Speakers:
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Ira Braunschweig, MD: … evening. It's a pleasure to be here tonight to tell you a little bit about bone marrow transplant for MDS and I think it's critical… These slides are from the Center for International Bone Marrow Transplant Registry which is one of the largest groups/organizations looking at bone marrow transplants.

So, I mentioned before that stem cell transplantation is the only curative therapy. It is. So, I think that can't be… it has to be at the forefront. This is a curative option. So, if it is a cure why doesn't everyone get a transplant right away and the answer is is because as you pointed out that it does have potential toxicities and serious side effects and perhaps even death, but again… so, we have to weight and we have to recommend and we have to use some crystal balls to the best of our ability and all crystal balls are flawed, but we have to try to sort out who recommends a transplant to and who we'd say this is perhaps not the best treatment for you. So, I'm going to try to give some clarify, add some clarity to that.

As far as what is a bone marrow transplant, the process of it, I think I only have a few slides. At the end what's the difference between a stem cell transplant and a bone marrow transplant. I could tell you about that, too, if you'd like.

So, the society is the American Society of Bone Marrow Transplantation has put out has determined with… in consultation with experts across the United States and actually the Western world when is a good time to refer? When should that doctor, that hematologist say you know, I think you should see… at least consult and explore your options for a bone marrow transplant. When should that happen? So, and the intermediate high risk IPSS. So, that is and we touched upon that. You want to know an informed patient and my colleagues have talked about this, but an informed MDS patient knows what their risk score is. That's very important and the main things that go into risk stratification is blast count, what is the percent of blasts, those leukemia-like cells; the levels of low blood counts - is someone just anemic or do they also have a white blood cell count that's low or do they even have platelets that are low and the chromosome abnormalities. The chromosome abnormalities also help us determine risk and we… scientists over the years have determined which are good, which are bad and which puts a patient at a high risk. So, any intermediate or high risk score and be proactive and find out your score or treatment related MDS. Someone like Robin Roberts who had breast cancer and was treated with chemotherapy. Refractory, low cytopenias or low blood counts. They don't really improve very much. Perhaps even with what Dr. Shastri pointed out growth factors treatment. Poor risk. Again, those poor risk cytogenetics. Those chromosome abnormalities which tend for poor outcome. Transfusion dependence is actually an indication that it should trigger a thoughtful

hematologist to say explore your option for a stem cell transplant and failure of those drugs called hypomethylating agents, the Azacitidine and Decitabine type of drugs and that also, I think, I would like to add to your question about when is… am I automatically… will be told about a clinical trial. I would say to the patient as some advice is that if things are going swimmingly well with the current therapy that patient probably doesn't need a clinical trial, but if a physician says not as good as we had hoped that would be a time to say well, do I have clinical trial options. So, failure… going back to transplant. Failure of hypomethylating agents is an indication. Transfusion dependence. So, you have to know your risk. It's very important.

This is… we're looking at survival curves. Survival curves if you're not familiar with that basically on the bottom is time and on the X axis… Y axis is survival and how many… what percentage of patients surviving and you could see that the patient with high risk MDS who is not treated… who does not undergo a transplant their survival is limited and we're looking at months. Now, if you look at that same group, that high risk group with MDS who have received a stem cell… who have received a bone marrow transplant that's in B. Right? For the group over here I'll come back. If you look just to make sure that you know what I'm talking about. So, if you look at the high risk group at about 25… this group, the As, didn't get a stem cell transplant. Right? The high risk group at about 25 months most of them virtually all succumbed to their disease, but those that did receive a transplant you see a… what we call a plateau in the survival curve meaning that they… the group that is over here remains alive. Now, it's not 100 percent or even 75 percent which we would like, but it is a definitive percent which is not in the non-transplant group. Does that make sense? This is time. This is percentage of survival. Those in the high risk group and, again, it's key to know one's risk. Ultimately, they all succumbed to their disease by about two years while in the group that did receive a stem cell transplant there is a definitive at least a quarter have been cured. It's not as good as we would like, but it offers hope to a patient with high risk MDS to be cured and the outcomes are better for the Intermediate-2 and Intermediate-1. So, it's even better for those that are a little earlier on in their course of disease, but that's the idea.

