Speakers:
Toyosi Odenike, MD
Satyajit Kosuri, MD
Andrew Artz, MD, MS
Jean Ridgeway, DNP, APN, NP-C, AOCN

Susan Hogan: Good morning and thank you all for coming and joining us today at our MDS Foundation Patient and Family Forum. My name is Susan Hogan. I met you outside. I'm currently Operating Director of the MDS Foundation and I'll be retiring in a couple months. So, you've met Tracey Iraca. She's our newly appointed Executive Director. So, you have the two directors here today with you.

In case you're not familiar with the Foundation, we're located in Yardville, New Jersey and for the past 23 years we've been dedicated to the study of the Myelodysplastic Syndromes offering support to MDS patients as well as educational programs and for caregivers and healthcare professionals and we're worldwide. We're international.

We have a full agenda in store for you today including presentations from three MDS expert physicians from the University of Chicago, Drs. Odenike, Kosuri and Artz as well as our nurse presenter, Jean Ridgeway. You may be familiar with all these people and I just wanted to thank all of them for taking the time for joining us today.

Just some housekeeping reminders. You've seen the restrooms. They're over to the side. Very easy access. We are audio recording this forum, so if you could the tabletop microphones, if you could remember to speak into them just so that we can capture all of your thoughts and questions and just another thing in your bag you will see this little sheet. I'm not sure whether some of you have talked to Audrey Hassan from our office. She's our patient liaison. She's looking for any patients interested in taking part in an interview. So, I just wanted to point this sheet out. There's a lot of things in your packet, but take a look at it and see if you're interested. Please contact Audrey at the Foundation. She'd love to talk to you.

So, again, a very warm welcome and a thank you to our supporters, Celgene, Novartis and Taketa for making this day possible. If you have any questions about the Foundation or about today's presentations please don't hesitate to find me and I'll turn the mic over to the presenters now. Again, welcome. And when you do do the microphones, please press… you do have to press the button. Press the middle button please when you talk into the microphone. Okay?

Toyosi Odenike, MD: Good morning, everyone. I hope you can all hear me. My name is Toyosi Odenike and I'm one of the doctors here, hematologist oncologist here at the University of Chicago. MDS is one of the blood and bone marrow cancers that I focus on. I'm grateful that you're all here today giving up your valuable Saturday morning to join us and I do hope that you will find our session informative.

So, my talk is going to generally try to cover give a broad overview of these three main questions which I'm often asked when a patient with MDS comes into my office. What is MDS, what are the treatment options and what are the some of the clinical trial opportunities available for patients with MDS?

So, Myelodysplastic Syndromes are actually a group of bone marrow disorders. So, although we talk about MDS as if it is one disease this is a group of diverse bone marrow disorders that are united by the fact that they share certain features some of which are shown on this slide. So, patients with MDS generally have cytopenias or low blood counts and this is can affect a human being variably by resulting in an increased predisposition to infections, bleeding or fatigue. Patients with MDS also have evidence on review of their blood specimens and bone marrow biopsies of what we describe as a morphologic dysplasia which means that when we look under the light microscope we can appreciate that some of the blood and bone marrow cells look abnormal. They don't quite look like their normal counterparts. MDS unfortunately also carries with it a variable likelihood of evolution to AML. This propensity to transform into AML varies widely depending on the MDS subtype and the prognostic risk subset which is one of the reasons why a careful assessment at the time of the diagnosis of MDS is important. These diseases I'm often asked by patients, in fact, it tends to be a lead in question when I am meeting a patient for the first time is this a cancer? These are scientifically in parenthesis or in quotation marks refer to as clonal hematopoietic stem cell diseases which implies that the inciting genetic event or inciting trigger is at the level of the hematopoietic or primitive hematopoietic stem cell and that leads to that cell then producing copies of itself, i.e., a clone or clonal expansion develops. This is a phenomenon shared by many cancers and so on a scientific level we do consider MDS as a malignancy or a cancer.

The classification of MDS has evolved over time. Many of you in the audience if you've had the disease for some time may know that there are various subsets of MDS. So, these were recognized as far back as the 1980s and this classification scheme has evolved over time. The significance of this classification is that we know that the disease severity increases as you go down from having perhaps one predominant cell line involved in MDS to having more than one cell line and/or to having an excessive accumulation of blasts associated with the disease. As blasts accumulate, the likelihood of transformation to AML increases. Now, one thing you'll notice is that there's a lot of refractory anemia, refractory cytopenia, refractor this and that that's encompassed in this classifications and very few reference to the word 'MDS.' So, to rectify that in the more recent iteration of the classification for MDS just this past year we are now doing away with the whole refractory anemia terminology and replacing it with the word 'MDS' which is, of course, what is common to all of these various diseases.

So, how do I approach the individual patient with MDS? Well, in my view and this is something that most of us do when we've met MDS patients we think it's important to establish the MDS subtype that we're dealing with 1) establish the fact, that this is MDS, and 2), of course, try to

get what the subtype is. We know that there are many conditions that can predispose to low blood cell counts. So, the fact that a human being has low blood counts does not necessarily the diagnosis of MDS make. Talk to the patient, look at what their blood counts have done over time. We do a morphologic assessment which is we lok at the bone marrow specimen and blood specimen to see whether we can appreciate characteristic changes of MDS. We, the pathologist, do a phenotypic or immunophenotypic assessment commonly to try to get a sense of whether there are blasts increased in the blood and/or bone marrow and the bone marrow specimen must also be sent for chromosome analysis or otherwise called cytogenetic analysis and finally in this day and age we are also increasingly doing molecular analysis which is to look for gene mutations that are associated with the MDS cells.

So, after getting a better sense of what kind of MDS the patient may have I then proceed to risk stratify the patient and the question is why do this and what does this entail? We know that this is a disease that's very heterogenous meaning that even when MDS cells between patients look the same under the light microscope, the patients may still do differently or the disease may behave differently over time and so risk stratification allows us to get a better sense of what these differences are and how they inform both how the patient may do over time and the necessity to intervene to try to modify the natural history of the disease.

So, what are these variables that influence risk in MDS? These include cytopenias which are valued at two, but although all patients with MDS will have some degree of cytopenias or lowering of their blood count the depth of the cytopenias matters. Someone whose hemoglobin which is a measure of the red blood cell count is at 12 which may be a little low for them is different than someone whose hemoglobin is at seven or 6 ½ where they may be needing transfusions and that's also applies for the neutrophils which is a subset of the white blood cells and the platelets which help blood to clot more normally. So, the classification systems these days are recognizing that how low these values are matter in terms of how patients may do over time. The blast percent is important whether this is within normal limits because we all have under normal circumstances very few proportions of blasts in our bone marrow. These are the primitive stem cells that go on to repopulate the bone marrow and lead to all the blood cells that we see in the blood under normal circumstances. When these blasts, however, accumulate because something has happened in the hematopoietic stem cell to trigger this sort of accumulation an ongoing increase in those blasts is associated with an increase in evolution or the risk of evolution to AML. So, we look at that carefully. We look at the chromosome abnormalities that may be associated with these MDS cells because depending on what the abnormality is it also informs how the disease may behave over time and finally in this day and age as I alluded to before, we are doing an analysis of gene mutations and I will be speaking more about that in a minute.

