

Speakers:

Patricia Kropf, MD

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Patricia Kropf, MD: Hello. Good morning. We are going to get started. I'm Trish Kropf. I work here at Fox Chase in the Division of Bone Marrow Transplant and Acute Leukemia. My boss is here, Dr. Fung, who's the chairman of our department. Henry, would you like to say hi?

Henry Fung, MD: Hi.

Patricia Kropf, MD: We're very happy to be here and I'm happy to be meeting with you this morning. What I'm hoping is that this can be a very relaxed meeting. Please raise your hand. Interrupt me at any time. If a question comes to mind, you don't have to wait till the end. I want this to be very a back and forth casual conversation.

Some of the slides that I'm going to go through today I'll go through quickly. Others I'll take longer to explain. What I really want to do is answer any questions you have. I have, of course, some of you probably know as much about MDS as I do. For others, it might be very new. So, what I did today is I put together slides talking about what MDS is, some of the prognostic markers, standard therapy and a couple newer therapies and we'll go from there.

So, what is MDS? MDS is... it's not one disease. It's a heterogenous group of diseases and MDS really is a spectrum where we see different characteristics between different patients. Today, I'm going to risk stratify patients with MDS by discussing about risk factors. I'm going to talk about something called epigenetics and I'm going to really try and simplify this for you, but it's a very, very interesting field in medicine right now because patients who have MDS are getting treated differently than patients who have other types of cancers and what we're learning by treating MDS patients is that some of the therapies available for patients with MDS are now being used in solid tumors and we'll talk about that a little bit.

MDS is a group of stem cell disorders and what I mean by that stem cells are cells that exist in your bone marrow in very, very small numbers. They are capable of self-renewal. They are able to form all of the different cell lines that circulate within your blood vessels. So, stem cells form red blood cells, white blood cells and platelets. What happens in MDS is one of these stem cells develops an abnormality either at the level of the genetic, the chromosomes, or with what I'm going to explain later, epigenetics. MDS is not curable outside of a transplant, though it's very, very treatable.

MDS overlaps with other types of diseases and you can see here on the left I have a chart. MDS, again, is a stem cell disorder and I show other types of stem cell disorders here and you can see that MDS, the incidence is increasing and we know that the incidence is increasing because the population is aging and many of our patients, the median age at diagnosis is 71. Now in our clinic, we see patients in their 40s and 50s, but the median age is 71 and, again, MDS overlaps with other diseases. Many of you may know somebody or personally have been diagnosed with MDS/MPD. So,

MDS with another type of disorder. We frequently see an overlap. MDS can progress into a leukemia. MDS at the time of diagnosis can look like an aplastic anemia or it can coexist with a myeloproliferative disorder like CMML.

Now, the chromosomes within MDS what we have found is that the DNA within these stem cells have many abnormalities and I'm going to talk about that in a couple of slide, but first in terms of the classification the French American British System classifies MDS according to what the cells look like on the bone marrow and also the percentage of blasts that the pathologist counts from the initial bone marrow and this really is pretty much a description. It doesn't necessarily give tons of prognostic information. The blast count, indeed, does, but the specific refractory cytopenia versus refractory anemia with ring sideroblasts, it doesn't make too much of a difference here. What really seems to make the difference is the blast count.

There are three main scoring systems for patients who have MDS and these scoring systems were developed to give patients an idea of what their prognosis may be. The three different scoring systems are the International Prognostic Scoring System and then the Revised IPSS, the WHO Prognostic Scoring System and then the MD Anderson Cancer Center model and what these scoring systems look at is three variables are determined - the bone marrow blast percentage, the karyotype meaning the chromosomes, are there abnormalities and then the cytopenias and by that I mean are your red cells low, platelets low or white cells low and then points are assigned for their specific blast percentage, the karyotype and then the cytopenias. Once you come up with your number, you then are assigned a risk group and what this risk group shows you is historically the median survival and then the time to transformation into acute leukemia. Now, I'm going to tell you that in my very humble opinion this is outdated and part of the reason is that when this was developed, we weren't doing transplant the way we are now. We're significantly better at transplant and our therapies are significantly improved. So while we still can get a sense of a prognosis, the survival is much, much better and is continuing to improve. Now, the Revised IPSS is the same thing I just showed you, but now we're including the cytogenetic abnormalities or the karyotype. So again, so in terms of the scoring systems we use them to help determine a sense of a prognosis, but again it's not set in stone and I firmly know that the overall survival is improving as the therapies are improving and as we're getting better and better at transplant.

In terms of chromosomal abnormalities, we look at the DNA to help determine how aggressive we think this MDS is going to be and some of the most common abnormalities including deletion in 5, an absence of chromosome 7 or a portion of chromosome 7, an addition of chromosome 8, an inversion or a flipping of chromosome 3, a deletion of part of chromosome 20 or the absence of chromosome Y in men. Now when we see some of these abnormalities, occasionally we can tell where the MDS came from and everybody asks me how did I get MDS? In the majority of case, it's sporadic meaning we don't know. It's a disease of an aging population and in many cases there's no known risk factor, but the risk factors that we do know of are chemotherapy radiation and if we... I have a lot of women who have had therapy for breast cancer and then are diagnosed with MDS and frequently we see an abnormality in chromosome 7 or part of 7. That's very, very common for patients who have received chemotherapy and then developed Myelodysplastic Syndrome.