So, then we come to the very hot topic what you pointed out. Low risk, but a very difficult… what about the patient with low risk disease that is transfusion dependent and has a poor quality of life. Well, the recommendations about whether to offer that patient transplant, again, it has to be taken with a paternalistic approach is not okay. So, I think that every patient should have the option knowing what they're going through and knowing the potential for cure as long as they know the risks and the data and the data and as long as they're aware they should be left to choose for themselves. Having said that it's been looked at. This question of who should we transplant or who benefits the most… which patient from MDS benefits the most from transplant if you look at these curves. So, on the bottom is the years in delay. So, who gets harmed? Who gets harmed by delay and the high risk group is below the curve. This is loss and discount gain or loss of life expectancy. Right? This is gain or loss of life expectancy. So, below this line is loss of life expectancy. So, the high risk and especially the Intermediate-2 risk patients have a loss of life expectancy if they're not offered transplant in this analysis while the patients who have a low

risk and Intermediate-1 type MDS they have a gain of life expectancy if they don't undergo stem cell transplant. If they… they have a gain of life expectancy if they do not.

Q1: If they do not.

Ira Braunschweig, MD: If they do not. The low risk. Now, we also have to recognize that crystal balls even scientific model's crystal balls are imperfect. So, what we consider by the IPSS as low risk, but that patient who needs a transfusion every week or every two weeks that patient believe it or not in the IP… that patient who needs a transfusion every week or two it's possible to be classified in the IPSS in that risk stratification system as low risk, but we all know and I think expert physicians recognize that that patient… for that patient that prognostic model is flawed. They are not the same patient even though they're both low risk, low risk. This one is transfusion dependent every week or two and this one is not. They're both low risk, but they're not the same MDS.

Q2: (inaudible 11:23 – 11:26)

Ira Braunschweig, MD: Yes.

Q2: Do you find in the terms of MDS?

Ira Braunschweig, MD: Yes. The main things that we look at in our crystal ball who will have a prolonged survival with MDS and who will not, again, it's a crystal ball, it's flawed, but for whatever it's worth we have models of who has… could live for many years with it. We look at three factors. The percentage of blast count. That's the immature cells in the bone marrow. We look at how many of their blood cells are low. Are they just anemic? Are their white cells also low or are their platelets also… do they have three low blood cells, one or two? And do they have any chromosome abnormalities which portend for a poor outcome? Every MDS patient who is thoughtful must know their score. I would argue more important than… every… I treat a variety of hematologist malignancies of blood cancers, lymphoma and myeloma. Most patients ask me… It's very interesting actually. A lymphoma patient for whatever reason knows to ask what is my stage. It's a very common question from patients. Very common. What's my stage? Yet, for whatever reason this hasn't been disseminated because it's a little more… stage we could all wrap our head around a little bit. It's here, it's there, but I guess it's because it's a little more medical stuff, blasts. What the heck are blasts? Chromosome abnormalities. So, that's… So, MDS patients typically do not ask what is my stage. How advanced is it, but those factors will answer that. If you could plug it into… You could go onto the Internet and plug those… if you have that information you'll know your risk right away and it's very important and I would argue probably more important than the stage of a lymphoma patient. Right?

Q3: And where would that be? Is it helpful in decision making or make it more frightening.

Ira Braunschweig, MD: Oh, right. It's also the... that's also the conundrum. Very true. It's easier to kind of look away sometimes, but if we're going to confront it and know what the right thing to do and give ourselves the best chance we have to know and, of course, you're very right. It's not easy. It's not easy for everyone. No. I'm not say it is. I'm saying… but I'm saying though you're doing yourself a disservice if you don't.

