and figure out how can we help patients that we know may have more negative mutations. Is there ways we can sort of optimize their treatment to help them to help improve these statistics.

So, I think with that that's the end of mine. Again, I just want to say thank you to Dr. Brown specifically. Of course, Dr. Cogle and then Dr. Norcken (sp? 34:29) and the other two are not here, but just for help with their slides and everything like that and with that I will turn it over if anybody has any questions or anything, can answer those.

**Christopher R. Cogle, MD:** Okay. Great. Dr. Narayan thank you very much. Any transplant questions?

**Q1:** (inaudible 35:18 – 35:32)

**Preeti Narayan, MD:** So, the question was how do we look for the donors? Do we do a blood test and actually that's a good question I didn't address. So, these registries now are so good they can send you just a swab kit actually that you just ask your donor to swab the inside of their mouth and that picks up enough DNA and then they can run that for these HLA markers and then find your match. So, usually they'll ask you if you have any family members, brothers or sisters are typically the first matched relatives we go to because your brother and sister share your genes from your mom and dad. As Dr. Cogle had mentioned, those 23 chromosomes. So, they have the best chance of actually being your closest related match, but then you can use these bone marrow registries that you may have heard of that people just go and donate or send a sample in and they're kept in a registry so that for people who don't have a direct family match they can next go to those.

**Q2:** How many HLA markers are there?

**Preeti Narayan, MD:** So, that's good. So, the question is how many HLA markers are there and I don't specifically don't know how many they test. Do you know, Dr. Cogle, how many they look at the (inaudible 36:46) typically?

**Christopher R. Cogle, MD:** So, (Attendee), there are many major HLA that are on your chromosome six and there 1,000 plus minor HLA to look at. Now, the ones we test are much fewer because of costs and necessity. So, if it's a sibling donor we only have to test about six. So, three on one of your chromosomes from your mom and three on one of your chromosomes



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for your dad which total to six. If your sibling matches on just that few number we know the rest are going to match, but if it's an unrelated donor like a volunteer in Germany that, for example, we would have to test many more and currently we're doing a total of 12, six on one chromosome and six on the other chromosome.

**Q2:** Originally, they kept referring to 10 of 10 and now it's 12 of 12 or so I...

**Christopher R. Cogle, MD:** Yeah. So, we used to do only six for a volunteer then we went to eight for a volunteer and when we did that we found we had better matching and lower graft versus host disease and then we went to 10 and we found even better matching and better graft versus host disease and now we're at 12 and we're hoping to find even better. When reading the DNA gets cheaper and faster we may be doing many more than what we're currently doing and get even a better match.

**Q2:** Thanks.

**Q3:** Okay. I hear people who are getting bone marrow transplants are having rejections and having to have multiple bone marrow transplants. Does that happen based on the higher... Even if your numbers are higher for matches, too, because that's a major concern.

**Preeti Narayan, MD:** Right. So, the question is is if even if you have a matched transplant could you have a higher rate of rejection? Generally speaking at least the better match you are ideally the less... That risk should go down, but it is always a risk. As I mention, it is a high risk procedure and so that's why it's just a matter. It's a long discussion, I guess, with your provider, too, in trying to figure out how... if it's worth the risks in your case based on your make up and I don't know if Dr. Cogle has more to say for that.

**Christopher R. Cogle, MD:** So, the other thing, (Attendee), is to make sure you get a distinguished... make sure if it's distinct between a second transplant or let's call it donor leukocyte infusion. So, a lot of times if the disease comes back after transplant and there's no angry immune system causing graft versus host disease we'll actually thaw out the donor's... some of the donor's cells and infuse that into the patient and what we're thawing out are donor white cells that attack the MDS. The term, the second bone marrow transplant is something different. That's where usually if there's graft failure it's within the first 30 days and actually... it's rare. We don't see it that often, but within 30 days if the new immune system hasn't declared itself yet then we would give more of the donor's stem cells to the patient and that's considered a second transplant, but what a lot of people that you might hear might have is called DLI, donor leukocyte infusion, and that's a dose of some cells to attack the MDS, but it's not considered a second transplant. Did I confuse you more on that?



