

Speakers:

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Rafael Bejar: So, it's twice that (inaudible 0:04) can talk about what we do when we think a person has MDS. So, if we see low blood counts in a patient and we've looked for all the usual causes of these things, low vitamin levels, low iron levels, inflammatory conditions, thyroid problems and we don't find anything, we often do a bone marrow biopsy and that's a requirement to diagnose MDS. Now, we look at the cells under the microscope, we see if they're abnormal and we see if they're not doing of differentiating as it should and that's part of the criteria we use, but then we look at the chromosomes. Here's an example of a chromosome spread from a patient where he has too many copies of chromosome 1's, have 3 instead of 2 and the last copy is abnormal. He's missing a copy of chromosome 7. So, why do we look at the chromosomes? It turns out it can help us make the diagnosis for the first time. If there is an abnormality like this, it's proof that this cell grew out from an abnormal cell and took over the bone marrow. So, it helps us establish that one of those 3 criteria that I told you before that this a clonal disease, but more importantly it helps us determine the prognosis. There are certain chromosome abnormalities that we know are more favorable and others that we know are less favorable that predict a worse outcome and finally it helps to select treatment options particularly in a case the patients who are missing part of chromosome 5. This is the 5Q deletion that you may have heard about. Patients with this have a really high probability of responding to the drug Lenalidomide and, in fact, that is the standard of care treatment for that condition. Now unfortunately, only 50 percent of cases have chromosome abnormalities that we can see when we look at the chromosomes this way. So, half of the patients we really don't benefit from all that this can tell us. So, my interest is to look a little bit deeper, to look not just at the chromosome as a whole, but to look at the actual sequence of DNA that makes up these chromosomes to see if we can find any other abnormalities that could help us in the same way.

So, these are single gene mutations. When I started in this field, we only knew about a few genes that were mutated in MDS. These are the names. They're not particular important, but they weren't that frequent. The majority of patients that we would test for these mutations didn't have any of them and even when we did find one, we didn't necessarily know what it meant to tell us anything about the patient that we didn't already know, but in the last 5 years with the help of the Human Geno Project and sequencing advancements, this is the list of genes that we're aware of now. Not every patient has every abnormality. In fact, most patients only have a few, but as you can see by the size of the circles, many of these genes are very common and not only that they've identified entirely new pathways that we didn't even know were involved in MDS a few years ago. This is a great thing. It helps us understand how the disease is formed and it helps gives us potential targets that we might be able to treat with the medication or a therapy or a drug that will help address this disease.

Now, not all of these mutations are clinically important. In other words, the presence of a mutation may not matter if it causes something that we already observed. So for example if it causes a very high blast count, well we see that in the bone marrow. So, knowing that the mutation is there may not be useful, but there's other mutations that tell us something we didn't

already know. I'll go into that right now. So, a couple of years ago my group published a paper where we looked at 439 MDS patient samples. So, this work was only made possible by patients like you who agreed to let us use some of the material from the bone marrow biopsy so that we could do research like this. It was really an entirely a patient driven process. What we did with those samples is we looked at mutations in 20 genes to see how often they occurred, what patterns they occurred in and more importantly what clinical features were they associated with. What could they tell us about the patient? So, we found mutations in a large number of genes. In fact, looking at those 20 genes, we could find mutations in close to 80 percent of the patients. So, much better than that 50 percent that I showed you for cytogenetics and in particular, we found mutations that were associated with features we already knew about. Like I mentioned, some mutations were associated with high blast count. Other mutations were associated with low platelet counts, but there were mutations in 5 genes that were associated with shorter survival than we would have otherwise predicted. So, this was a little bit surprising that if we took everything we knew about the patient, if we looked at their IPSS score, they're one of the prognostic scores that we use in the clinic, if we knew their mutation status, they told us that the IPSS was underestimating the aggressiveness of their disease. So from my standpoint as a clinician, that's a really important thing to know because if I have a patient who looks like they're going to do okay, they have intermediate 1 risk or low risk disease according to the IPSS and they carry one of these mutations they may actually behave like someone who has higher risk and I base my treatment decisions on the risk that I think patients have. So, if I think they have higher risk then I will treat them more aggressively. If I think they have lower risk, I'm going to spare them the side affects of that more aggressive therapy that may not help them in the long run. Now, these mutations weren't rare. About 30 percent of patients will have the mutation in 1 of these 5 genes. So, testing for these genes, in my opinion, in the right context can be important to help predict risk.

More recently and I mean, in the last year or so, mutations of another gene, TET2 may actually predict a favorable response to Azacitidine cytidine. It's not something that we currently use clinically, but it's something that I see on the horizon that when we do mutation testing, will include genes like this. It might help us predict outcome to therapy, the same way that we use the chromosome 5Q deletions for Lenalidomide and in my work recently identified mutations in 2 genes that may predict a poor response to stem cell transplantation. So if we have a patient that has a mutation in one of these genes, we may want to consider alternative options if we think the transplant is going to be the best one for them.

Now, what I shown you, only a little bit of it is actually even clinically available. Those 5 genes that I mentioned, that grabbed the interest of a company, actually a local company here in San Diego, that wanted to offer that test clinically and as of mid-2012 they made that available, so doctors can order that test and see those mutations. This is a company that licensed that product from us and that I advise.