Now, we tend to categories like we categorize everybody. We put everybody in sort of an area to try and determine what they'll respond to and what the best treatment is for them and we know that abnormalities involving 5Q is more favorable because we can treat these patients with Lenalidomide and they do very well. Chromosome deletion 20, if it's the sole abnormality in MDS, it is considered a favorable prognosis, but frequently it's not the sole abnormality. Less favorable includes inversion 3, monosomy 7 or three or more abnormalities in the chromosomes and then intermediate is trisomy 8. So, the addition of chromosome 8. We're paying a lot attention now on gene mutations, When we do our marrows now, we not only look at the chromosomes, but we look for the presence or absence of different gene mutations and we know what some of these mutations can give us a prognosis but at this point we're not really using the mutations to guide therapy yet. What we're really doing is gathering a lot of data, we're following patients on clinical trials and we're trying to determine the significance of a lot of these mutations. Some that we do know, a TET2 tends to confirm more favorable prognosis. An abnormality in DNA methyltransferase, when you have a mutation there, patients tend to have poor survival and more progression to AML. So if I have a young patient, let's say who has an abnormality here, I'm likely to take them to transplant up front rather than waiting.

Now, epigenetics. So, this is my favorite topic and Henry, signal me if I talk too much because I could talk about this forever. We have an amazing epigenetic institution here. The grandfather of epigenetics is within our department. He's the scientific director. His name is Jean-Pierre Issa. I'll show you his picture at the end and mark my words the man will win a Nobel Prize. Won't he, Henry?

Henry Fung, MD: Yes.

Patricia Kropf, MD: He will. I mean, he's gonna. He is the grandfather... I try and explain this to people because he's right here and it's crazy.

Henry: He's younger than me.

Patricia Kropf, MD: By like a year, Henry. A year.

Henry: A few months.

Patricia Kropf, MD: But no one looks as young as Henry. So, I'm going to talk about Dr. Issa and epigenetics because he's really at the forefront of this field.

So, what is epigenetics? This here is your DNA. It's in a nice double stranded DNA. Watson and Creek. Now, this is called the promotor region and within the promotor region, this controls whether the DNA makes functional proteins, proteins that are necessary for healthy cells. So, the promotor region controls if this DNA makes the healthy proteins, so you have nice white cells, red cells and platelets. Within the promotor region are areas with cytosine and guanosine. These are the building blocks of our DNA. So, this is the promotor region and, again, this controls whether your DNA develops or produced is healthy protein. Am I clear? I tried to explain this to my husband last night who's an orthopedic surgeon who said it was totally confusing to him.

Now, this enzyme that's coming up on the screen is something called DNA methyltransferase. It's an enzyme that exists in our stem cells. This enzyme puts something called methyl groups. One carbon, and three hydrogen, attaches these methyl groups onto the cytosine and guanosine in the promoter region. When this happens, we don't get healthy expression of protein. So, DNA methyltransferase attaches these groups to these amino acids within the promoter region and there you go. You don't get white cells, red cells and platelets. Okay?

What's interesting about epigenetics is this has nothing to do with your DNA. Your DNA is the same. Your chromosomes are the same. It's what you were born with. It is the addition of these groups to your DNA that is causing the disease and what I want to show you here is the way that we initially understood epigenetics was one mouse was impregnated with baby embryos that were identical. We shouldn't talk about cloning, we're not talking about cloning, but identical. The mouse was given different, the mother, was given different doses of folic acid with each pregnancy. The DNA is identical between the baby mice. One mouse has blonde hair, the other is dark. This is simply a result of giving the mother different doses of folic acid. The DNA in this mouse is identical to the DNA in this mouse. So, it's not like you have four kids, one's blonde, one has dark hair. Think of one of your children. That child is cloned. One has red hair, one has blonde hair because you as the mother were taking folic acid at different doses during pregnancy. So, why is it folic acid? Because folic acid, let's go back, is the building block for these methyl groups. So,

I'm going to go through this. Now, we know that it is these epigenetic changes, the addition of these groups that causes some of the problems in MDS. This is a complicated slide, but what I'm showing you is these are all patients who have MDS whose stem cells were taken out and the level of epigenetic difference between one MDS patient and another MDS patient was determined. So, this patient has MDS. This patient has MDS. What we see is that everybody's different. So remember, this is a spectrum. Patients who have more methylation, more of those groups attached, do worse than those who have less. Now, the two active agents right now we all know the most active agents we would say are Vidaza and Dacogen. What do these drugs do? My patients are always talking about chemo. This isn't chemo. Chemotherapy kills cells. That's what chemotherapy is. This is epigenetic therapy because what Vidaza and Dacogen do is they go into the cell and they render this enzyme inactive. So, there are no longer methyl groups added to the DNA. When this is inactive and these groups go away, you get healthy expression of your DNA and you get healthy cell production. So, we know that Decitabine and Azacitidine are very active agents in MDS. Decitabine prolongs the time to transformation to acute leukemia. Azacitidine improves overall survival compared to supportive care meaning transfusions or growth factor alone and, again, we know the reason that these work is because they take away those methyl groups. So, we know that bad methylation is a hallmark of disease both in MDS and AML. The drugs we use to treat MDS are active. They don't lead to a cure. So, what we're doing now is we're looking for more therapies. I talked about the hypomethylating agent. Lenalidomide we use for 5Q- and we also use transplant.