So, this is more data though. The survival of non-transplant patients by low, Intermediate-1 and Intermediate-2, high risk, again, the combo of the blasts, chromosomes, low blood counts. That's the IPSS in MDS patients. So, again, if you look at the intermediate and high risk groups without a transplant they did really not very well. This is 45 months. Virtually, they were all gone by then, but here and the low, intermediate, significantly better. This is… so we generally look at about what is the survival, 50 percent survival. So, here half of the patients were alive at 75 months. That's how many years is that? Six years. Right? Six years or so. Here 50 percent. In the high risk group 50 percent were alive at 18 months. That's not so good. Right? You see that. Fifty percent were… at the 50 percent mark you go over here and you go down about, well, let's say 25… let's say 25 months. Fifty percent were alive at 25 months. In the low risk, well, it's quite a bit better thankfully and 50 percent… Fifty percent… at… 50 percent of the patients were alive at 75 months. That's better, but the high risk group that's serious. They're both serious. Now, if you look at the survival with transplant. The survival with transplant, again, this was the group, high risk group that did very poorly without a transplant and they just kept on going down like this. They didn't make it. Here is, again, that plateau in the survival curve. A portion of them, hmm, about 30 percent, maybe 28 percent have been cured. They remain disease free. Better in the low-intermediate group. Almost 40 percent that have that plateau in the survival your patients who are cured.

(Inaudible 17:12 – 17:26) have a stem cell transplant. So, the best thing is to have a sibling that's a match with you (inaudible 17:31 – 18:43) serious toxicities and there will be early deaths. There will be early deaths post-transplant and that's indicated by, look…it's a steep fall after transplant. It's a steep fall, but those that didn't succumb in the first year or so they flattened out. So, there is a steep drop off because transplant has graft versus host disease, transplant has rejection, transplant has infections, but there is a segment that are cured.

What is this? Also the… Okay. This also gets to your question very importantly. What's a RIC? What's a RIC HCT So, that's a tough question, but (Attendee) knows the answer to that. Okay, (Attendee). Hit us.

Q4: The fewest impacts will (inaudible 19:41)

Ira Braunschweig, MD: Yes. Thank you. Reduced intensity conditioning which means when I was a lot younger just starting out the doctors came up with a way to do a bone marrow transplant with not full blown take the gloves off chemotherapy. Full blown, take the gloves off chemotherapy in order to get a transplant to take is probably not appropriate for most people over

the age of 55. But doctor's over in the last… doctors over the last, hmm, now, it's going back, way back, it's the mid-'90s. In the mid-'90s they say you know what? We don't have to give them take the gloves off chemotherapy in order to get a… stem cells to take. We could give a… just immunosuppress a patient that even an older patient would be able to withstand and the stem cells still take over and still do their thing. So, that is what is known… that opened the era of reduced intensity. We give lower doses and much better tolerated doses and doses of chemotherapy that an older patient or a patient with those going back to that word comorbidities, a diabetic, a patient with hypertension, they could still withstand that chemotherapy and the stem cells still take and it could still be successful. So, that opened up the door. Most patients with MDS as Dr. Verma pointed out are older. They're not… we're not dealing with 30 year olds. Most patients are older than that. So, this opened the door for an older patient with other medical problems to have a stem cell transplant and be successful. So, that is reduced intensity conditioning, hematopoietic cell transplant. So, that brings out that point. Now, is it risk free because the chemo is lighter? No. It's still… you still have this, but you still have this.

So, in summary I would tell you that know your risk, find out your risk. Currently, for most a true low risk we say that we probably do not… we probably say to hold off on transplant. For certainly the high risk patients if they have a good donor or we could find an appropriate donor on the unrelated donor lists we recommend to go… we recommend it as a curative option and, of course, I'm glad you brought that up. Patient's preference. A knowledgeable patient who understands the risks and benefits, the ball is in their court and thank you.

(Applause)

Questions?