What we'd really like to do here at UCSD is test not just for 5 genes, but test for 45 genes, test for a lot more of those genes that I showed you in that initial figure and we want to do it in a way that forms part of a standard of how we treat patients where a patient comes in the door, we ask them if they want to participate in the study. If they agree, we take a sample from them whenever we draw blood or do a bone marrow biopsy and we put that sample in a tissue bank and at the

same time take a part of it and run it through a sequencer where we look at 45 different genes many of which tell us something about the patient that we wouldn't learn otherwise. Then we figure out a way to validate that mutation, make sure that it's correct and return that information to the clinicians, so they can use that information in the therapy of their patients. The second part of this is that it makes work like the ones that I showed you possible in that it provides samples for doing future research that may not benefit the person who donated the sample, but will be of great benefit to the people who come after. Now, both this type of study is not something that we can do by ourselves. It's entirely dependent on patients being able, willing and eager to participate and it's also dependent on funds. So, our ability to do this is actually due to a recent gift that a donor has given us and we're very grateful for that opportunity.

So now, I want to talk about new therapies for MDS. What is on the horizon and by that I mean in the near horizon, in the near future. So, one of the drugs that I'm excited about is oral Azacitidine. We already use Azacitidine as a standard of care for patients with typically aggressive disease or disease that requires transfusions, but as you might know it's not the most convenient therapy. It's IV or even subcu under the skin. It's given every day for 7 days in a row every month. So, that requires frequent visits to the clinic, some waiting in the (inaudible 8:32) center and it can be quite a crimp in your lifestyle. Oral Azacitidine, however, is a pill. You can take it at home. It has a slightly different pattern of side effects, but they're not particularly worse than the side effects that we see with IV Azacitidine and in a recent study that was just completed, the dropout rate was about the same between the 2 drugs and the expectancy was about the same between the 2 drugs. So, I think this will be a good quality of life for treatment for patients who would benefit from Azacitidine. It's currently in a phase 3 clinical trial and I expect it will be approved in the next 12 months or so.

Now, the other therapy that we've had for awhile that is getting more traction is iron chelation. There has been a big argument about whether this is useful in MDS and one of the problems is we didn't have very good studies that looked at patients who were getting iron chelation overtime. Now last year in December at the American Society of Hematology meeting, a couple of studies were reported that has I think begun to change minds about this. From one study in particular it demonstrated that patients who had very iron levels almost entirely due to having received a lot of transfusions, if they could tolerate iron chelation, if they could take a medication that grabbed the iron and allowed them to discrete it from their body for up to a year, that 20 percent of them no longer needed transfusions. So not only did it get rid of iron that we think of the toxin in the body that might cause complications down the road, it actually made their anemia better. So, this is a therapy that I think will be used more and more. I have to admit, I haven't used it very often in my patients, but I'm reconsidering that in the right setting.

Other drugs, you've heard of Lenalidomide I mentioned. It's next generation version of Pomalidomide was recently approved for use in a different disease, multiple myeloma. It hasn't yet been extensively studied in MDS, but I think it will and whenever we have another drug even if it acts in the same way and had different side effect profiles, it will expand the options for patients who are taking medications in this class. Altrabag (sp? 10:31) and remaplustin (sp? 10:32). These are both drugs that are already FDA approved for another indication. Their goal is to increase platelet counts. They are platelet growth factors just like... you may have heard of Aranesp or Erythropoietin. That's a red cell growth factor. This is designed to increase platelet

counts in patients. It's useful in 2 particular ways. One is the patients who are platelet transfusion dependent, maybe they won't be if we can give them a medication like this that stimulate the production of their own platelets. The other thing that we see often is patients who receive therapy but is Azacitidine or Decitabine. We'll see their platelet counts fall pretty dramatically especially early on in therapy. If we can give them a platelet growth factor during that time, we may be able to allow them to tolerate that therapy better and give them a better chance for response. We don't have to dose reduce. We don't have to stop the medication. So, that's something else that's being studied in that context and will be considered more and more in the future.

The next thing we're seeing now are combination therapies. Both Azacitidine and Lenalidomide are approved for the use in MDS, but up until recently they hadn't been combined. So at the same meeting in December, I saw an article about phase 2 trial combining these 2 medications. The good news is that they were very well tolerated that they didn't seem to have dramatically greater side effects in either drug alone, but they did seem to have a slightly better response rate. Now, this is not something that we can conclude from this study because they didn't have a control arm, but the response rates were better than we would have expected based on historical data and interestingly they had a few patients that had stopped responding to Azacitidine and that when combined with Lenalidomide they showed a greater response. So, it may be what we start doing more in the future. Now, there is a trial going on right now, a phase 3 trial. It's a very large trial that has many centers across the country involved that looks at this combination of Azacitidine and Lenalidomide, compares it Azacitidine alone and also compares it Azacitidine and another drug called Vorinostat. So, it's a 3 arm trial and it'll answer that question. It'll say is this combination better than Azacitidine alone and how well does it actually work? So, this is an exciting thing to follow. Unfortunately, it's a few years out before we have a definitive answer, but since both of these drugs are already FDA approved and we have some evidence that they're safe and tolerable together, I bet we'll be seeing more of this combination going forward.

The final combination I want to talk about is Azacitidine plus the red cell growth factors. It's a small study and it needs to be confirmed, but both of these drugs are FDA approved already for use in MDS and what we saw is that patients who didn't respond to Erythropoietin by itself had a greater chance of responding when you combined it with Azacitidine. So, the goal for this is to make patients no longer transfusion dependent and this might be a way that we can do that.