Now, I'm going to tell you about the newest hypomethylating agent and this was developed in part by Dr. Issa who works with us. SGI-110 is a second generation, simply meaning the newest hypomethylating agent. This is a fairly scientific slide, but just read it. Just listen. What Dr. Issa did along with his colleagues as Aztecs Pharmaceuticals is they took Decitabine and what they did was they linked an amino acid called guanosine to the Decitabine and produced a compound called SGI-110. So again, the Decitabine it's the same drug we've been using for years, but it's now linked to an amino acid and what happens when the Decitabine is linked to an amino acid and you have SGI-110 is when the SGI-110 is given to patients it's metabolized very, very slowly. Decitabine is metabolized within minutes. SGI-110, the half-life is in hours. So, what that translates to is that the stem cells, the bad stem cells, are getting much more exposure of the drug. We participated in the phase two trial meaning we were looking for an effective dose and then once we found the effective dose, do you think that's better? Once we found the effective dose, we then treated many patients to see how they did and we found that the patients did very, very well. Now, we can't say SGI-110 is better than Decitabine and better than Vidaza until we do a phase three study which compares SGI-110 directly to Vidaza or SGI-110 directly Decitabine. We are doing that now here at Fox Chase in AML. We're going to be meeting in December down in Florida to talk about when we're going to open the trial for patients with MDS. So, it's coming. Right now, we're doing it for patients with AML. So really, I think that this is going to be one of the greatest therapies that will become available to patients with MDS. Again right now, it's not FDA approved. It's still... we're doing the phase three trial right now. It's a very effective therapy.

Q1: Clinically what do you look for to see whether it's working or not?

Patricia Kropf, MD: So for in SGI-110 and in with Vidaza and Decitabine, when we start treatment, we know that everything's going to get worse before it gets better. So for the first two to three months, I tell my patients just look ahead because your counts are probably going to get worse, you're probably going to need more transfusions, you may become neutropenic. So, it could be a difficult three months. At the end of three to four months, the first thing that we look for is healthy hematopoiesis. So, I draw the labs and I see a hemoglobin of 11 that wasn't from transfused blood. I look for platelets over 70 or 100,000. So, that's my first sign then we do the marrow, but I never do a bone marrow until least three or four cycles because it takes three or four cycles or months for these drugs to work. So, the first thing I look for is healthy blood cell production. The second thing that I look for is I do the bone marrow and I want to see what that bone marrow looks like. Do I see dysplastic, funny looking cells or do I see health cells? Is that...? Good.

Okay. So here we have a trial that we're enrolling on right now and what we are doing is we're comparing Decitabine which is the standard of care to Decitabine and a drug called Carboplatin and Decitabine and a drug called arsenic.

Q2: Arsenic?

Patricia Kropf, MD: Yes. True arsenic and it's funny because every patient that I have talked to about this trial the first thing they say is, "Arsenic?" We've actually been using arsenic for years to treat certain types of AML, acute leukemia, and it happens to be very, very well tolerated and it's a very active drug and I may be explain to you why we developed this trial. So within Dr. Issa's lab, we decided to look at 20 FDA approved drugs that are currently used to treat cancer and we look to see do they have hypomethylating activity like Vidaza and Decitabine? Do they render that DNA methyltransferase inactive, so these methyl groups aren't put on the DNA and what we do is we look to see if protein is present. If we treat cells with these drugs, we should see healthy protein being produced. What we found after looking at screening 20 drugs is that carboplatin which is a chemotherapy drug we have used for years and years and years may lead solid tumors but also for types of lymphoma and leukemia had a lot of hypomethylating activity, worked similar to Decitabine in taking off those methyl groups. So, that was the first one we found and then when we combined the carboplatin and Decitabine and treated cancer cells we saw that even more of those methyl groups were removed. When the methyl groups were removed, we see healthy protein. The second drug that we found that had potent hypomethylating activity or was very active was arsenic, both alone and then in combination with the Decitabine. So, we then developed... we're on our... it's been now 2 ½ years, a trial where we compare the standard of care which is Decitabine to either Decitabine and carboplatin or Decitabine and arsenic. Now, this is a randomized trial. So, we put a number into the computer and the computer tells us the arm that the patient gets. The way that the trial was designed though is that if we see there's an advantage to one arm, more patients are enrolled on that arm. What we are finding is that we're seeing more responses in the arsenic arm. The patients are responding faster and we're seeing deeper remissions meaning there's some level that you can have a complete response meaning there's MDS. You can have a partial response meaning you still see abnormalities or you may not respond. We're seeing more patients achieve a complete response in the arsenic arm. Now, this is a randomized trial, so if Mary comes to see me, I clearly want to put her on the Decitabine/arsenic arm, but I can't. The computer generates a number and that's what happens. Now that we're seeing this though, the trial is going to close and we're going to be opening a trial using arsenic, but instead of with Decitabine, with SGI-110, the newest Decitabine. That is not open yet. We're in the process of doing so.

So, those are really the two new... I wanted to talk to you about was the SGI-110 and then also talk about the trial we have here and what's going to be up and coming and then very briefly I just quickly want to touch upon transplant because transplant is the only known cure right now for patients with MDS. So in transplant, cells are taken from a donor and infused into the patient after the patient has received some type of a prepared regimen or what we call a conditioning regimen. We can collect stem cells from the donor through their peripheral blood meaning through their... just a big IV. We can take them to the operating room and we do what we called a bone marrow harvest. We take the cells from the donor's bone marrow. We'd take about two liters or we can do a cord transplant. Cord transplants, we don't do them at Fox Chase. When

you can't do... When you don't have a sibling and you don't have an unrelated donor then we look... we call it an alternative donor transplant. What we do at Fox Chase quite successfully is we do haplo identical transplants which means if your sister or brother is a half match, we would use that donor or if you have a mother or father who's alive or a child then you have a donor. My dear Dr. Fung is from Hong Kong. So in China, many people have one child. So, they are the experts in haplo identical transplant because their transplant... everyone has a mom and a dad or you hope you have a mom and dad or you have a child. So, that's where we got all of our data with haplo identical transplants. So when Dr. Fong came and became the chairman of our program, all of a sudden we're doing more haplo transplants than anybody because he is very good at it.