So, it's looking at all of this together gives us a more comprehensive idea of how this disease may behave over time. Many prognostic systems for MDS have been developed. Suffice it to say that the IPSS is the go to prognostic scoring system in our day and age for MDS and the IPSS

has undergone some recent refinements to try to improve the ability of the scoring system to give useful or more accurate information about how patients and how the disease in particular may be predicted to behave over time in the absence of therapeutic intervention and so one of the major refinements that the IPSS-R has undergone is to get a more nuanced view of the kinds of chromosome abnormalities associated with the MDS cells so that that may more appropriately discriminate between chromosome abnormalities that may predict a more indolence disease versus chromosome abnormalities which would be like the very poor or poor abnormalities that may predict that the disease might progress more quickly over time and, again, as shown in this slide these chromosome abnormalities give us information about how the disease may behave over time in terms of overall survival and risk of progression to AML in the absence of therapeutic intervention.

So, how do doctors treating patients with MDS go about assessing risk? How do we make those classifications? It's a fairly simple scheme for the IPSS-R where points are assigned, zero meaning good risk, four meaning not so good risk or poor risk depending on where the chromosome abnormalities seen in the bone marrow fall, where the blast percent falls and the degree of lowering of the blood counts or cytopenias that we see and so based on that we can appreciate with the more… with the IPSS and the IPSS-R subsets of MDS that are thought of as lower risk. Those tend to be the low or Intermediate 1 risk groups versus subsets of MDS that are higher risk which are like the Intermediate 2 and high risk disease or the high and very high risk subsets of the IPSS-R and untreated those have a significantly higher likelihood of shortening a human being's life expectancy.

Now, I've spoken a lot about chromosome abnormalities in MDS and giving you the idea that these are very important and that is correct. However, we are finding that chromosome abnormalities or the bone marrow cytogenetic abnormalities are maybe the tip of the iceberg in this disease because we know that about 60 percent of patients with MDS, their MDS cells will actually have a normal chromosomal appearance or normal karyotype and those patients would traditionally be categorized in the good cytogenetic risk group. However, we are now realizing that mutations occur in the majority of patients with MDS only approximately 10 percent in today's day and age will not have mutations. So, the chromosome part be normal doesn't tell us the whole story. Genes live on the chromosomes and we do know that the number of gene abnormalities that can be associated with the disease and these abnormalities, the significance is that they fall along discreet cellular pathways in the cell and dysregulation of this cellular pathways is predicted to lead to the development of MDS. So, one can see how this mutations might inform pathogenesis or the propensity for MDS to occur. It is important as we are discussing this issue of gene mutations to emphasize that these mutations are… they are acquired. These mutations that I'm speaking of are not of the inherited kind and we are realizing that, like I said, the variety of those mutations, some of these mutations may predict a poorer outcome in MDS in the absence of intervention and we're also finding that the converse is also true that there are specific mutations that could predict good risk in MDS and we are finding that as mutations accumulate in the disease this tend to be associated with more aggressive types of

disease associated with excess blasts, etc. and the propensity for transformation. This is all useful information to have because it may influence how we approach that individual patient with MDS. So, these mutations are frequent and they do inform prognosis and/or how the disease may behave. It would be nice at some point to have that information about gene mutations incorporated into our usual clinical prognostic schemes like the IPSS-R. That's a work in progress, but it is something that we believe we will get to in a few years.

So, now that we may have established the MDS subtype, getting a better assessment of where the prognostic risk falls for that individual patient, my next question is to try to get a sense of does this patient with MDS need any particular treatment or intervention to be instituted and broadly the indications for treatment in our view is if the blood counts are significantly low where they're putting a human being at risk of complications we do generally recommend a treatment. If the patient has higher risk disease where we feel like the likelihood that the individual may succumb to the disease or that the disease may progress or evolve to a more aggressive phenotype like acute leukemia, we also generally recommend treatment. Now, those recommendations for treatment have to be taken into context for the individual person looking at that person's level of fitness, where they are in their life, what their goals and aspirations are. These are the potential risks of the treatments that we're offering them.

And so what are these treatment options? These treatments vary from a lower intensity treatment such as growth factors and a fairly common one or common group of growth factors that I used MDS are erythropoietin stimulating agents or ESAs. Popular names for those are Erythropoietin or Procrit and Darbepoetin or Aranesp. The major goal here is to improve the red blood cell counts in patients who have lower risk disease and who their major problem is anemia and there are other growth factors that are utilized to a lesser extent to improve white cells or platelet counts and then we move to hypomethylating agents which are generally recommended for patients with higher risk disease as the goal here beyond improving blood counts is also to try to delay transforation to acute leukemia and improved survival because I have already alluded to the fact that those subsets of MDS are more inclined to significantly shorten survival in the absence of treatment and to also progress to AML and then we have allogeneic stem cell transplant also generally recommended for the same reasons for patients with higher risk disease and herein as with all other treatments, but particularly with this one, a careful assessment of the potential risk versus the benefits is very important and this is why we have two other talks here today focused on transplant. As I have alluded to this treatment intensity varies from the ESAs which are… tend to be very well tolerated not much in the way of risk to other approaches where the risk is somewhat higher.

Hypomethylating agents deserve a little bit more of a mention because they're so commonly used in this disease. The two that are approved in the US are Azacitidine or Vidaza and Decitabine or Dacogen. These drugs improve bone marrow function and blood counts in approximately 40 to 50 percent of patients. This is one area, many areas in MDS, but this is definitely one area where I would say patients' needs to be exercised both on the part of the

patient, their caregivers and their doctors in terms of waiting and allowing enough time for these drugs to act and not stopping treatment prematurely. The average time to onset of response is two to four months, but responses can take up to six months or longer to occur and the risks include significant lowering of the blood counts which will generally occur before they now start to improve, a few months down the line when the bone marrow is working better. These drugs carry with them the potential to improve survival which was best demonstrated in this study where Azacitidine or Vidaza was compared with other regimens, conventional care regimens including even standard leukemia type chemotherapy in patients with higher risk MDS and as you can see at the two year time mark there were more patients alive on the Vidaza compared to those who were treated with conventional care regimens. So, this is a favored drug to be used in patients with higher risk MDS who are need of treatment.

There are other subsets of MDS that deserve particular mention. One of them is this deletion 5Q MDS where deletion 5Q as shown on the slide in the lower panel it's the only other major cytogenetic abnormality in the most recent classification (inaudible 26:48) for MDS, we do allow patients to have one other chromosome abnormality besides the deletion 5Q and still be regarded as having deletion 5Q as long as that's a good risk abnormality. These, they have dysplasia in one or more lineages, they generally do not have an increase blasts in most cases and the significance of the MDS doctor recognizing this particular subset is because this has an excellent response to Lenalidomide. Lenalidomide is an immune modulatory agent. We don't understand completely yet how it works, but suffice it say that in patients with deletion 5Q MDS they become red cell transfusion dependent, more than two-thirds of them who are treated with Lenalidomide and in the US this is approved only for deletion 5Q MDS.