Now, another area where there's a great need in MDS is what to do after Azacitidine stops working. Right now, there is no FDA approved medication for this. There are several treatment options. Some of them including intensive chemotherapy or reduced intensity chemotherapy like (inaudible 13:40), but there's a new drug on the market that's in phase 3 that targets this indication. The drug is called Rigosertib. It's an IV infusion. It seems to be fairly well tolerated and there's some indication that chromosome abnormalities may predict response particularly patients who have trisomy 8 and this is a therapy that also has an oral counterpart, but may come down the road, but it really addresses an area where we don't have a lot of therapeutic options available. Erlotinib is a drug that we use in lung cancer. It hasn't been studies extensive in MDS, but there's 1 trial that looked at using a Erlotinib in patients who had failed or stopped responding to Azacitidine and there was a 17 percent response rate which is... it doesn't sound

like a great number, but it's actually pretty good for a patient population where you have few treatment options.

Lastly, I want to make sure everybody knows about clinicaltrials.gov. This is a great website. It's put together by the National Institutes of Health and it's designed to be patient friendly. It allows you search for any clinical trial in any field of medicine by disease type, by drug type, by location types so you can see how many trials there are in California. You can zoom in and see how many trials there are in San Diego. You can see how many trials involve some of these newer drugs and it's a great way to see which center is doing what and a great way to compare what options you have and I recommend that you go check that site out.

Now in addition to everything that I just mentioned, there is a humungous pipeline of new drugs that are entering early phase clinical trials or early clinical development. The interesting thing about these is they target a lot of those pathways that I mentioned in the beginning. They're completely new in the sense of how they act. So, they may either do things that we haven't seen other drugs do before, but it may be particularly useful in combination. So, our list of options is growing dramatically and hopefully that will help us reduce the suffering associated with this disease.

And finally, everything that I talked about are all therapies that are designed to coax those cells that are abnormal in the bone marrow, to produce more normal blood cells or slow the rate of division, but none of these things really represent a cure. Right now in MDS the only therapy that we have that can rid of the disease and cure the disease is a stem cell transplant and I don't know if you saw that at the recent Robin Roberts interview, but her story has been pretty inspirational. So far, she seems to be doing extremely well after getting that and I'm really glad that she's bringing attention to this disease and to this option. So to talk more about transplant, I'm going to ask Peter Curtin to come up. We'll have a lot of time afterwards for questions. So, we'll make sure we can address anything you have to ask us.

(Applause)

Peter Curtin: So, that was a very exciting update of a lot of great research going on in MDS. So, I'm the Clinical Director of the Bone Marrow Transplant Program here. I'll just also mention that I also take care of MDS patients in the nontransplant setting as well and run some clinical trials as well. So what I'm going to do is very briefly cover some of the basics of bone marrow transplant and its role in MDS. Some of this I think you'll be familiar with going backwards.

So, allogeneic stem cell transplant for MDS. The goal here, obviously, is to replace a dysfunctional bone marrow with a normal healthy bone marrow and in many cases, it's also a goal to eliminate malignant or blast cells. Many patients that come to transplant have excess blast and so we need to eliminate those cancerous cells. Now, the word 'allogeneic,' 'allo' is the Greek word for 'other' and so in myelodysplasia where we're typically doing a transplant with someone else's bone marrow because the patient's own bone marrow is not suitable because of the disease being there and I'm going to talk a little bit more about this, but there are a number of different sources of bone marrow stem cells including related donors, often brothers or sisters, unrelated donors and in recent years the use of cord blood which is enriched in stem cells and

can be very useful in certain settings. So, Dr. Bejar talked briefly about the hematopoietic stem cell. It's a cell that's been studied for many decades and it's a cell that's been in use clinically for many decades. This is... the hematopoietic stem cell is a cell that's really programmed to produce blood cells. It's capable of self renewal. So, it's a renewable resource capable of producing red cells, white cells and platelets and obviously in my business most importantly it's transplantable and can repopulate, completely repopulate a bone marrow and I show the same sort of slide here just to point out that from the hematopoietic stem cell, not only do you get red cells and platelets and the neutrophils and cells that are very important in fighting infection, you're also get the lymphocytes and the lymphocytes are kind of the brains of the operation of your defense system and that's kind of the good news and the bad news and the kind of transplant because you're getting someone else's bone marrow, but you're also getting their immune system and that can have good and bad effects in patients. So, where you get these hematopoietic stem cells, obviously, they live primarily in the bone marrow. However, there are a number of different medicines available now that can induce these stem cells to come out of the bone marrow into the peripheral blood where we can collect them using a machine that looks like a washing machine, but basically is a sterile centrifuge called apheresis machine. So, we can collect bone marrow directly from bone marrow. We can also drive it into the peripheral blood where we can collect it and then finally cord blood which is really blood from the baby's side just before birth. Cord blood is naturally enriched with hematopoietic stem cells and so that is another source of stem cells that can be useful and one of the interesting features of the cells in cord blood is that they're immunologically naïve as you would imagine. The baby has not been exposed to much of anything and because it's immunologically naïve, we can get away with less precise matching. So, cord blood transplant has become more and more important in recent years.

So, one of the major barriers that we need to overcome when we find a donor is the HLA barrier. The HLA system is a system that your body uses to distinguish yourself versus everything else and we typically will carry out HLA matching between the patient and the donor in order to decrease the risk of rejection, that is of the patient rejecting the transplant, but also to decrease the risk of the donor rejecting the patient and that process which is called graft versus host disease is one of the major challenges in this kind of transplant. Obviously, our immune system that were designed... our immune systems were designed to distinguish ourself versus everything else and they're pretty good at doing that and so one of the challenges when you put someone else's immune system into a recipient is getting that immune system comfortable thinking of the recipient as self and that's one of the hard things sometimes with some patients getting these transplants.