Now, you can see here this is the indications for transplant in 2011 based on the CIBMTR data. This is for all transplants including autos meaning your own cells, but right here this is MDS. So, you can see AML, ALL, MDS. One of the most common indications for a donor transplant. These numbers are much higher now in 2015 simply because we have more patients with MDS. We're transplanting older patients with MDS and we're doing it quite successfully because we have found that we can use a reduced intensity approach. So instead of very rough conditioning regimen or prepared a regimen, we're finding that we can transplant these patients with a reduced intensity, lower amount of chemotherapy and they actually do quite well.

I'm going to end this here because I really don't... I could go on about transplant forever, but I'd really rather hear about your specific questions. This is our team. This is Dr. Fong. This is Jean Pierre Isa and, yes, he is younger than Henry and then this is Stefan Barta who is part of our team and my research staff who couldn't be here today.

So now, I'd like to just open this up to any questions you may have, thoughts.

Q3: What would the age restriction be on getting a transplant? You're talking about transplants. How old would you say would be the limit on getting this transplant?

Patricia Kropf, MD: So the question is what's the age restriction on transplant? We don't have a firm cutoff because what we really look at is how fit a patient is. So, we look to see if they have other diseases. We look to see how their heart is functioning, how healthy their kidneys are. We look at the liver and the lungs. I know some 74 year olds that never sit down, running around, running here and there and some 55 year olds who have many significant other medical problems. So, we really try and look at the level of how fit a patient is, but I would say in our program, we have it... I would say under 74 would be, I think, probably a fair number. Do you agree, Henry?

Henry Fung, MD: Yup.

Q4: I'd like to know what percentage of black people with no history of cancer, with no history of anything that developed this.

Patricia Kropf, MD: So, the question is what percentage of black people who have no history of cancer develop MDS. You know, I can't give you... I'd have to look up the exact percentage in terms of ethnic background and race. I can't tell you the exact percentage. Within our clinic, it's fairly equal, but again most patients, remember, don't have a preexisting risk factor. So, the majority of our patients don't have a known risk factor and develop MDS, but we see as many blacks as we do whites, I would say, for the most part within our clinic who have MDS.

Q4: May I ask you another question?

Patricia Kropf, MD: Sure.

Q4: Is there... I'm told that there is a difference with blacks and the blood count being low.

Patricia Kropf, MD: Yes, you got it. You're correct. So, the question is there's a difference with... in the... with race, specifically black patients have lower blood counts. So, that's actually somewhat true. It is true. Many black patients just naturally have a slightly lower red cell... I'm sorry, white count and that's considered normal. That's something that we see in patients when they're young and as they age, but that's not MDS. That is just when we look at what's considered the norm, you have this bell curve and there are many black patients who simply have a lower white count. They're five percent of the bell curve, but again that's not MDS. They just simply have... many patients simply have a lower white count.

Yes?

Q5: I have a dumb question.

Patricia Kropf, MD: No questions are dumb.

Q5: This one is. You said you don't know what causes MDS? Well, many people have told us because we live in the coal region that may be a factor. Is it?

Patricia Kropf, MD: In the coal region?

Q5: People have had coal furnaces.

Patricia Kropf, MD: Yes.

Q5: When we grew up.

Patricia Kropf, MD: Okay. So, 1) there are many patients where we don't have a known risk factor or a known cause. However, patients who have been exposed to carcinogens, we know they may have an increased risk for different types of cancer. So, the coal furnaces. We know that coal is a carcinogen. Does specifically cause MDS? I can't answer that. Could it? Yes, but not... coal isn't... doesn't specifically cause MDS. It may cause any type of cancer or be associated with. So for instance, radiation. When patients have been exposed to a lot of radiation like Chernobyl. Those patients develop many different types of cancers. So, a patient could develop MDS, a patient could develop leukemia, a patient could develop thyroid cancer, lung cancer. So, carcinogens can cause any kind of cancer.

Q5: How about radon?

Patricia Kropf, MD: Radon in large doses is considered a carcinogen. Is it known to be a cause of MDS? No.

Yes?

Q6: When do you give them folic acid for?

Patricia Kropf, MD: What do I give folic acid for? I only give patients folic acid if they're deficient in folic acid or outside of MDS if they have what's called a hemolytic anemia meaning they break down their red cells because they have an antibody then I will give folic acid, but I do not give folic acid unless a patient has folic acid deficiency or hemolytic anemia because remember what's the building block for the bad proteins that attach to the DNA? Folic acid. So, I take my patients off folic acid when they come into the clinic. I take them... as long as they're not deficient.

Yes?

Q7: I'm a little low grade...

Patricia Kropf, MD: Low IPSS.

Q7: Yes and I get shots once a week and you said for bone marrow transplant, you need to be in good health. Why do they make me wait? I know I'm a low grade, but why they make me wait? I stay in shape. I work out. I push myself every day.