So, to sort of summarize what I tried to say so far about my approach to MDS it's evidenced on this slide. I do try to establish the diagnosis then risk stratify and then determine lower risk versus higher risk. If someone is lower risk we generally employ growth factors to help boost the counts unless they have the deletion 5Q where we give Lenalidomide and if they're higher risk we consider them for allogeneic stem cell transplant is one of the early questions that we ask when we first meet a patient. We do use Azacitidine and Decitabine commonly as I have shown you and we use clinical trials. That is also amongst the first things that we recommend when folks are come into our office and they need treatment for their MDS because we know that there's so much more room for improvement which brings me to the issue of clinical trials.

Why do we do clinical trials in MDS? We do this, obviously, because we know that a lot of the standard therapies are still not adequate. So, our job is to try to constantly improve upon the standard. In patients who have lower risk MDS who do not respond or are predicted not to have the high likelihood of response to agents such as Procrit or Aranesp, anemia remains an ongoing problem and there's a lot of effort towards trying to understand why patients… why this anemia develops and how to overcome it. So, one agent to watch in this space is this drug called Luspatercept. It's a drug that enhances red blood cell production but inhibiting processes in the bone marrow signaling pathways that suppress red blood cell formation in MDS and the early

phase clinical trials, this is phase one and small phase two trials that have been done show improvement, have been encouraging and so the way to, obviously, try to prove that this is useful would be to implement larger clinical trials. These are now ongoing. There's a large phase three trial where individuals are randomized to either getting that agent if they have lower risk disease that's not done well with drugs like Procrit or Aranesp or where we believe that those drugs are less likely to work. Those are the individuals who are being considered for this trial and we're eagerly awaiting the results and hope that perhaps we will sometime in the not so distant future have other drugs to join the treatment (inaudible 31:17) for anemia in MDS.

There are many other investigational approaches for patients with MDS particularly those with higher risk MDS. There are too many to enumerate. I will spend the last few slides just giving you a flavor of some of these approaches.

So, one group of agents to think about in patients with MDS oral equivalence of those drugs that I was talking about, Azacitidine and Decitabine. So, Vidaza, Dacogen, these drugs are given by injection. I've already told you it takes a while for them to work and so a human being is coming back and forth to the office several days in a row, month after month. It can cause significant disruptions and in one's day to day life. If they could be given by mouth this would be a significant advance in terms of the convenience. Besides the convenience it's also possible that we could development treatment schedules that would allow these drugs to be used longer because if you're taking a pill at home it's easier to take it more chronically and for your doctor to tweak the way it's given and this may then perhaps translate even into improved outcome. These are some of the hopes with looking at these class of drugs. The problem with giving these drugs y mouth is that they are rapidly broken down in the gut by a particular enzyme called cytidine deaminase. So, there are now formulations where they're pairing these oral equivalents of drugs like Decitabine. There's also an oral Azacitidine formulation. In this particular trial oral Decitabine was paired with an inhibitor of this enzyme with the idea being to allow this drug to then be able to hang out and increase the viability within the human being with MDS and we were able to… we and others who participated I this trial were able to demonstrate that it worked the way we thought it would work. So, the big arrow there shows that when you give Decitabine IV which is in the blue curve and versus when you give it orally which is in the dashed line and pair it with this inhibitor of the enzyme you get similar exposure levels whereas if you give the oral drug by itself without pairing it with an inhibitor of the enzyme you don't get much drug levels. In addition, the toxicity was similar, nothing unusual that we've seen compared with the IV and we also saw encouraging signs of clinical efficacy. So, this trial is now… the next iteration of it it will be a bigger trial designed to really try to get a sense of how well it's working in MDS.

Other approaches include harnessing the immune system because we know that these drugs, Vidaza and Azacitidine they some experimental evidence that they may work as immune sensitizers and so if you now pair them with agents called immune checkpoint inhibitors which will ease the break of the immune system you might have a chance of boosting response and this

approach is being looked at now. There are a number of trials that are now ongoing looking at that. Another target that's been looked at is this one called BCL2. BCL2 is a protein that's when it's over expressed it contributes to disease progression in various diseases and including diseases like MDS. The idea is to inhibit it with a drug called Venetoclax and then add an agent like Decitabine or Azacitidine, so Dacogen or Vidaza in the view to try to improve outcome.

So, I told you a lot earlier on about gene mutations in MDS or at least I give you a flavor of it. You know, obviously, we think that these gene mutations are important in leading to the development of MDS. So, how about developing a drugs that could perhaps target specific mutations. One group of mutations of particular interested just by sheer number of patients that have been with MDS at displacive factor mutation which occur in almost two-thirds of patients with MDS. So, what about trying to develop drugs that can affect or inhibit this particular pathway and so there's now a really early phase trial that we and other institutions will be participating in looking at this class of drugs in patients whose disease may not have done well with drugs like Azacitidine or Decitabine. So, many trials ongoing here and at other places for patients newly diagnosed looking for a way to try to participate in an effort to improve upon the standard and who need treatment with drugs like Azacitidine or Decitabine. These series of trials pair new approaches with the standard treatment and we also have a number of ongoing trials for patients who also have MDS, needing treatment. They've had Azacitidine, Vidaza or Dacogen, didn't do so well with it or the disease progressed and, again, these trials are not just ongoing at our institution, obviously. They're ongoing throughout. You can find more information on clinical trials in MDS on clinicaltrials.gov.

So, in summary I hope have demonstrated to you through this talk that this although we think of it… although we say MDS it is really a diverse group of diseases and therefore just as we are diverse as individuals in terms of how we present and other individual characteristics MDS cells also have these individual characteristics. So, an individual treatment or individualized treatment approach is necessary in our view and there is also a significant need for new treatments and approaches and we and so many others are participating in that effort. I have not spoken about transplantation at all in my talk except to mention it briefly as we do this, but you're going to hear a lot more from my wonderful colleagues who've also volunteered to speak in this forum in the next couple of talks. So, I really want to acknowledge patients and their families without which we would know nothing about MDS and it is our utmost hope that we will continue to be able to make progress in this regard. I also work with wonderful colleagues some of whom are here in our different programs that contribute to taking care of doing research and trying to improve outcomes in patients with MDS. Thank you for your attention.

(Applause)

Questions? No questions. Alright. We can reserve any… Okay.

Q1: The question I have pertains to the dissemination of this information to the various medical centers. How is that arranged and organized?

Toyosi Odenike, MD: Okay. Dissemination of… I'm assuming you mean information about MDS or about clinical trials or some of the things I've spoken about here?

Q1: I think both because I'm not aware at the institution where I attend they're getting all of this information.