So, here's the basic procedure of allogeneic stem cell transplant. First, you identify an HLA compatible donor source of stem cells. You then collect those donor stem cells either by a bone marrow harvest which is a operative procedure or by peripheral blood stem cell collection. Cord blood units are frozen away and so they're an available resource and that has some advantages in terms of timeliness. You then do what we euphemistically call preparing the recipient and that's the transplant regiment that we give just before the transplant procedure. That transplant regiment in a 20 or 30 year old can be very intensive chemotherapy and radiation therapy. However, in a disease like myelodysplasia where the median age is in the 70s, we have to use less intensive preparative regiments and the preparative regiments we use in older individuals are

much more immunosuppressive suppressing the recipient's immune system so they will accept the transplant and I'm going to talk a little bit more about that in a minute. Then the transplant itself occurs which is when the stem cells are infused into you really just like a blood transfusion and the stem cells, of course, are well designed and have tags on them that send them directly to the stem cell... to the bone marrow where they set up housekeeping and start repopulating the bone marrow. About 2 weeks after infusion, typically marrow engraftment occurs where the marrow is growing with the hematopoietic elements and the blood cells start recovering and then a much slower process is what we call immune reconstitution and so your blood counts come in a couple weeks, but your whole immune system takes about a year before it's back to full function and to give you an idea about what we're talking about, we actually revaccinate patients at about the 1 year mark just like you're a newborn child with all of the standard vaccinations and that's because this new immune system has developed from stem cells and hasn't met the polio antigen and hepatitis antigens, etc. So, here's a cartoon of the process. Here is the stem cell donor. Stem cells are collected from this donor either from the bone marrow blood. There often is some processing of this bone marrow and in some cases actually the stem cells are frozen and so in some circumstances the donor stem cells are frozen and then can be thawed and given later. In other circumstances, especially if you have a sibling donor who comes to your center to get collected, you may collect those stem cells on the day of transplant and infuse them fresh. In any event meanwhile back at the ranch, the patient is getting chemotherapy and/or radiation therapy and the dose and intensity of that depends upon the patient, their age, their disease, etc. That chemotherapy is usually given over 5 or 6 days and then immediately following that the stem cells are infused into the patient and the process of engraftment starts.

There have been a number of developments in the last decade or so in allogeneic bone marrow transplant. Probably the most important one is the development of reduced intensity conditioning regimen. So if you go back to just before the turn of the century in the late 1990s, someone the age 55 or 60 would not have been considered for an allogeneic stem cell transplant. That was because the regimens that we were using to allow transplant to occur were so intensive that they were just too toxic for the average person who was 55 or 60 or above. So in the last few years of the last century, investigators around the world asked the question whether we can do kinder and gentler preparative regimens that might extend allogeneic transplant to older individuals who not just in MDS, but in acute leukemia and in lymphoma and many other diseases are often the preponderance of patients with these diseases who need transplants and so a number of different reduced intensity regimens were developed with decreased toxicity of allogeneic stem cell transplants. They also keep the graft versus disease effect and I haven't talked about this at all, but a very important part of allogeneic stem cell transplant is that the donor's immune system is often more intolerant of the disease than the recipient's immune system has become and in fact that graft versus disease effect is a very central part of allogeneic stem cell transplant. So, decreased toxicity, keeping the graft versus host disease. This allowed us to offer allogeneic stem cell transplants to patients above the age of 55 – 60 and even into the mid 70s in some cases and so that... this is a very important development of the last, really, 12 or 15 years.

In addition, there's been an increased in donor availability. The unrelated donor registry or used to be about 9 or 10 million people. Now, it's about 18 or 20 million people worldwide who have given a couple tubes of blood, had their HLA information determined and that information then

goes into national and international databases. So, these are people who have basically said if I'm a match, I'm going to serve as a donor for somebody who I've never met who needs a transplant. It's obviously one of the most altruistic things that anyone can do, but (inaudible 27:10) donor registries have grown and grown over the last years and that increases the likelihood of finding a donor for most patients nowadays. Really in the last 8 or so years, the use of cord blood transplantation has really gotten better and better and better. Cord blood transplantation was primarily used initially in the pediatric setting because the number of stem cells you get in a cord unit tends to be sufficient for a smaller individual. In recent years, we've started using 2 cord units in larger adults and the outcome of those transplants has gotten better and better and better and it's really coming along very well and has become a nice alternative for patients who can't find a good HLA match unrelated donor and then sort of paralleling the development of cord blood transplants have been increasing protocols using what are called haplo transplants. 'Haplo' is the Greek word for half and as you can imagine genetically, your parents are half a match for you and your children are half a match for you and so those kind of people are often not only available, but nearby and handy and so these are transplants that are, I think, emerging as another option for patients who don't have a sibling transplant option or an unrelated donor option and here in the United States where we are genetically and ethnically so intermingled, it's often hard to find a good unrelated donor match in certain populations and then finally and very importantly supportive care has improved tremendously in the treatment of cancer and in transplant patients and by supportive care I mean antibiotics, graft versus host disease medications, etc. have really improved a lot and have made marked improvement in outcomes of transplant patients.