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**Q4:** It's a second treatment, but it's not a second stem cell (inaudible 41:10).

**Christopher R. Cogle, MD:** Right. So the art of bone marrow transplant is once the stem cells are in the art is in getting off the immune suppression and easing off of it so that the donor cells can be educated and can learn what's the new environment they're in because if you rapidly take away the immune suppression that new immune system goes crazy in attacking the normal body parts. You got to ease off of it. You can't be on high doses of immune suppression for too long because it's going to dampen the immune system to find those MDS cells. So, you have that you have to contend with as well. So, you have to know exactly when to pull off of the immune suppression and allow that new immune system to wake up and attack the MDS cell.

**Q3:** So, are you using the initial donor's stuff for the additional treatment?

**Christopher R. Cogle, MD:** Yes. So, (Attendee), we're... so in the situation where you've done all the immune drug manipulations and it's still not working then you go back to the frozen cells from the original donor, thaw out one of those small bags or two of those small bags and then give that to the patient as a way to give a boost of immune cells.

**Q4:** So, you're basically trying to trick it that it's not a foreign body but more of common cells from the donor.

**Christopher R. Cogle, MD:** Yes. (Attendee)'s right. It's very much tricking the donor cells. Yeah.

**Preeti Narayan, MD:** Yeah. That this is okay. That the recipient is the same on the same team as the donor.

Go ahead, sir.

**Q5:** When you say you give more of the original donor cells to the patient, what are you (inaudible 43:05) a second transplant or a boost?

**Preeti Narayan, MD:** That could be like a boost. It depends if your counts have come back after the transplant and then you just need a boost because as Dr. Cogle mentioned the MDS looks like it might be coming back then you could get what you call this DLI infusion which is like a booster. If it's more that you didn't take the graft in the first place then you may need a whole second transfusion basically to try to get your bone marrow to respond.

**Q5:** From a different donor or from the same donor?



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**Preeti Narayan, MD:** It could be from the same donor. I think... we try not to go to a different donor until we're really sure that the first donor itself that it just didn't take the first time that it's a matter of just or giving you a boost. Finding a second donor would be more maybe if you again went for a long time and then maybe relapsed and you didn't have any more of that original donor pool of cells and it was thought that maybe you need a second donor. That's when you would consider a second donor, but typically as long as you have enough cells from that first donor you should be able to get the boost from them.

**Q6:** I don't know if this will be very beneficial to everybody, but my question is I had a bone marrow transplant 23 years ago for CML and my brother was my donor and we were 100 percent match and I was cured for CML, but now with all this talk I'm now wondering. I've just developed bone marrow issues and so I'm wondering what could possibly be his chances of also developing issues? I'm 100 percent his bone marrow.

**Christopher R. Cogle, MD:** That's a great question. So, it's very rare for a transplant to... it's very rare for the donor's disease to show up in the recipient, the transplanted recipient. It does happen. We've seen it, but it's been absolutely the exception rather than the rule. Depends on what those blood abnormalities are. So, if it MDS with genetic abnormalities happening in the donor's... for certain the donor cell, then it's certainly begs a consideration to go back... it would beg to go back to your brother and make sure that he's okay, his blood counts are okay and that he could have... he himself could also be in parallel developing an MDS if truly his cells inside of you have the genetic chromosome abnormalities that are growing up at this time.

**Q6:** Well, currently I don't show any chromosome that's more genetically though I don't think Dr. Moore tested me for that yet. I'm not sure.

**Christopher R. Cogle, MD:** Right. So, that would be your first question to Dr. Moore. So, you definitely do that to know exactly what it is because you're right it has implications when it comes to your brother. Absolutely. There are other reasons for blood counts going down after a bone marrow transplant.

**Q6:** Well, it's been 23 years.

**Christopher R. Cogle, MD:** That's why I'm... First of all, congratulations.

(Applause)

**Christopher R. Cogle, MD:** That's really wonderful, but there's lots of other... There's stromal like scaffolding, fiber blast issues in the bone marrow that could be doing that. It could be stem





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cell exhaustion. There's lots of other reasons that beside something having to do with your actual brother's... the integrity of your brother himself.