Toyosi Odenike, MD: Okay. Well, that's a… It's an excellent question. Dissemination of information occurs in various ways. So, we as hematologists and oncologists belong to professional organizations. These include like the American Society of Hematology, American Society of Clinical Oncology. We have big meetings where research is presented. We as individuals working here at the University of Chicago because we have a vested interested in this group of diseases, for example, sometimes we'll volunteer to speak to professional colleagues. So, in professional development seminars there's lots of information available online that doctors can also kind of refer to and most physicians who are treating patients with MDS even if they're in smaller practices in community settings usually know of people who may have more information that they may or may not be privy to who they can call up or perhaps refer the patient to if it's a specific question about treatment or something like that, but… and we're all supposed to be participating in continuing medical education forums of different sorts to be able to try to remain current.

Q2: So, is the rate of MDS among the population increasing at a particular rate or is it just seem like there's more people because I'm in this little community now. How is that working?

Toyosi Odenike, MD: We're all living longer. MDS is a disease of older adults. So, in that vein the incidence is probably gradually rising, but I think that perhaps even more is the issue of increased awareness and more blood counts being done. So, these days you're going to the doctor's office and whatever… for whatever the reason might be. Somebody decides, well, you know, maybe we should check your bloodwork. The blood counts are checked and we find that one more cell lines are lower than they should be and they may watch it for a bit and then decide oh, perhaps it's time for you to see a hematologist to look into it further if no other obvious cause can be found because it could be a nutritional deficiency or intercurrent illness, other things, yeah, but I think some of it we're just doing more blood counts and more patients have been found that way.

Okay.

Q3: I have a question. I live on an island surrounded by Lake Michigan and so I'm in rural Wisconsin and I'm having a difficulty. I want to certainly as you've answered this question, you would hope that your local oncologist would be on Internet and consulting with the MDS

specialists, but I have not understood that being the case because of the transportation and the distance issue. Are there MDS specialists who will look at a person's data and mine is extravagant. I've had four bone marrow biopsies in four months or since December. Could someone consult without having the person actually come to Chicago which is a huge challenge?

Toyosi Odenike, MD: Yes. The short answer for that question is yes. That can be done. That sort of consultation always comes with a caveat that a) it is relatively informational because the patient's not sitting right in front of you. So, it's reviewing a series of records and talking to the other doctor. So, I mean, it can be done. Things can be… but this is the caveat. One thing we always emphasize, I do that and so do many of my other colleagues and other MDS experts is we think that it's also very important to review the material that the slides, the bone marrows and things to have those reviewed at our institution, for example, if the consultation is coming from us because that just gives us more degree of comfort. The consultation is only of value if the consultant feels like okay, I do have the enough information to be able to give some useful advice here, but the consultant is not sure that well, I didn't really see the slides or the bone marrow. I'm not really sure. How can I be sure that this is what's really going on. Then it's not very valuable to the patient. So, being able to look at the material, I think, is important. It's also very nice to be able to see the patient, but most doctors if your doctor went to call them up would try to do the best they could to help in any way that they could if it turned out that the individual was not able to travel.

Q4: I did not hear you mention a donor lymphocyte infusion. Can you explain how and when that is possibly used?

Toyosi Odenike, MD: Okay. The donor lymphocyte infusion, we consider that as part of the whole transplant kind of treatments approach. So, that is going to be in the transplant session which is coming up next. Dr. Kosuri can… will be happy to answer that question.

Q4: As an MDS specialist, do you ever use that to treat "MDS?"

Toyosi Odenike, MD: Donor lymphocyte infusions are a transplant modality. So, the short answer is yes and Dr. Kosuri will be talking about that in his session that's just coming up. We try to separate… it's a lot of information to cover at once and we try to separate this into sessions that focus on… so, mine was a general overview. I talked briefly about transplant, but he's going to… he's a transplant focused physician who is going to be able to give you a lot more about this.

Q4: I want to say thank you for your dedication, your training, your passion and your gifts that you're sharing with us today.

Toyosi Odenike, MD: Thank you. Those are kind words. Thank you. Dr. Kosuri, I think (inaudible 48:14)

Satyajit Kosuri, MD: Good morning, everyone. Thank you all for being here and thank you to Dr. Odenike and the organizers for inviting me to talk to you all today about stem cell transplant for Myelodysplastic Syndrome.

As Dr. Odenike mentioned, my name is Satyajit Kosuri. I'm one of the physicians here who has a focus on stem cell transplantation especially for myeloid malignancies and, obviously, this is a very expansive topic in which we'll have a short period of time to cover. So, I'm going to use kind of broad brushstrokes here and what I hope is that you'll be able to walk away from this talk kind of getting a general sense about what are the indications for a stem cell transplant for patient with a diagnosis of MDS, which patients can go onto get a stem cell transplant, when we do it and a little bit about how we do the stem cell transplantation.

So, I like to look at stem cell transplant as a tabletop that's very sturdy, made of oak, but it needs basically some pillars or legs to be able to stand on to be able to provide patients with Myelodysplastic Syndrome the possibility of long term disease control and please forgive me, I'm not a graphic design artist here, so my table doesn't look so great, but these legs are very important and I call them the four pillars of transplantation and this is something that I talk about with the patients when we have a transplant consultation. First of all, does the patient have an indication to move ahead with the stem cell transplant, what is the disease status at the time of transplantation? These are two things that are obviously very important. Number two, is the patient physically and psychologically fit to undergo a stem cell transplant because as you all know this is a procedure that has inherent risks associated with it and a long term recovery in the post-transplant period, 3) is quite obvious. You have to have a donor to move forward with a stem cell transplant and something that I think is not talked about enough or emphasized enough is the idea of social support. So, after a stem cell transplantation patients need to have caregivers pretty much around the clock for at least the first three months and depending on the type of stem cell transplant maybe even six months or more. So, these are kind of the four kind of main categories or pillars upon which we can build and hopefully administer a successful stem cell transplant for patients who need it and if you can imagine if any of these are missing aside from the donor then the table gets a little bit wobbly and you don't necessarily have the conditions for success in regards to the stem cell transplant.

Now, this, obviously, it's a very exciting time. I'm sure many of you have seen on the television or read the *New York Times*, *Time*, etc. about immunotherapy for certain blood cancers. You probably read that patients are able to take T cells which are part of their immune system, engineer them outside of the body like they're attack dogs, place them back into the patient and have them go after the cancers and eradicate them which is really great and it falls under the umbrella of immunotherapy and oftentimes patients will ask me during a stem cell transplant consultation is this available for Myelodysplastic Syndrome and even though this type of immunotherapy that you've heard about more recently isn't available for MDS, I often inform patients and their family member that the allo transplant is actually the original immunotherapy

and if you think about it you're taking healthy cells from a donor, immune cells and the stem cells that are there and you're infusing them in a patient who has MDS and those T cells that are there as part of the package of the immune cells that come from the donor help to attack and eradicate disease that's there as well as allowing those stem cells to blossom over a period of time, create a new immune system which will hopefully allow the patient to be disease free for a long period of time and this is basically what I think is the ultimate in immunotherapy. So, if you think is immunotherapy there for MDS the answer… my answer would be yes. It's just that it's been around for a very long period of time and it's not kind of the more flashy type of thing that you hear about in the media right now.