So, this is just a slide that kind of reiterates what I said about the nonmyeloablative. The word 'myelo' 'ablate'. 'Myelo' refers to the bone marrow and 'ablate' means to wipe out. So traditional bone marrow transplants are myeloablative in that you give very high dose chemotherapy plus or minus high dose radiation therapy and wipe out the bone marrow before you did the transplant. You also would be wiping out the immune system as well to allow that transplant to take place. In the decade or 15 years, we've done these nonmyeloablative transplants which are much more typically used in patients above the age of 55 or 60 and those are much more immunosuppressive regimens and don't necessarily squash the patient's bone marrow at all. Less toxicity and mortality, less late effects. It has made treatment of elderly patients feasible with allogeneic transplants. It's also allowed us to transplant patients with significant cardiac disease, lung disease and even patients with ongoing active infections in some cases. Some of these transplants can actually be carried out on an outpatient basis and I haven't mentioned this, but I'm sure many of you in the audience know that when we do 1 of these transplants often, you're looking at 3 to 4 weeks sitting in a hospital and that gets old really fast. People get cabin fever very quickly. So, some of these reduced intensity transplants are actually done in the outpatient setting.

So, this is a slide that I just wanted to... a couple slides to show that transplant is becoming a modality that's used more and more for grown up people like myself. So over here is autologous transplants. We're not going to talk about that. Here are the allogeneic transplants and the green bars are numbers of... or percent of allogeneic transplants being done in patients above the age of 50. So, you can see up to 1995, we're talking about a few percent. Almost nobody above the age of 50 was getting these kind of transplants. By the year 2000, it's about 20 percent and by

the year 2009, it's approaching 40 percent and I think in not too distant future given the Baby Boomers of which I'm one and many in the audience are Baby Boomers as well, I think that it's going to be 50 percent or more will be in patients above the age of 50 and a lot of this bulge here is really the development of the reduced intensity transplant approaches.

This is a kind of a similar slide that I just wanted to point this out because that last slide says 50 years of age and this is similar data, 2000 to 2004, 2005 to 2009 for people above the age of 60 which is this white bar and I think if you had gone back to 1995 to 2000, this bar would have been essentially nothing. It would have not existed and so this is a growing percentage of the allogeneic transplant are patients above the age of 60 and, indeed, some patients above the age of 70.

So once again, allogeneic stem cell transplant for MDS, we want to replace the dysfunctional bone marrow. We want to eliminate the malignant blast cells and all of this is done with pre-transplant chemotherapy and radiation therapy and by that I mean in the week prior to transplant and then over the long term the graft versus disease effect is really what we're counting on to keep this disease under control and to eliminate it. More intensive myeloablative or wipe out the bone marrow kind of regimens are used for younger patients; less intensive non-marrow blood regimens for older individuals.

I just want to point out one thing. So, this is a slide for the Center for International Bone Marrow Transplant Research. The CIBMTR is kind of our global organization that looks at the outcomes of all autologous and allogeneic stem cell transplants in the United States in the world, in fact, and here is the number of transplants allogeneic in green, autologous which is cell transplants in yellow for a variety of different diseases. As you can see down here, MDS with MPD which is myeloproliferative diseases, but this is mostly MDS transplants are down here. The number is somewhere south of 1,000 per year in the year 2009 and if you recall, one Dr. Bejar's slide, the incidents of MDS in the United States is between 15 and 45,000 new cases per year and so some of the difference between this number and that number is that that many patients with early stage, low grade MDS were a transplant is no the right idea at all, but I think on the other hand, I think there are plenty of patients with more aggressive of a more advanced MDS where allogeneic transplant really should be considered and isn't for a variety of reasons and we can talk about some of those reasons at the end.

So once again, standard myeloablative of transplants for younger patients, reduced intensity transplants for older patients. There's some advantages and disadvantages to both of them. One of them I would say for the standard myeloablative transplants, we've been doing those since the '70s, I would say, so we have a lot of data on those. Reduced intensity transplants really started in any great number about 2000. So, we kind of have 12 years of data, of outcome data, on those. As you can imagine, as the reduced intensity data has looked better and better in older individuals, transplant physicians like myself have started saying I wonder how well these would work in younger individuals because the treatment regimens, the myeloablative treatment regimens are very intensive and can be very harsh even for a 20 year old and so now there are a number of clinical trials that are ongoing looking at younger patients with MDS or AML who potentially going to be randomized to more intensive versus less intensive treatment regimens to see which is better and you can imagine that with the more intensive regiment, you might have a

potentially reduction in disease reoccurrence, but you might have treatment related morbidity and mortality from the intensity of the regiment whereas with reduced intensity regiment the morbidity and mortality of the regiment is going to be less, but perhaps the relapse will be higher and so that's what we have to sort out.

I don't want to spend a lot of time on outcome because I think outcome really depends a lot of on each individual patient, how old you are, how fit you are, what kind of donor you have, what kind of MDS you have and Dr. Bejar at the very beginning said something that I always say in my MDS talks which is MDS is really a spectrum of disorders. Some patients are going to live a decade or more without very much interventions, some of the lowest risk MDS patients. Other patients with higher risk MDS basically have something like acute leukemia, very much like acute leukemia and in some ways worse than average acute leukemia. So, it really depends a lot.