**Q6:** Well, I'm more concerned for him now. Thank you.

**Christopher R. Cogle, MD:** I think we're going to go next. Thank you very much, Dr. Narayan that was wonderful.

So, we're now going to move into the experimental investigational part of the day. I've asked Christina Cline to come and first of all present four examples of clinical trials. What she's going to educate you guys on is phase one, two, three and four and after that we're going to break for lunch and have you guys think about some questions. We have some citizen scientists who are in the back who are going to help moderate a discussion on some of the questions that we're going to ask you because you're going to be teach us after you are now educated on how we see the world. So with that, we have Christina Cline. We're very lucky to have her coming this weekend and present. Many of you might know her because she's the one that is teaching people about clinical trials in the clinic. She also goes through the nitty gritty of what being in a trial is all about. She might have been the person that helped you sign up for a clinical trial. So, she's an obvious expert person to come in and talk about it. Thank you, Christina.

**Christina Cline:** Good afternoon. Thank you for having me and for inviting me and thank you for taking the time to listen to me to present to you this afternoon.

For the sake of time I am going to scroll directly to the clinical trials that we offer at the University of Florida for patients who have MDS. So, we offer a variety of clinical trials in many different phases like Dr. Cogle said. We'll offer phase one, two and three clinical trials here. One of the first trials I want to talk about is our OxY trial. It's a phase one trial that uses this drug OxY4503 in combination with Cytarabine for subjects who have relapsed refractory AML or MDS. We launched a study here a few years ago using this drug in the clinic as a phase one and it's now moved onto bigger and better things with a sponsor and it's now open at six other sites that are using this study to treat patients. So, what the objective of this study is to find the maximum tolerated dose of this drug OxY4503 in combination with the drug called Cytarabine. OxY4503 is vascular disrupting agent and so what Dr. Cogle and his group found in the lab was that leukemia cells are very smart and work with endothelial cells to protect themselves and kind of create this niche that protects them from the exposure of chemotherapies which increased the risk of relapse or refractory disease after they've had an induction or have had previous treatment and what OxY goes and then does is it goes in and actually disrupts this vascular nature that these cells have created which then exposes the leukemic cell and initiate cell death and we think that with the intermediate dose Cytarabine it will then come through and kill an residual leukemic cells that may be floating around in the bone marrow.



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**Christopher R. Cogle, MD:** And so the teaching point on this when we prepare you for the conversation we're about to have is that this... a phase one study is mostly interested in the drug. Of course, we're interested in the patients, but the goal of a phase one study is to see how much drug we can give before it becomes too toxic to give. We don't ask about whether it works and that's sort of the secondary question, but the primary question is how much can we give of this drug. That's phase one.

**Christina Cline:** So, this treatment does require some hospitalization. It could be up to 30 days depending on how you respond to the therapy and any post treatment complications. It does affect the blood counts and when your blood counts are affected it increased the risk for infections. You can receive up to four cycles of treatment on this study and there's a follow up period as well. Inclusion, I particularly included just the inclusion for MDS since it is open for AML subjects and so for MDS you need to have blasts in the bone marrow greater than five percent and have at least failed one treatment with hypomethylating agent. Clinical trials. We have inclusion and exclusion criteria and this is to make sure that we are putting the appropriate people on these studies to answer these questions as the way the protocol is asking and to make sure that it's safe for the patient. So, depending on this study if you have high blood pressure... high blood pressure, any major bleedings or heart failure that could be an exclusion of why the study might not be fit for you. The OxY treatment itself is over 10 minutes. It's given on days one and four. The Cytarabine infusion is a two hour infusion. It's given on days one and five and on days one and four the Cytarabine is actually given four hours after the OxY and that's because the OxY is kind of going in there and being that primer to get those leukemic cells out to where they can then start cell death and be killed by the Cytarabine. Some of the most common side effects that we've seen with this are fever, flu like symptoms, bone pain, high blood pressure and some change in the bleeding as well as low blood counts and all of these typically resolve within 24 hours on their own and we also have medication that can help prevent some of these symptoms and reduce the severity of these symptoms in our patient population. The drug itself has been tolerated very well so far.