And as Dr. Odenike was mentioning previously, myeloid diseases can occur on a continuum or they can occur on a spectrum and it's something that I look at in regards to stem cell transplantation. You have patients here on one side, you can't see my cursor, such as MDS and myeloproliferative neoplasms which over a period of time that disease can evolve eventually getting over to acute myeloid leukemia and two factors that we evaluate when we see patients for a transplant consult is what is the risk that this MDS will eventually move on its way over to AML or where are we catching MDS in its evolution over to acute myeloid leukemia and these are two important factors When we sit down with a patient that we consider in regards to when and if we move forward with a stem cell transplant.

This is a slide put out by the Center for International Blood and Marrow Transplant Research showing you the utilization of transplants across the board and you can see here in blue these are the allogeneic stem cell transplants. You can see the major utilization is amongst those patients with a diagnosis of acute myeloid leukemia and then following in second here you see those patients with Myelodysplastic Syndrome and myeloproliferative diseases such as myelofibrosis utilizing allogeneic stem cell transplant and the idea is as a physician who does stem cell transplantation how do we harness the efficacy of the stem cell transplant, what we call the graph versus tumor or graph versus leukemia effect while balancing the what we call transplant related complications such as graph versus host disease or infectious complications with the transplant and this is always kind of the balancing act when we talk to patients and evaluate them.

So, I'm just going to touch very briefly on those couple of ideas of infection and graph versus host disease. When a patient gets a stem cell transplant, obviously, they're immune suppressed. They're immune suppressed immediately after the transplant and as the donor's immune system is growing within the recipient there's a period of time up to one year where the immune system isn't completely, I would say, online yet and during this whole period time patients are, I would say, obviously, more at risk for a whole host of infections. So, both during the transplant and even in the period after the transplant, transplant physicians are watching over very closely in regards to the development of certain infectious complications for their patient. So, this is a major thing I always ask patients to keep in the back of their mind as one of the risk factors associated with even successful transplants is infections complications. The other thing is graph versus host disease and there are forums that take days to explain and go over the treatments for

graph versus host disease, so I'm going to simplify it here in a few seconds, but basically what I tell patients is that imagine when you receive the product, the stem cell product from the donor you are getting a whole bunch of different cells including stem cells, including T cells which I liken to the policemen in all of our bodies. The T cells help to keep us infection free and when there are certain mutations or irregular cells in their body the T cells help to eradicate those cells as well keeping us healthy. So, when you take T cells from a donor and you put it into a recipient or a patient those T cells will help as I mentioned previously to eradicate diseases. They'll see a leukemia cell or an abnormal blast and they'll say okay this is not supposed to be here. This is not "self" and they'll eradicate that cell. On the same token, they could also possibly do their job a little bit too well meaning they'll go around a new neighborhood which is the recipient's body and they'll see oh there are slight variations and differences in those skin cells or the liver cells or cells of the gastrointestinal track and they are programmed to attack and so that's where the idea and the term graph versus host disease comes into play and we do a lot of… we put a lot of effort in the pre-transplant or I should say the time of transplantation and even in the post-transplant period in order to prevent graph versus host disease from happening. If you were to look at percentage, I would say in all comers if we take transplant in general you could say 30 to 50 percent of patients who receive an allogeneic stem cell transplant will have some form of graph versus host disease. Now, most of this graph versus host disease is easily treatable with steroids and then there's a slight smaller percentage of graph versus host disease which what we call steroid refractory and that's a whole other topic which has other complications, but basically this is the balance, using those T cells to utilize what we call the graph versus tumor effect, but controlling them enough so that the patient doesn't experience graph versus host disease.

Now, we understand that transplant can be an important part of the treatment paradigm for certain patients with Myelodysplastic Syndrome, but with the things that I had previously mentioned there are certain barriers to referral as has been brought up already. There is historic negative perceptions about the risk of allogeneic stem cell transplant and this is especially true it needs to be taken into consideration for patients in the advanced age group which entails many patients with Myelodysplastic Syndrome, but in spite of this and this was a graph put out by the European Bone Marrow Transplant Registry, in spite of those risks what we're seeing is across the board the utilization of stem cell transplant for Myelodysplastic Syndrome is increasing and even if you were to stratify according to age group, we are seeing an increased percentage utilization of allo transplant for MDS.

Now, just kind of a historic perspective here when if a patient needed an allogeneic transplant, let's say in the 1980s. If you were above the age of 50 or 55 even if there was an indication for transplant that patient would not receive a stem cell transplant because at that time they believed that the mortality and the complications associated with an allo transplant were too high for patients above that age group and then we started tinkering with the transplant process itself, we started improving it and we started to realize okay we can do patients older than the age of 50 and but if they're older than the age of 60 nope, we're not there yet. So, in the 1990s to up to the year 2000 we're holding off on doing allo transplants if we could on patients older than the age

of 60 and then we said you know what? We can actually do it to patients older than 60 but once we hit 70 we should definitely hold off, but now what we're able to see is that there are patients who are 70 years old and older that are able to receive an allogeneic stem cell transplant and actually tolerate it quite well. I put this picture here of a Japanese gentleman named Yuichiro Miura who actually he's up here at the top of Mt. Everest. He did it first at the age of 73 and then 10 years later at the age of 83. So, what I'm trying to basically emphasize is that there are patients who are advanced age that are physically fit that should be able to be offered a stem cell transplant. So, it's not particularly the age that should be the barrier, but it's what is the physiologic age of the patient and I'll talk about that a little bit later on and this is especially pertinent to patients with MDS greater than 80 percent of whom are over the age of 60 and the median age at diagnosis is close to 70.

So, I'm going to touch very briefly on this study that shows us why we're able to have that change from how we were looking at transplant from the 1980s to how we're looking at transplant in the more modern era and this study looked at patients who were transplanted from 1993 to 1997 and compared them to patients transplanted from 2003 to 2007. All of these patients were receiving their first allogeneic stem cell transplant and basically this is just highlighting that the majority of these patients had a myeloid disorder whether it was acute myeloid leukemia or Myelodysplastic Syndrome and basically the gist of it is this in regards to the toxicity associated with the liver and the kidney those patients that were transplanted in the more contemporary time period had less toxicity and when we looked at the complications associated with stem cell transplant those patients that were transplanted in the more contemporary time period, 2003 to 2007, had a lower risk of developing complications that led to death and overall survival was also improved in those patients in the more modern era. Now, there are many reasons for this but some of them are the refinement in patient selection that we take patients to transplant, the timing of transplantation, the… what we call a conditioning regimen or the chemotherapy that comes as part of the package with a stem cell transplant and the intensity that we basically reduce to make it more tolerable, new drugs that Dr. Odenike had mentioned previously that help patients to achieve remissions prior to entering transplants, improvements in supportive care and basically what this has done over a period of time has made the process of stem cell transplant more inclusive for advanced age patients.