This is data... this is fairly recent data from the CIBMTR. I was looking at the time period from 2000 to 2009 and looking at early stage MDS and they still use the FAB classification, but looking at about 1,500 patients with earlier stage MDS. These typically are patients who had early stage disease for awhile and it become progressively... have progressively lower and lower blood counts that were requiring frequent transfusions of red cells and/or platelets. In any event, really with a sibling or unrelated donor transplant, they have about 50 percent 3 year disease free survival. Just wanted to point out that not so very long ago, maybe 10 years ago, having a sibling donor was way better than having an unrelated donor in terms of outcome. As you can imagine if you have a matched sibling, your genetic matching is probably going to be a bit better than some unrelated individual who's an HLA match for you, but really in the last 10 years or so, using DNA based HLA typing, we are now able to get really, really good matches. Matches that in the past that had looked good actually weren't so good not when we did DNA based typing. So, I guess my message is nowadays sibling donor and unrelated donor transplants can have very similar outcomes. Now in more advanced stage MDS, refractory anemia with excess blast, chronic myelomonocytic leukemia, you can see the numbers are a bit larger and the outcome is not quite as good and that's because and the biggest problem in these patients is disease recurrence, getting rid of that malignant clone sometimes works and sometimes it doesn't work. The other thing I would say is that so here over about a 10 year period, 4,000 transplants were reported and I think what that tells you is that the incidents of transplant is going up as time goes on and that's because in the year 2000, we really couldn't transplant the vast majority of patients with MDS. They were too old for the kind of transplants we were doing back then, but really between 2000 and 2012, we've gotten better at reduced intensity transplants and are now able to offer transplants to the majority of patients who have this disease.

Okay. So, just one final slide. Allogeneic transplant can be cured of MDS. Myeloablative are very intensive regiments are the current standard for younger patients although there are clinical trials to decide whether that really remains true and then nonmyeloablative, the other phrase you'll here is reduced intensity transplants is the current standard for older patients and I think for most older patients, old patients above the age of 60 who have advanced MDS, I think referral to a transplant center makes sense because you want to look at all of your options and, obviously in MDS, we have developed a number of treatment options currently, but that number is still small and many of you, many of the patients, will try those options and they'll either not work or they'll work for a period of time and we don't have a whole lot of other options. So, I

think it's important to think about and determine whether transplant is potentially the right thing or something to consider for you. So, I think I'll stop with that and Dr. Bejar and I can take some questions.

(Applause)

Peter Curtin: Especially easy ones. Hard ones for him.

Q1: I got an easy one, but I'm so dumb. How do the transplanted cells get into every bone when they only take a little shot from your hip?

Peter Curtin: The question is... I think the question is how do bone marrow stem cells make their way back to the bone marrow?

Q1: All the bone. Isn't there bone marrow in every bone?

Peter Curtin: Yeah. So in adults, most of your active bone marrow is in your pelvis bones, in your femur, especially the proximal part of your femur, in your back bones, but to be honest most bones in your body can have the capability of supporting a bone marrow function and in some patients, a good example would be cycle cell anemia patients whose bone marrows are cranking to try and make red cells throughout their life. You can actually find evidence of active bone marrow in their skull, everywhere. So, your whole bony system has inside of it tissue that is capable of supporting bone marrow function.

Q1: You can put it in once place and it will travel?

Peter Curtin: So, yes. When you... So when we do a transplant, we typically... it's an IV and it's a bag. It looks like a bag of blood and those cells go in and circulate around in your circulation and they have little proteins on their surface that look for and make them find their way to the bone marrow and sit down in the bone marrow. So, it's obviously a very nicely... and just for the record, your stem cells do circulate in the peripheral blood all day every day. It's just at very low levels. So, they do come out, swim around for a little while for some reason and then go back in. It's an interesting question.

Q2: How much blood is required when you do the peripheral blood donation or a transplant?

Peter Curtin: Yes. So, we probably... The question is when you do peripheral blood donation, how much blood is removed, I think. So maybe I can answer that in a different way. When you do a bone marrow transplant, when you literally take it from the bone marrow, you usually take about a liter of bone marrow which is your blood volume is probably 4 ½ liters or... So, it's a fair amount. When you take peripheral blood, you're not taking very much volume because all you're doing is your putting... the blood is spinning, the red cells on the bottom, plasma on the top, white cells are in a layer that you can look at, put your collection port right into the white cell layer. So, you're really just taking off white cells over about 4 or 5 hours. So, the volume that's really removed from the donor is not very much. The percentage and this is always another question donors want to know how many of my stem cells are you taking and sometimes donors

don't appreciate that stem cells are a renewable resource, but we think when we collect the bone marrow harvest, we maybe collect 2 to 5 percent of your stem cells. So, it's a modest amount of stem cells which are renewal resource. I mean, they make themselves over again.

Q3: I have two questions. They're pretty quick. Is there any difference in the efficacy of frozen versus fresh stem cells?

Peter Curtin: So, the question is frozen versus fresh. Obviously, if you're going to get seafood, you... So, that's a very good question and I can tell you that different centers preferentially do frozen or fresh. I was up at Oregon where we did fresh most of the time. Here at UCSD, we do frozen. There's no difference in outcome and even the immune cells... It turns out stem cells are pretty tough cells. They're sturdy cells. They're designed that way. Some of the other cells are not nearly as sturdy for freezing and thawing, but so the answer is frozen or fresh really no one's ever shown an outcome difference between them.

Q3: Okay. Thank you. And the second one is does the number of transfusions a patients have impact the success of a transplant?