The next study I'm going to move into is a phase two and phase two studies are looking at the efficacy of the drug, how is it affecting the body and as well as looking at continual safety with the drug itself. So, for this study, this is a phase two which is evaluating the Azacitidine in combination with a drug called derva... that's what I call it. Durvalumab in patients that are untreated with high risk MDS over 65 years of age who are not eligible for stem cell transplant and so this is used with (inaudible 53:51) compared to Azacitidine alone. So, this is a randomized trial which means by the flip of a coin a computer system will then identify which arm you would receive. Would you receive Aza alone or would you receive Aza with this drug as well. This drug is a human IG kappa monoclonal antibody that is directed against program cell death PDL1 which...



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**Christopher R. Cogle, MD:** So, cancer cells are very crafty and one of the ways that they evade and hide from your immune system is they spit out a protein called PDL1. So, in these MDS cells spit out PDL1 what it does is it numbs the immune system. So, the T cells, the lymphocyte cells, fall asleep when they get around some MDS cells and other cancer cells. They fall asleep because of this PDL1 protein that's out in the... that's out floating around the MDS cells. So, there are many methods to prevent this numbing one of which is to give an antibody that attaches to the PDL1 and prevents the lymphocytes from going to sleep. So, when the lymphocytes stay awake they see the MDS cells and they kill it. It turns out that Azacitidine can actually make the MDS cells not only can Azacitidine kill some of them, but the Azacitidine can force the MDS cells to spit out more PDL1. It's the opposite effect. So, that's the reason why this durvalumab antibody is being added to Azacitidine is because we want to be able to gobble up all of that PDL1 numbing protein so you get both the good Azacitidine effect and you keep the immune system awake. That's the rationale for this. So, the question at phase two is does it actually reduce the disease. That's the question.

**Christina Cline:** Thank you, Dr. Cogle.

So, some brief information on this. Inclusion criteria is that you have not had any untreated primary that you previously have untreated primary or secondary MDS and intermediate risk MDS or very poor cytogenetics or you can have high or very high risk MDS. Your participation in the study can last up to 27 months and you could be followed up to three months until after the last subject reaches the 23<sup>rd</sup> month of treatment. The durvalumab is given IV on day one of each cycle. The Azacitidine is given subcu on days one through seven. Arm B is just subcu Azacitidine and some of the side effects that we know with Azacitidine, of course, is low blood counts, nausea, vomiting, fatigue, diarrhea. The durvalumab can cause some immune related side effects such as rash, itching, diarrhea as well and when your blood counts are low you're at risk for infections. So, we want to do everything we can to keep your body safe and prevent those from occurring.

The next study I'm going to move into is a phase three study. So, when a drug reaches phase three, it's now basically being compared to what we already know might work. Does it work just as good, does it work better and maybe does it provide less toxicity? So, it's kind of like we're comparing Coke to Pepsi maybe in the sense and so this is a phase three randomized study. It also moves into a bigger subject population than how we treat phase one and phase two, but this is to see the overall survival in patients using the drug Rigosertib compared to physician's choice. So, this drug Rigosertib is stops tumor cells from dividing and growing and it blocks proteins involved in cell division which causes these cells to die. So, currently when patients have been exposed to hypomethylating agents and these agents are no longer working what can we do to treat our patients afterwards? Most of the time it's standard... it's supportive care or