Patricia Kropf, MD: So, I'm going to tell you why. There was a very large study that was done years ago at Mayo and they looked at patients with MDS and what they found from this study was that taking patients who had low risk MDS to transplant early versus later made no difference. So for the patients with low risk, it was okay to wait. This study in my opinion is somewhat outdated. The way that we practice and I would say most physicians, I would say,

practice now is this – if a patient needs growth factor that could go on for years. So, I agree with waiting in many cases. There would be a few other variables I would look at such as the chromosomes, but as soon as I think a patient needs treatment, I get them ready for transplant because...

Q7: What's the indication (inaudible 34:26)?

Patricia Kropf, MD: So if your platelets are dropping, if you're not responding to the growth factor or you have a leukopenia or a neutropenia. So, low white count. So if I see the platelets go to 75,000, I would go ahead and get them ready because they're going to be needing treatment at some point. If their neutrophils are low, then I get them ready for transplant because as soon as there's an indication for treatment, low blood counts that aren't responding to growth factor, you have to start therapy and we know the therapy is not curative. So, I'm not going to treat my patient for a year and wait for transplant. I tend to transplant much earlier than later and that's because of what you just said. You're fit, you're running around, you're staying healthy, you're not getting any younger, but with the growth factor that could go on for years and transplant's not easy. So, we do tend to wait. I agree with your point and I see your point, but the reason that we still do this is from the large study that was done showing that the patients who like you did just as well if you waited to transplant them.

Q7: I don't agree (inaudible 35:43).

Patricia Kropf, MD: And you've communicated this with your doctor?

Q7: Well, I go to the University of Penn to Einstein. Because I am fit, they think that I'll last 10 years, but you never know what's going to happen. You don't know what course the disease is going to take.

Patricia Kropf, MD: You're right.

Q7: And I'm telling you I push myself... especially the day after my shots, I get in that gym and I sweat because I swear sweating really helps get those toxins out of your body, helps gets those toxins out of your body and I feel better.

Patricia Kropf, MD: Yes. One thing that we do at Fox Chase, so if we have a patient who's low risk. We think they could go on for years. The first thing we always do though is look for a donor. So, we make sure we have a donor and if we do see anything change, we have all of our ducks in a row and we can go directly to transplant.

Q7: I have a brother and sister and they haven't asked even once yet.

Patricia Kropf, MD: I bet I know who your doctor is. Okay. Next question. I know exactly who it is.

Q8: So, I have a specific question in regards to my mother just got diagnosed with MDS and she was treated with FCR for CLL. So, her CLL is still in remission, but now she's developed MDS. So, her platelets we're just figuring out what course of action to take and she is with Dr. (inaudible 37:11) at Thomas Jefferson. We're getting a second opinion, but her platelets have been dropping to around 32,000 and her chromosome, there are chromosome deletions in 5 and 7, but minimal blasts and so based on that very general criteria, what would your recommendation be for the next course?

Patricia Kropf, MD: It depends on your age. I don't know how old you are, but have you started therapy yet?

Q8: No, not yet.

Patricia Kropf, MD: So, I would start treatment and go right to transplant and by right, I mean you have to get several cycles of the treatment, but directly to an allogeneic transplant.

Q8: She's doing steroids right now and... pertuxin, but it's a two week wait period and then we go back and see him. So, it's very new diagnosis.

Patricia Kropf, MD: I understand and I know.. I understand, but you need treatment and then go to transplant. There's no question.

Q9: I'm kind of piggy backing on this gentlemen who's low risk and I'm in the same general category. Presently, my DNA's being sequenced.

Patricia Kropf, MD: Oh, wonderful.

Q9: What should I expect might be the next step? I'm not transfusion dependent, but I'm pretty low, probably I'm in the 9s and I'm beginning to suspect that the poietin is not really effective anymore.

Patricia Kropf, MD: Well if your hemoglobin's 9, probably not.

Q9: Yeah.

Patricia Kropf, MD: And you get it once a week?

Q9: Yes. Procrit.

Patricia Kropf, MD: I would start treatment.

Q9: So, that would be...?

Patricia Kropf, MD: So the standard of care would be Vidaza or Decitabine. That's the standard of care. Different clinical trials offer different options. Like I said, we had the SGI-110... it's not closed for MDS. It will be open again. The greatest trial we have now is what I just explained with the carboplatin and the arsenic. So, you have to make a decision whether you want to be treated with the standard of care or you want to go on clinical trial, but you should... I believe you are probably approaching the time to treatment and I'm going to go back to this dear gentlemen here and I'm going to be very frank and I hope I don't get in trouble from Henry. So, allogeneic transplant carries roughly anywhere between let's say a 25... depending on your age. Let's say 25 to 30 percent chance of death in the first year because patients are on immunosuppression. They can develop graft versus host disease. They can get infection. So, I take you to transplant now and heaven forbid you're one of the 25 percent and your wife comes back to me and says, "We could have four more years." So based on the data, I can't disagree with her. It is simply a risk that the patient and the doctor have to be willing to take knowing those numbers, but that is a very real scenario and that is a possibility. If one in four... Now, I think we're much better than that, but those are the national numbers. The national numbers are one in four could die in a year due to a complication.

Q10: So, why risk. That's what you're saying.

Patricia Kropf, MD: And I'm not saying that because you're in such good health, you may have a beautiful outcome, but the numbers are the numbers and you very well could have several years doing exactly what you're doing.

Q11: I got a couple of questions. You don't mind, do you?

Patricia Kropf, MD: No, not at all.

Q11: Tell me the difference between Revlimid and Thalidomide (inaudible 41:25). I know what Thalidomide is. How do you feel about that?