Peter Curtin: So, very interesting question. Does the number of prior transfusions a transplant recipient has had prior to the transplant influence outcome. So, iron loading can potentially influence outcome, number 1. So, how much iron is on board and that's actually a little bit of a controversial issue, but most people think that if you're iron loaded your outcome is not quite as good. Number 2, transfusion of red cells, for instance, is a little bit of a vaccination or potential vaccination event against HLA, the HLA targets, and so in certain circumstances, heavily transfused patients may have a slightly increased likelihood of transplant rejection, their immune system and especially if you start to use the really kinder and gentler transplant regimens that can be a little bit of a problem. It's not usually a major problem. So, the answer is for most patients it doesn't seem to make a huge difference.

Q4: The question to Dr. Bejar, in the clinical trials that are indicated for new therapies on some of these medications being considered as maintenance for patients that have gotten prior therapy?

Rafael Bejar: So, the question is whether some of the newer agents that are in clinical trials are going to be considered as maintenance medications, patients that have received prior therapy. So, many of the medications that we use now for MDS are really given until the time that they stop working. They're not given for a set period of time and then discontinued and I think that will probably be the pattern with the newer medications as well. Now if a new medication is approved, that person's already received prior therapy, the only reason to try that new medication would be they have... are in a state where they need to be treated again. So, I wouldn't do it prophylactically for example. Let's say a person is doing well after receiving a therapy but stopped it because they don't like the way it makes them feel or something like that, but wouldn't necessarily add another drug unless they really needed to be retreated.

Q5: (inaudible 47:10) chelation, you indicated that the amounts of something showing that that the evidence of accumulation of the iron has having a beneficial effect on anemia. I have severe

anemia and that's one of my problems. Yet my blood transfusion not only increased, I'd like to know anything more you have on that.

Rafael Bejar: So one of the challenges of understanding whether iron chelation is a good idea is that in the past we have only looked at who got chelated and that isn't a good way to do a study because maybe doctors are only giving chelation to patients who are otherwise doing well and maybe they're offering chelation only to patients who have very, very high transfusion loads. The best way to study this is the way it was recorded in the recent study that I mentioned which is to take patients up front and give them chelation and then see what happens. So, you're not necessarily selecting patients for the amount of iron you have on board or the severity of the disease and you can imagine that someone who has received more transfusions and it may have more aggressive disease. So, it's possible that their elevated iron level is just a marker of having more aggressive disease and that is why patients have poor outcomes after transplant, for example, and not because the iron itself is there. So, it doesn't tell us that getting rid of an iron is going to be beneficial. So, the interesting thing from this study which I mentioned was supposedly unexpected was that when patients who had a lot of iron on board already and received well over 20 transfusions in their lifetime and had ferritin levels of greater than 1,000 were given iron chelation. At 6 months, about 5 percent of them no longer needed transfusions. At 9 months, it was closer to 10 percent and at 12 months it was closer to 20 percent just about 19.7 percent and that was surprising and that tells us that iron isn't just an innocent bystander that accumulates with transfusions that it really is a toxic agent that affects not only the organs that it deposits in but the bone marrow itself and that in certain situations it would be useful to try to do iron chelation and one of the things that I didn't mention about that study is that not everybody can tolerate treatment for a year. There was a very high drop out rate, about only about half the patients could make it that long in part because many patients the side effects, but also because the disease is progressing during that period and they may move on to other therapies or other treatments.

Q6: At what point is the cord blood taken? Right at birth?

Rafael Bejar: Yeah. Literally at when the placenta is delivered, you put an IV in to the umbilical cord vein and draw it out and save it and so there are cord blood banks, cord blood registries around the country and obviously it's a resource that otherwise... it would be discarded. So, it's really a wonderful thing to save it and as I alluded to the fact that the immune system is not so developed so you can actually use 4 out of 6 or 5 out of 6 matches and have pretty good success whereas if you did the same sort of mismatching with an adult donor it would be big problems because the adult donor's immune system is savvy, has been educated.

Q6: Are you seeing an increase in people that are willing to do that type of donation?

Peter Curtin: Yes. I would say it's become more and more common around the country. Not every OB setting is set up to do it and so it sort of depends and I must admit here in San Diego, I'm not connected with that end of medicine which... (inaudible 51:05) for instance, but yeah, more and more it's being collected around the country and around the world.

Q7: My question is regarding Procrit shot. If Procrit shot stimulates the bone marrow to increase the red blood cell would that at the same time increase the bad stem cell?

Dr. Bejar: That's an excellent question. Your question was if Procrit shots stimulate the bone marrow to produce red blood cells, wouldn't that not also stimulate the growth of the abnormal cells in the bone marrow. So, for Procrit, it turns out that it really acts on cells that are already partially differentiated. So, what happens in MDS is that cells begin this process of turning into mature cells and somewhere along the way they die. Typically, they commit suicide because they're abnormal and really don't know how to proceed. What EPO does it acts on those later cells and tells them to not give up, keep going, keep producing those cells. It doesn't have much of an affect on the earlier stem cell that I mentioned, but I'm glad you asked that question because the other growth factors that I mentioned, the platelet growth factors, do have that concern. The platelet growth factors affect differentiating cells like EPO, but they also affect some of the earlier stem cells and they can increase their numbers. So, one of the reasons that this is being looked at very closely in clinical trials is out of a concern that it might increase the number of abnormal cells that are there. Now, what we've seen so far, what seems to be the case, is that you can see a small rise in the number of abnormal cells in the bone marrow patients treated with platelet growth factors, but when the platelet growth factors were stopped that goes back down. So, it isn't clear that it's driving the progression of the disease. It just makes it look a little worse under the microscope during the period of treatment and that's what's going to be, I think, the determining factor in the clinical trials and how we use those medications is what effect does it have on progression of the disease.