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maybe some other agent Lenalidomide that a physician might go to try to help treat the MDS. So, if they're... for this particular study this is adding... this is now introducing Rigosertib with best supportive care or you would be randomized to receive best supportive care with the physician's choice. For this particular study you have to have one of these three pancytopenias which is an ANC less than 1,800, platelet count less than 100,000, a hemoglobin less than 10, progression or failure to achieve a remission or a partial remission or you cannot tolerate the hypomethylating agent that you're receiving and it also has a strict criteria as far as being... receiving these hypomethylating agents for less than nine months or a total of nine cycles within a 12 month period of time and so what this drug as far as the infusion is it's a 72 hour infusion. So, for three days you would receive a continuous infusion with this drug. You would come to clinic. The bag would be changed every 24 hours. It goes home on a little pump. It almost looks like it's called a CADD pump. So, I don't know if you've seen insulin pumps on patients that go home on insulin pumps, but it's a small pump that you go home on and it administers the infusion for continuously and you would receive that every two weeks for the first 16 weeks. So, on days one through three. We also have nurses that are on staff to help with any troubleshooting issues that might occur after hours as well. It's very well tolerated or we would not be allowing you to go home on a continuous infusion. So, there's very minimal side effects as far as the infusion itself goes and how the infusion is tolerated. Some of the side effects of the drug itself though can, of course, cause low blood count, some fatigue, nausea, vomiting, diarrhea as well as some of the other ones that are listed below on the slide.

Is there anything you would like to add regarding...?

The next trial I want to talk about is the Clinical Trials Network. This is a transplant trial. It's a multicenter assignment trial that's comparing reduced intensity allo transplant to hypomethylating agents or best supportive care in patients that are age 50 to 75 years of age with intermediate to high risk MDS and so what the objective is is like I said to compare reduced intensity transplant to the hypomethylating agents that are out there and best supportive care. So, for treatments you could receive the transplant which involves some chemotherapy and radiation followed by a stem cell transplant from a donor and the hypomethylating agents are pretty standard. Azacitidine days one through seven, every 28 days and Decitabine days one through five every 28 days. Your participation in the study could be up to three to four years. The inclusion is that you're newly diagnosed with Intermediate 2 or high risk MDS, you have less than 20 percent blasts in the bone marrow and you're between the ages of 50 and 75. If you've had therapy related MDS or you are currently progressing to AML or have had a prior transplant then those would exclude you from the study and as was discussed earlier about side effects of transplant we have slow count recovery, graft failure, graft versus host disease, organ damage, infections, potential relapse of disease and, of course, the effects that it has on our reproductive risk. Side effects of the chemotherapy are infection, bleeding, fatigue, nausea and vomiting and



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diarrhea and I think this study was designed to help with the insurance of covering for approving for transplant for MDS up front.

**Christopher R. Cogle, MD:** Yes. This is that genetic study that we're doing. This is called I Care for Cancer Patients. This is where we're doing next gen sequencing on patients with MDS and AML in particular here at our center and we provide the genetic information back to the treating doctor who then sits down to talk with you about it. Now, it's very difficult for physicians to talk about genetic results to patients because a lot of physicians struggle to even understand what they mean. It could easily take a while to understand the genetic mutations and so we have a lot of studies about how this information is gathered, but also how it's delivered to the patients and that's a great segue for lunch now because over lunch we would like you guys to consider several questions that our citizen scientists who are joining us are going to help in moderating. So, is that...? Christine, is that all you're going to present...

**Christina Cline:** This is my last slide.

**Christopher R. Cogle, MD:** Okay. Great. So, Christina, thank you for excellent survey of the kinds of clinical trials and how doctors are thinking about MDS. We're now going to shift to how patients with MDS look at MDS and what's important to you. So, we'll break for lunch right now and then our citizen scientists will be handing out a question sheet that we'd like for you to think about over lunch and then around 12:45, which is only about 20 minutes or so for now we will then begin a public and formal discussion about the answers.

Thank you.

**Christina Cline:** One more thing. I'm sorry. I just wanted to bring to your attention you guys might have received a little card that was passed out to you all earlier. This is our navigation app for our trials here. So, you can download this app on your phone and if you go here to Find Trials by Disease site you can look at the various different disease sites that we have here at the University of Florida to offer clinical trials for and if you click on MDS, it then will open up a portfolio of clinical trials that we have to offer for newly diagnosed, relapse refractory, supportive care or correlative trials and then when you go into the actual app it will give you some basic information about the studies, some inclusion/exclusion criteria as well as a direct link to call the coordinator of the study and to actually go onto [clinicaltrials.gov](http://clinicaltrials.gov) to find out more information about the study as well and it is free. So, spread the word.

Thank you.