Patricia Kropf, MD: About the difference between Revlimid and Thalidomide? It's an identical compound with, I think, it's the addition of an amine group, right Tammy? It's the addition of an amine group on the Thalidomide ring which forms Revlimid but Revlimid is very different Thalidomide with respect to side effects. It's much better tolerated as compared... We don't use Thalidomide anymore. So, it's a very active drug for certain patients with MDS.

Q11: I was a chemical transporter for 48 years and dealt with every chemical you've ever heard of in your life. Exposure, those days wasn't as it is now and also I had to have some radiation in 2000. Is there a difference between either or or maybe none at all?

Patricia Kropf, MD: So, is there a difference in terms of your risk?

Q11: Why it happened?

Patricia Kropf, MD: Why you developed MDS. It could possibly be linked to the chemicals and it could possibly be linked to the radiation. We won't know.

Q11: How aggressive should a doctor be with your treatment?

Patricia Kropf, MD: It's not the doctor. It's the patient and the patient's lifestyle and type of support that the patient has. So, remember what I told you. The first few months on treatment are difficult. Patients will require transfusions. They may have a very low white count and develop infections. So, these patients need support. You need a driver. You need somebody who can make sure you're doing okay at home. There's some people who don't have that. So, it is a very personal and tailored decision that's made between the doctor and the patient.

Q11: I think I'm pretty lucky. I'm kind of on the low end of anything and I can handle my life okay and the last question is Revlimid and Promacta mixed together. I just started that Promacta stuff. What do you think of that?

Patricia Kropf, MD: Revlimid and Promacta? I don't have much experience with it.

Q11: She said the Revlimid is to prevent the disease from progressing and the Promacta works directly on my platelets and I take them together. I just started the one yesterday again. It's extraordinarily difficult to get...

Patricia Kropf, MD: I don't have experience for using that combination. I mean, Revlimid we use for certain patients all the time.

Q11: It's kind of the lesser of the treatments of 5 milligram Revlimid. It's not a real dangerous dosage.

Patricia Kropf, MD: No. No. Not dangerous. No.

Q11: Good. I want to outlive it.

Patricia Kropf, MD: Super.

Q11: Thank you.

Patricia Kropf, MD: You're welcome. Yes?

Q12: In the trial that's coming out SG...

Patricia Kropf, MD: SGI-110 and arsenic.

Q12: Is that the one that's going to be a transplant at like a little bit lessor degree of a transplant.

Patricia Kropf, MD: No. That would be...

Q12: That one is coming up. That's almost close to (inaudible 44:12).

Patricia Kropf, MD: So, I think I probably wasn't clear. So, the SGI-110 and arsenic is going to be a therapy available for anybody with MDS. The transplant is totally separate and that's not a clinical trial. That is just a different type of approach for some patients who are getting a transplant where instead of wiping out the whole bone marrow, we give lower doses of chemo just to make room for the donor cells. We do that all the time for many different types of blood disorders and then decision if you're going to get a reduced intensity is what your disease is like at the time of transplant, the age and a few other factors.

Q12: Because my father was diagnosed and he... I think we gave him like 30 percent probably for transplant and he's at Thomas Jefferson and they said there's another trial coming up that's close to approval for a little bit of... but I understood is like a little bit of a lesser degree of a transplant.

Patricia Kropf, MD: So, you know what? That might be a trial just at Jefferson I bet. So, it's probably a trial unique to Jefferson. They're probably looking at different preparative regimens and trying to see one is safer than the other and it's probably unique to Jefferson alone.

Q12: Oh, you've never heard of that.

Patricia Kropf, MD: (Disagreement sound)

Q12: I have one more question. Since the last MDS trial, is that the one you were talking about with the arsenic or the (inaudible 45:38).

Patricia Kropf, MD: No, this is different. So, this is a different type of study using Azacitidine with another drug. It's called an HDAC inhibitor. It's different. We don't have this open, but it's interesting study.

Q12: What that one uses what type... what do they call it...? Is that any of the ones that you discussed already?

Patricia Kropf, MD: Vidaza? It uses that but then it uses another investigational agent. We didn't actually discuss this just because we don't use... We're not looking at that agent here. We really focus on... we have a few trials that we think are very effective and we try and keep the trial number fairly small simply because we put a lot of effort and time into thinking what we believe at least is a very valuable therapy. So, we try and limit other trials here, but that may be very effective.

Q12: Okay. So, you have your own trials.

Patricia Kropf, MD: Yea. So, we're not participating in that trial, but that is a national trial. So, if you go on www.clinicaltrials.gov that will list all the trials and you could find that if you were interested.

Yes?

Q13: You talked a lot about epigenetics and I don't know if there's any new news in the (inaudible 47:16) therapeutic.

Patricia Kropf, MD: So, we're not using a lot of immunotherapy in MDS. That's an excellent question because we're using immunotherapy in a lot of other diseases and AML, ALL and we're using it after transplant, but not up front yet in MDS, but that's a great question.

Q14: The procedure that you're speaking of here, is it anywhere else where you're doing chemo and the transplant?

Patricia Kropf, MD: So anybody who... any institution that does... offers and allogeneic transplant knows what a reduced intensity transplant is. So, Penn, Fox Chase, Jefferson, Hackensack, any transplanter in 2015 is comfortable with either an ablative or a reduced intensity transplant. That's standard.

Q14: What about (inaudible 48:11) at John Hopkins.

Patricia Kropf, MD: John Hopkins is great. I wouldn't worry.

Q14: She told me about two different trials.

Patricia Kropf, MD: They have... Like I said every... many institutions have their own trials. There's some that are national and we might all participate, but then every institution if you're in

academics, they have their own trial. So, that probably is why I might not be familiar with some of those.