Now, we'll get kind of to the crux of things. How do we start looking at patients and choosing them in regards to who can go for a stem cell transplant or if a stem cell transplant is indicated in a certain patient and it basically comes down to risk stratification as Dr. Odenike had mentioned previously in her talk and when we talked about transplantation it's very similar. We're looking at disease based risk stratification which what I'll be talking about for the bulk of the rest of the talk and also patient base risk stratification which I'll mention towards the end.

As you've already heard there are numerous risk classification or stratification criteria that are used for Myelodysplastic Syndrome. The one that we focus on and that we use very widely in regards to transplantation is as you've already heard the International Prognostic Scoring System

and the reason we use this is that it's widely used in clinical decision-making across the board. It's used also in clinical trials and the FDA and their European counterparts use this classification scheme for approval of novel drugs for Myelodysplastic Syndrome and just briefly I'll mention again it entails the percentage of bone marrow blasts that are present in the patient, the karyotype of the cytogenetic abnormalities that are helping to drive that disease and the number of low blood cell lines whether it's just white blood cells, red blood cells or platelets and you basically receive a score which puts you into a low, Intermediate 1, Intermediate 2 or high risk category.

This was a study that was put out in 2004 that kind of helped to establish how we approach risk stratification for patients with MDS without… in regards to allogeneic transplant utilizing the IPSS risk stratification and what we see here, this top panel, are those patients with high risk, Intermediate 2, Intermediate 1 and low risk scores who did not receive an allogeneic stem cell transplant and I would say that the main attention is really paid to these patients here in the higher risk category who did not fare as well over a period of time. So, this B panel is showing those same risk stratified groups but in patients who underwent an allogeneic stem cell transplant and the gist of this here is that those patients with Intermediate 2 and high risk categories of MDS actually benefited from an allogeneic stem cell transplant compared to those with low risk or Intermediate 1 who really did not and if we looked at delaying transplant we saw that there was a detriment to life expectancy in those patients with high risk disease and Intermediate 2 risk disease.

This is a study kind of making the same or asking the same question I should say. Panel A are those patients who have low risk or Intermediate 1 disease and this yellow bar represents non-transplant therapy and you can see over… and the blue bar represents those patients who received an allogeneic transplant and you can see over the period of time those patients receiving non-transplant therapy did quite well even when compared to those patients receiving the allo transplant and their quality of life was actually improved. The C panel here represents those patients with Intermediate 2 and high risk disease and over a period of time you can see those patients here in blue that received an allo transplant fare better than those patients who receive non-transplant treatment modalities.

This is just a kind of numerical representation of the previous graph, so I'll just move on from here.

So, basically just to summarize very quickly what we just saw, using the IPSS at diagnosis those patients who fall into the Intermediate 2 and high risk categories for MDS, allogeneic transplant is something that we definitely need to consider in those patients unless there are some clear comorbidities or the patient's disease is not sensitive. Transplantation for this patient group soon after the diagnosis confers that best prognosis because the rate of transformation as Dr. Odenike had already mentioned to acute myeloid leukemia is higher in this patient group usually occurring within the first year to year and a half. In those patients with low risk and Intermediate

1 Myelodysplastic Syndrome supportive measures can provide an excellent survival ranging anywhere from five years or longer, up to a decade in that low risk group. There are certain caveats here for those patients in the low risk group especially those Intermediate 1 patients that need to be taken on a case by case basis where you would consider allogeneic stem cell transplant if there are certain cytogenetic abnormalities that she was mentioning or even more recently molecular abnormalities that we're talking about. If patients stop responding to EPO or Lenalidomide for 5Q- disease or if there are signs of progression of the allogeneic transplant in regards to blast progression or bone marrow failure meaning increased cytopenias or increased what I should say a decrease in further cell lines. If you just have anemia now the white blood cells are coming down or now the platelets are coming down. So, that's something to consider in regards to how the disease is progressing.

She did mention the refined IPSS score and as you already know this has a more inclusive cytogenetic risk profile and also quantifies kind of the difference in regards to where the cell lines are - how low is the anemia, how low are the platelets and what is the absolute neutrophil count? So, this is something that's been refined and you also fall into here depending on the amount of points that are accumulated a very low risk group, a low risk group, intermediate, high risk and very high risk and when we look at stem cell transplant in regards to the refined IPSS, what you're seeing here are those patients with good cytogenetics or intermediate risk cytogenetics do pretty well when you compare them to those patients who have poor or very poor risk cytogenetics and one of the causes of that and one of the problems that we identify is the risk of relapse for those patients who are in the higher risk groups and it's something that we have to address and when we think about failure of a stem cell transplant there are two reasons it occurs. One is transplant related mortality or basically experiencing the complications associated with the transplant whether it was from an infection or graph versus host disease leading to death or the number one cause and I think this is a take home point, relapse is still the number one reason for failure of a stem cell transplant for patients with Myelodysplastic Syndrome and kind of the drivers of this are what is the status of the disease coming into the transplant and it logically makes sense that if a patient has a burden of disease coming into transplant there is a higher risk that the disease will come back on the other end of post-transplant. If patients coming to a transplant in remission there is, obviously, logically a higher chance that they will remain in remission after the stem cell transplant comparatively. The other thing is the cytogenetic risk or the molecular risk which also helps to drive the relapse risk after the transplant and it's very similar to what we saw with the IPSS scoring.

So, what do we do for patients or what can we do for patients who are at high risk for relapse after a stem cell transplant? There are studies that have looked at hypomethylating agents as Dr. Odenike had mentioned a drug called Azacitidine which can be used in the post-transplant period that has been studied. However, the question remains how long does the effect last and how long do you use these drugs for and that's something that's still relatively unanswered and there's also various clinical trials. I should mention here that here at the University of Chicago, Dr. Hongtao Liu has a study with a agent that falls under the immunotherapy umbrella called a checkpoint