Q7: So, do you need to do some biopsy to find out how it is (inaudible 53:04) or simple blood cell will show it to you?

Rafael Bejar: So, that's an open question. I think we don't necessarily know how to monitor that yet and that's one of the reasons the clinical trials are going to be particularly useful. I think right now the safety in lower risk patients, patients who don't already have too many of those primitive cells in their bone marrow is well established and in those patients we may not have to do any sort of monitoring like that at all.

Speaker: We have a question way, way in the back.

Q8: With regards to everything you discussed, obviously it costs money, but does Medicare cover most of this or traditional (inaudible 53:40) insurance medical plans?

Rafael Bejar: That's a great question. You're asking about would Medicare covers most of these things. So for the FDA approved therapies, Medicare does cover them and I haven't had any difficulty. I don't know if you've had any difficulty getting coverage from us for those medications. Private insurance can be trickier. There are some that are better than others and we have had some situations where an FDA approved therapy like Lenalidomide, for example, is not made available to a patient on a private insurance. In those situations, often the companies that make these expensive medications have programs that will help patients receive them. Essentially, they're patient assistance programs.

Peter Curtin: I would just say with medicines... insurance coverage for outpatient medicines in America is a big problem or cost to bore. I mean, in other words, very often health insurance will take care of you in the clinic, take care of you in the hospital, but when you have a pill at the pharmacy that... things get much dicier and as some of you have been on Revlimid know, Revlimid costs many thousands of dollars per month and similarly Exjade which is the oral iron chelation agent is very expensive and so that can be a big challenge. Very often if it's impossible for the patient then we will often go to the company and say can you help us? And often they will help us. In terms of transplant, it's very interesting. Medicare really gave the blessing to MDS transplants in the last 2 or 3 years. Prior to that, it was very hard to get approval for those transplants and so that's one... another reason why MDS transplants are shooting up is that a lot of patients with Medicare now are able to get a transplant whereas before unless you really harassed them and even then often it wouldn't work, you wouldn't get coverage. So, it's now covered, a covered benefit. Yeah. Way in the back.

Q9: With regards to the ECH2 mutation, you indicated that you need to show that the disease is more (inaudible 55:47). What does that mean in terms of like a transplant?

Rafael Bejar: That's a good question. You're asking about a specific gene mutation in a gene called ECH2. So what we found is that patients that have mutations in ECH2, for the most part looked like they had low risk disease. They didn't have very profound low blood counts, they didn't have too many blast cells in their bone marrow and they typically didn't have very abnormal chromosomes. So, we were surprised to see that patients that had that mutation seemed to have a more rapid pace of progression or a disease that affected them more severely than we predicted and we don't necessarily know why that's the case. So, we don't... I can't tell you that it's true for every person that has an ECH2 mutation. All I can tell you that as a whole, that group behaved that way. So, what that does in my mind is it takes a patient that looks like they have lower risk and actually puts them in a higher risk category which means that I'm going to treat them as if they're in a higher risk category offering the medications like Azacitidine cytidine earlier in the course of the therapy or even transplant earlier in the course of the therapy than I otherwise might have.

Q10: I have a couple of comments about 2 questions already. One is you asked about the EPO affecting something. I've gotten Procrit from the beginning. A Chicago clinical study was passed onto my doctor in Monterey that... what's the word... Neupogen which is for white cells which I have a plethora of kind of goes the Procrit to do its job a little better and so I've been taking both of those every week. The other thing is about the Medicare is that always paid except when we try to increase the Procrit from 60,000 units to 80,000 units, they said no, you can't do that.

Rafael Bejar: Interesting.

Q10: They cut it off. They said no, no, that's too much or I don't know what their reasoning was but speaking of (inaudible 57:58) every (inaudible 58:00) says 60 plus. Does it go up to 80 also? I'm in the age.

Peter Curtin: So, for transplant.

Q10: In all of this.

Rafael Bejar: I'll let Peter comment, but my comment is that after age 50, age is a relative term and we use it as a guideline but then we adjust it up and down based on everything else that's going on.

Q10: Well, his is 60. Yours is 50.

Peter Curtin: I would say we do transplants into the 70s. We don't do many transplants into the 80s, but it really depends on your physiologic age more than your chronologic age and, obviously, a lot of things are factored into that.

Q11: With Obamacare coming about in 2014, where does that leave the patient when you mention a pill that cost \$20,000. I've heard... I don't if it's a fact or not, but I've heard that there'll be a 15 man panel, man or woman panel, that will decide whether you get healthcare or not and not one of them is a doctor.

Peter Curtin: You want to handle that one?

Rafael Bejar: Your question is a good one. What will the impact of the Affordable Care Act have on medicine in general particularly MDS therapies that are very expensive. I don't know the answer to that. I think the panel you're referring to is not a panel of non-specialists that decide whether or not you get treatment or not. The only thing that I'm aware of in the Act that affects choice of therapy that will be covered or not is what they call a comparative effectiveness panel that says if we have 2 drugs, best one for how each behave and if they are equally good in a clinic, but one is 2 times more expensive, we're going to preferentially cover the first one. It doesn't mean that we won't cover the second one and maybe individual people that may need that medication, but we're going to say they have to try the less expensive one first.