Q15: Hi. How are you doing today?

Patricia Kropf, MD: Good. How are you?

Q15: Still (inaudible 4:44, but I'm (inaudible 48:45) go to the hospital eight months and they keep pushing off on account of my age. I had an ulcer in the stomach which was repaired 30 years ago and I used to be a smoker two years ago and he gave me a risk factor of 30 percent chance of surviving. Now, they keep on telling me they wrote a new chapter (inaudible 49:08) for me where I can go through it like you just mentioned, little mild. Why couldn't they give me that mild trans thing that you're talking about instead of waiting for someone to approve their (inaudible 49:22)?

Patricia Kropf, MD: So, the question is why wouldn't they take you to a reduced intensity transplant now and that's probably because the number that they gave you for survival based on your lung tests, liver tests and heart tests was with a reduced intensity transplant. I think at Jefferson they're trying to do like a reduced, reduced, reduce intensity and they won't know if that's going to be effective. It's a trial. You don't know, but I believe they gave you that number using a reduced intensity transplant because even a reduced intensity transplant is still a transplant. You're still on immunosuppression. You're still at great risk for infection. So, that's why.

Q16: I've been diagnosed with MDS for quite a few years. I get no treatment at all except I'm monitored and you're talking mostly about medication, drugs and different trials and things and I'm wondering am I being shoved to the side? They keep saying I'm too well to be that sick. That's scary.

Patricia Kropf, MD: So, the question is or what you're telling me is that you were diagnosed with MDS, but you're not on any treatment even growth factor.

Q16: No.

Patricia Kropf, MD: If you're not on growth factor, I would assume that your hemoglobin is pretty good, your red blood cell count.

Q16: Probably about 10 or so.

Patricia Kropf, MD: So, that's good and we don't want to give growth factor to increase the hemoglobin too high because in some studies that has been associated with the clots. So, it's a

fine line. So, we don't want to push your hemoglobin to 14, but we really don't want you at eight either, but if you're around 10 and you're staying there, I think that sounds just right.

Q16: Alright. I just sounds, you know like...

Patricia Kropf, MD: I understand and there's enormous, enormous component of anxiety. One of my patients told me that he feels like a ticking time bomb and I said, "You know what? All we can do is monitor you and have a plan. If we have a plan and you know the plan and I know the plan and things are in place then we're going to be okay."

Q16: I think it's been stable for a while.

Patricia Kropf, MD: That's super.

Q16: I had four bone marrow biopsies.

Patricia Kropf, MD: That's great, but I think you're actually probably being monitored well then, being treated quite well. Yes?

Q17: You mentioned at one point that you used the phrase that you go right to lining up donors. Can you talk to me a little bit about that process of lining up donors? In my case, I have two siblings both who are over 70 years old and a single child.

Patricia Kropf, MD: So the question is how do you identify a donor and what we do is for the patient it's a blood test and what we do is we look at what's called HLA antigens. We looked at your cells and we looked to see what type of HLA antigens are on your cells. Everybody has... We look at 10 of the antigens. So, we test the patient. That's called HLA typing. We then send kits out to siblings and we test the siblings. They can go to any lab, Quest, LabCorp and we test their blood. To be honest, we don't tend to use donors that are older simply because younger stem cells are healthier. Remember these stem cells are self-renewing. So if a patient has a 70 year old sibling, I would look... I would definitely test the child. In addition, once we have your HLA make up, we can look in the National Donor Database and we can look to see who appears to be a match for you and let's say we see 10 people all over the world that appear to match your HLA antigens. We then contact the donor registry where that patient lives and we ask for blood from the donor to see if they, indeed, are a match for you or for the patient.

Q17: One follow up question. Can you describe to me what would I be asking someone to do, what risk would I be asking them to take by doing something for me?

Patricia Kropf, MD: So the question is what risks will the donor go through or what are the risks for the donor? So, there's two ways to collect the stem cells. One is through a catheter either placed under the collar bone or even a large IV in the arm and the donor is given a shot

called Neupogen which increases white cells, but it also increases stem cells and allows for the stem cells to circulate. The donor will take a shot, give themselves a shot of this Neupogen every day for several days. They then come to clinic and we collect their stem cells through either a large IV or a catheter and what that looks like is the patient is...or the donor, I'm sorry, is hooked up to what's called a pheresis machine and it's very much similar to a dialysis machine. The blood goes into the machine. The machine extracts the stem cells and then the patient gets their blood back. For the donor, it's most likely just a one day process, several hours. Another... It's the only... the risks are very, very low with that approach. Patients get bone pain from the growth factor, from the Neupogen, but they can take an oxycote or a Tylenol. I mean, it's bone pain and it's not even... In some cases it might be bad, but you take a pill. The other way to collect the stem cells is through a bone marrow harvest where the donor goes to the operating room. They do get general anesthesia and then we harvest or take out a good amount of bone marrow, about two liters from the hip bones. Those risks are higher because it's associated with... any general anesthesia carries its own risk, but with the bone marrow, I mean, most of you have had a bone marrow. The patient's asleep. So, the next day they're just a little bit sore. We do keep them in the hospital overnight just to make sure they're doing okay. They'll need blood. That kind of thing, but the risks to be very honest are fairly low for the donor. Really.

Q18: How do you choose what option you're going to go with? You extract the bone marrow...