inhibitor and the volume (inaudible 1:15:23) for patients with high risk diseases, myeloid diseases including Myelodysplastic Syndrome to see if post-transplant the remission can remain for a long period of time. That's a trial that's ongoing and then there are those patients who have had an allo transplant, but their disease has come back and the question is what do we do in that situation? Well, there is the idea of immunosuppressive withdraw. What this means is as Mentioned previously there are drugs that we use in order to prevent graph versus host disease from occurring in patients. Those are immunosuppressive drugs. When we dial back on those immunosuppressive drugs it kind of takes the brake off of the new immune system that's in the patient's body and so it allows those T cells to say okay, I don't have to be as calm anymore and I can go ahead and try to attack any of the disease that's left over. Once again, hypomethylating agents the use of Azacitidine or Decitabine in the post-transplant period. Once again here we don't know how long the effects will last especially in the with the fact that the disease has already come back and then the question regarding donor lymphocyte infusion. Just to explain very quickly donor lymphocyte infusion is where we will go back to… we'll go back to the original donor of the stem cells and we'll ask them for more T cells. So, we're not going back and asking them for another transplant, we're saying, hey, can we have some more of your T cells. We take those T cells and then we infuse them in the patient to kind of give an immunologic boost in order to try to eradicate the disease. Now, that can work in controlling the disease and patients my need more than one donor lymphocyte infusion. However, some of the risk that you can, obviously, think about already is that there is an increased risk of graph versus host disease because if you're putting more T cells in the patient's body and they're doing their job they can still continue to do it maybe too well and attack the patient as well. So, graph versus host disease is a risk of DLI. DLIs can be effective if there is low burden of disease. If there is a high burden of disease then DLIs may not be as effective and it's something that needs to be kind of evaluated on a case by cases basis in regards to are the DLIs being effective and what are the side effects that are occurring with these donor lymphocyte infusions in the patients that are receiving them and there are, of course, the options of chemotherapy. Again, after relapse which causes a lot of toxicity, there are the idea of a second transplant which adds even more toxicity to the overall picture and to be honest with you second transplants are very rarely successful for long term disease control and I will also mention here that at the University of Chicago there is another checkpoint inhibitor trial that is being run by Dr. Justin Kline looking at patients with relapse disease after an allogeneic transplant. So, that's something that clinical trials are often in this space as well.

So, we talked a lot about the risk stratification according to disease, but we also have to be able to look at the patient and see if that patient's able to tolerate a stem cell transplant. One of the methods that we use to help us is something called the stem cell transplant comorbidity index and it takes into account the patient's medical history such as cardiac history, the patient has a history of diabetes, how well are their lungs working, their pulmonary function, how well is their heart working, how well is their liver working. Basically, what is the risk of developing organ toxicity from the transplant procedure itself and as you can see here there's a weighted score and patients who have scores of less than three, the idea is that the transplant related mortality would

be less. Now, if patients start accumulating the points it gets to a point where you have to consider the risk of putting the patient through an allo transplant as they actually may not do so well in regards to transplant related mortality.

So, kind of putting the two together and kind of closing the loop here. When we look at patients with low risk MDS or Intermediate 1 MDS, if they have a poor performance status we would always not consider an allogeneic transplant. For patients with good performance status who do not have poor risk features such as cytogenetics or molecular abnormalities we would look at non-transplant modalities of treatment. Now, if patients were to receive these non-transplant modalities of treatment such as Decitabine or Azacitidine and their disease continued to progress or what we call hypomethylating agent failure then we have to consider a transplant in those patients once the disease maybe can be under control on some other clinical trial and for those patients who have good performance status with very poor risk features and they have a matched sibling donor or an adult donor, transplant is something that can be discussed on a case by case basis depending on the risk and when we look at those patients who fall into the higher risk or poor risk categories for MDS, obviously, poor risk, no transplant… or I'm sorry, poor performance status no transplant. If you're fit and have a good performance status and there is an available donor then the idea is to go ahead and move forward with transplant and I put in here for those high risk patients as we've already talked about you would consider post-transplant strategies for those patients.

There was a question regarding ferritin levels and how they affect stem cell transplantation and this is something that has been studied in a retrospective manner quite a bit and what we see is that higher ferritin levels are associated with an increased risk of transplant related complications. However, the reasons for this are not very well defined. It's not necessarily that the ferritin is causing the problem, but it's the issues that are causing the ferritin to be elevated that lead to a higher risk. So, for example one of the things is if patients are heavily transfusion dependent then, obviously, prior to transplant their ferritin levels will be higher. So, it's not the ferritin that's driving the risk. It's the fact that their disease is transfusion dependent and they receive many transfusions which puts them into a higher risk category that's driving the risk in order… as far as transplant related mortality is concerned and also one of the things that we have to consider is ferritin is something that we called an acute phase reactant meaning if there's any kind of infection, inflammatory disorder going on in the body then ferritin levels will be elevated. So, that's also something to keep in the back of our minds. So, there's a limitation of the ferritin measurement in regards to transplantation outcomes and approaches to prevent severe iron overload are reasonable and warranted. It is recommended to use iron chelation before transplant in selected patients with iron overload although no definitive cutoff for ferritin or liver iron has been systematically defined. One of the things that I will mention that I didn't write down there is basically using an MRI to evaluate the deposition of iron in the liver is something that can be done. I'm not a radiologist, but I'll tell you one of the things when an MRI is used is they use a measurement called T2 and T2 is measured in milliseconds. So, how do you know if you were to get an MRI that you actually need a drug like Exjade which is an iron chelator? The

higher the… they measure it basically if you have 20 milliliters, your T2 is 20 milliseconds, sorry, then that's considered normal and if you have between 10 to 20 on your MRI that's considered mild, if you have between five and 10 that's considered moderate and if you have less than five milliseconds on the T2 weighted MRI image that's considered severe and most physicians may start drugs like Exjade when you have moderate deposition on the MRI which is 10 milliseconds or less.

So, I'm just going to end here with some take home points. When deciding if transplant can benefit a patient with Myelodysplastic Syndrome in addition to the IPSS that we've spoken about we have to take into consideration the behavior of the disease. Is the disease evolving regardless of what the IPSS score is? Is the patient becoming more transfusion dependent? So, that's an important point and also we have to take into account patient fitness as I've mentioned. Those with an IPSS Intermediate 2 or IPSS high risk or patients that are transfusion dependent or have high risk cytogenetics are ones that we need to consider for an allogeneic stem cell transplant. It needs to be talked about on a case by case basis for those patients with Intermediate 1 disease and disease assessment along with the patient assessment which was the stem cell transplant comorbidity index is something that is extremely important. The risk of the underlying disease have to be balanced against the comorbidities and the hazards of an allogeneic transplant procedure. We have also to take into consideration the patient's preference. Some patients may have the perfect donor situation. They may have the indication for stem cell transplant and they may be physically fit to undergo a stem cell transplant. However, they don't want to do it and we, obviously, have to respect those wishes for those patients and we have to look at other therapeutic alternatives and for the future additional attention needs to be paid to the monitoring and treatment of what we call minimal residual disease. So, patients who have disease a little bit of disease going into transplant and after transplant and think about specific interventions which could help prevent relapse in the post-transplant period and once deficiencies are identified in a patient's health that's fine, but the question is what do we do about it? What can we do to minimize the risk moving forward when the patient has to go to a stem cell transplant and I will leave that there because that's where Dr. Artz will pick up next in regards to how do we optimize patients and really tune them up so that they can have a successful transplant.

I would like to thank you all for your attention and I'll try to answer any questions that you may have.

(Applause)

Q5: Dr. Kosuri, what is your opinion on haplo identical transplants?