Patricia Kropf, MD: It depends on many different factors. It depends on the patient's disease, the level of the match between the donor and the patient, the age and the type of transplant. That's a long... That could take me about an hour to really explain, but there's many factors and I'll just say disease, age and the type of chemo we're going to give first. We do way more stem cells than bone marrow, but we still do do bone marrow, but we do way more stem cells because it's much easier and the risks for the donor are minimal. Yes?

Q19: Someone told me that instead of using 50 percent of my donor's stem cells, if I used 100 would be less intensive for me. Is that true?

Patricia Kropf, MD: I'm not familiar with that. Oh, you mean HLA typing.

Q19: Yes.

Patricia Kropf, MD: So, that's the whole haplo identical. It's a 50 percent match. So five out of 10 antigens are the same between you and the donor. So, it's be like you and your daughter or you and your son. A sibling or an unrelated donor that's a 10 out of 10, we do both. The risks really aren't... They do equally well. It's the same. If you're not good at doing haplo identical transplants, so if you're a center who doesn't do them that's a bad idea to get a 50 percent match to transplant. You want to go to a center who routinely does that. So before Dr. Fung came, we did... I mean, a couple a year. Now, I mean, he's cranking out haplos left and right and the patients go to transplant quickly because almost everybody has a donor that's available, but the

haplo identical patients do very well. I mean, they do just as well as a 10 out of 10 unrelated donor. Do you want to comment, Henry?

Henry Fung, MD: Well, every patient is different and I've seen the best outcomes you have to have the best doctors. So, go to (inaudible 58:04).

Q20: So, is there is a significant rejection rate?

Patricia Kropf, MD: The question is is there a significant rejection rate?

Q20: In the first year?

Patricia Kropf, MD: That's a very good question. So with transplant when we infuse the donor cells, there's always the risk that the patient is going to reject those cells. There's several factors that go into this. The amount of chemotherapy or immunosuppression that the patient is on. So if you get an ablative transplant and you're on good immunosuppression and you have a 10 out of 10 donor the chance of rejection is lower, maybe three percent, maybe even less. A reduced intensity haplo identical transplant has the highest rates of rejection. Hopkins will tell you that it's like seven percent. I'm going to tell you it's closer to 10 percent. So, I'd say anywhere between two percent to 10 percent, but what it... the important factors are the immunosuppression, the amount of chemotherapy given beforehand, whether you use marrow versus stem cell and the level of match. So, a lot goes into determining the donor, the conditioning regimen, the type of transplant.

Jayshree Shah: There's a lot of questions it seems like for transplant related, what to do, when to do it and how to go about it. To me when... I'm Jayshree. I'm the nurse that's going to speaking on the next topic with you guys. Working at a transplant facility, it really involves to me about a good hour plus conversation with a consultation. It's not a tid bit, a here and there and there, just answering little bits of it. Getting bits of information is good, but I think it really involves a true consultation to discuss the ins and outs of what it entails with going through an allogeneic transplant.

Patricia Kropf, MD: It takes about a year to understand the process, but all information is good. Yes? Can I help you.

Q21: Another dumb question. We're kind of new at this. How long can you have MDS before they check if you have it?

Patricia Kropf, MD: How long can you have MDS before you're diagnosed. So, it depends on how progressive the disease, how fast it's accelerating. Some patients if you have a low risk MDS like this gentlemen and he's active. He doesn't notice that his hemoglobin is low. You could have it for years. Some people... most... many patients are just diagnosed on a blood test

and their doctor is trying to figure out why their red cells are low or their platelets are low. Then there's a good portion of patients who develop shortness of breath. They're just so tired. So, they present either to the doctor or the emergency room. So, it could be years. It could be months.

Q21: Because like I said, we just started this, but until a year ago like this gentleman down here, my husband was just like him. Very active, very energetic, (inaudible 1:01:22), running, jogging.

Patricia Kropf, MD: If you're active and you're running the chances are you probably... if you're older and you're active and running you probably don't have a low hemoglobin because hemoglobin carries oxygen. Now, he's probably adjusted to a lower level than let's say many... or I may have because he's working with a hemoglobin of let's say 10, but if you're used to a hemoglobin of 13 and over a month or two it drops to 10 and then nine you're going to feel it. You're going to feel it quickly.

Q21: When he started, he said he was so weak and so tired and I kind of laughed at him because I said, "Well, we're no spring chickens anymore," and that's what we thought it was. He's going to be 73 and that's what we thought it was and from then it's just been downhill.

Patricia Kropf, MD: I'm sorry. I have one more question and then I know we have to...

Q22: (inaudible 1:02:11) me that this lady spoke on. Since 1996, mine has been low. Okay? Nineteen ninety-six. I am low risk. I have swam all year all my life. It's at 9.9 right now. I don't feel any change. So, I want to know why I'm being presented with possible medicine to start in...?

Patricia Kropf, MD: I would have to look at your case really thoroughly. I'd have to know your chromosomes, your cytogenetics, the mutations, the trajectory of your counts and if you're being treated at Hopkins, I have immense respect for the doctors at Hopkins.

Q22: I don't have anything.

Patricia Kropf, MD: Didn't you say you were seeing somebody?

Q22: I see her and she watches me.

Patricia Kropf, MD: I would have to see your records and your case, but I have to say I do a lot of work with the doctors at Hopkins. We're part of Stand Up to Cancer. We have a huge grant and we write trials together. So, I think that institution is really premier and the physicians are excellent, but I can't really comment on your specific case because I don't know enough.



I just want to thank you all for coming today. The best part of my job is just my patients. I love what I do because I absolutely love my patients. It's the best decision I really ever made I guess except for choosing my husband and having my kids.

(Applause)