Satyajit Kosuri, MD: So, that's a very good question. I didn't touch upon donor source here and there are various ways that we can procure stem cells. Obviously, logistically and I'll just kind of give a general spiel about it is that if we can have a matched sibling donor, a brother or sister, that would be optimal because logistically it's very easy to go to the brother or sister and say

hey, listen, we would like your stem cells, we need to move fast, this is how we have to go, but about 30 percent of patients who need an allogeneic stem cell transplant regardless of disease have a matched sibling donor. That leaves 70 percent of patients that need to go outside of their family. The next thing is to, obviously, look for a matched unrelated donor, but for patients who are of certain ethnic groups such as Asian, patients from South America, patients from Southern Italy, African Americans, patients from Africa, the likelihood of finding a matched unrelated donor in the transplant registry which comprises of more than 14 million people is actually less and then we have to start thinking about alternative donor strategies and when you think about alternative donor strategies we're talking about cord blood, which I'm sure many of you have heard of and we're talking about haplo identical which is basically a half match. Now, at the University of Chicago one of the things that we do is that we can combine the two because very quickly cord blood takes a long time for the cells, the stem cells, to engrapht and so those patients are left with a period of time where they're really exposed for up to three weeks to infectious complications without having infection fighting cells there and so we use a haplo identical source to kind of formulate a bridge over until the cord blood transplant can come over and take over. Now, more recently what we're been able to see and what's been utilized quite a bit is something called a haplo identical transplant by itself and haplo identical transplants, I think, are… I think can be used in patients if that's kind of the stem cell source that is left. When we compare haplo identical stem cells transplants to a cord blood transplant among the alternative donor sources what we see is that there is a decrease in the initial transplant related mortality. So, the upfront risks are less with a haplo identical transplant than compared to cord blood. However, when we look at kind of the overall life of the patient what we see oftentimes is that patients who receive a haplo identical transplant have a higher risk of relapse compared to cord blood or other donor sources. Now, it gets a little bit detailed in nuance because this also depends upon what is the conditioning regimens that we're using with the transplant. The higher the intensity that we can go in a patient the more successful we can be in regards to preventing relapse, but not… especially with MDS we're not necessarily able to go in patients who are 70 years old with a very high intensity regimen. So, we have to take that into consideration when considering the stem cell source. So, I do think that haplo identical stem cell sources if that's what's available can be used and it can be used successfully but we have to keep in mind the risk of relapse in those patients.

Q6: What's the period of time that an MDS patient will develop into a leukemia usually?

Satyajit Kosuri, MD: So, that is really dependent upon the risk of the MDS. So, one of the things… if we took kind of all comers we're looking at those patients who have a high risk classification in regards to their cytogenetic profile. They can evolve into an acute myeloid leukemia within a year to a year and a half and that's something that is often seen. Patients who fall into that low risk category as Dr. Odenike was mentioning in a previous slide, they may be able to just receive supportive therapies and not evolve into acute myeloid leukemia for anywhere from five to 10 years and so it really depends on cytogenetic risk classification and it depends on the behavior of the disease. How is the disease evolving? Is it just kind of staying put

therefore your risk would be lower or is the disease starting to move where you're starting to see more blood cell transfusions, increased cytogenetic markers that are higher risk? So, that's something that has to be taken into account when thinking about it. So, high risk a year to a year and a half. Lower risk, you can go many years without having to evolve into acute myeloid leukemia.

Q7: I have a question about minimal residual disease. Is it difficult to detect and does the University of Chicago have that ability to do that or do you send it out?

Satyajit Kosuri, MD: So, that's a very good question. So, in the post-transplant period one of the things… one of the tools that we use is something called a chimerism study and what a chimerism study is is if you think chimera, it's a mix. Right? You're looking at how much of the patient is the donor after the stem cell transplant and how much of the patient is still the patient? Our goal is to make sure that the patient is as much donor as possible and we want to get rid of the patient. So, we want 100 percent donor and we want zero percent recipient and that's often what happens after a stem cell transplant. We monitor that very closely at day 30, day 100, day 180 when we do bone marrow biopsies in the post-transplant period and when we see those chimerism start to fall we start thinking okay this is a risk of relapse. So, that's one of the ways in which we can think about MRD or minimal residual disease, but the other factors are something called a flow cytometry which basically shows morphologically are there abnormal cells that are still present after treatment. We do have flow cytometry here. We are in the process of kind of, I would say, utilizing it more in the myeloid malignancies because the flow cytometry is kind of a moving target. It's constantly evolving, it's constantly getting better. So, that's one way to look at MRD and the other way to look at is at Dr. Odenike was mentioning is molecular risk stratification. Sometimes morphologically when we look under the microscope we don't see blast cells there or we don't see the dysplasia that was present previously. However, on molecular studies we'll see those molecular abnormalities or the cytogenetic abnormalities that were present and driving the disease and that's what we can do that here and that's one of the ways we look at minimal residual disease and that also helps us to risk stratify patients kind of on a clinical basis.

Q8: What is CD33? I've had a bone marrow transplant in 2010 for acute lymphoblastic leukemia which was diagnosed in 2009 and now seven years later my blood counts are dropping and my CD33 in December was 60 percent my donor, my T cells remain 100 percent my donor, but in April those CD33s went to nine percent donor and some people are saying I have MDS and some are saying this is murky and complicated. What's CD33 that seems to have fallen significantly?

Satyajit Kosuri, MD: So, in the post-transplant period there are a couple of cell lines we look at in regards to chimerism. Now, CD3… there are two things. CD34 are stem cells and CD3 is our T cell compartment and when we get the chimerism studies we look at kind of the overall sense of what the patient is is 100 percent donor and then we look at how much of that… how much of the T cell compartment or the CD3 compartment is donor. So, when we see as I was mentioning

I would have to sit down with you and look at kind of your actual report before I can tell you this is what is happening, but just in general sense when we're looking at the chimerism and we see initially let's say a patient at day 30 or day 100 has 100 percent donor. We're happy. It means that the transplant has taken and that the transplant is continuing to work. As time goes on if we see that CD3 becoming less donor, more recipient or just the overall chimerism becoming less donor and more recipient we're starting to think in the back of our mind about relapse of disease. So, that's where we start thinking about donor lymphocyte infusions. We start thinking about diagnosis with a bone marrow biopsy to make sure that the disease is not coming back or evolving into something else. So, that's where CD3 comes into play. CD34 are basically stem cells. I would have to sit down with you and look at your report before I can kind of definitively give you an answer in regards to your specific question.

Q9: Is it appropriate to believe that a doctor would be able to speak to me and that I could appropriately expect to be able to understand this?

Satyajit Kosuri, MD: I think this whole process is hard to understand even for physicians and it's very important and one of the things I try to do with patients is try to put it into as laymen's terms as possible so that patients can understand 1) what they're getting into in regards to the stem cell transplant. When I sit down and they come with the post-transplant visits I like to go over what we're looking at and explain to them okay this is what we're looking at and this is what it means and I'll show them the results. So, I think that when you sit down with your transplant physician it's imperative for the patients to ask what are you looking at, what does it mean and what does it mean for me and that kind of forces the physician's hand into explaining things to you in a very simple term which then you can keep track of every time you go and visit the transplant physician.

You guys have a great lunch. Get some food in you and I think Dr. Artz will be speaking next. Thank you.