Erica D. Warlick, MD
Jean Ridgeway, MSN, APN, NP-C, AOCN

Jean Ridgeway: Good morning everyone. How are you all? Good. Welcome. Welcome. My name is Jean Ridgeway and I'm the nurse practitioner of (inaudible 0:09) Campus. I came here from Chicago. I flew in last night. So, I'm here as part of the Myelodysplastic Foundation and this great MDS symposium. So, just let's just do a couple housekeeping things and then we'll get started with Dr. Warlick.

This room is for us today. We have some A/V people sitting back there. If you're tired of sitting feel free to get up and stand maybe you can sit in the corner. A lot of us have cell phones. If you wouldn't mind putting them on mute or vibrate. That will be helpful for us all. Restrooms when you leave this little area, you'll see an information desk. Restrooms are down to the left. We will have lunch together. The agenda this morning looks like this. Dr. Warlick is going to spend some time with you talking about new therapies from 10:00 until 11:00 or later. That's fine. She'll leave it open for questions and answer afterwards. That's great. Your hard stop is 12 o'clock noon for lunch. So, we'll play with that and then have lunch in the same place where you had coffee this morning out in the atrium. You can go outside and take a walk, etc., but lunch will be provided out there this afternoon then starting back in this room at one o'clock is time for going over some additional information. Caregiver support, just additional information about myelodysplastic syndrome. If you stopped at the front desk and you met Dee Murray. She's our staff person on site. She came here from Philadelphia on behalf of Myelodysplastic Foundation. If you don't know that much about the organization, she can answer lots of questions. I can answer some, not a lot, but I can answer questions. Our onsite contact person is Michelle. You want to waive your hand for those of you involved in the study that's been ongoing. Michelle has been quite involved with that. So, I'm going to leave it over to the next speaker. If there's any questions, I can be found hiding in the back. So, welcome.

Dee: Can I say one thing? If you didn't receive a *Building Blocks of Hope* booklet, did everyone get one? The *Building Blocks of Hope*. Yeah. That's it. The *Building Blocks of Hope*. That's it. I have some extras out here in case you didn't get one and if you didn't sign up with me, maybe during a break, a lunch break, if you sign up. If you don't have what you need, just give me a call on Monday and the phone number is in here and I can say the phone number. It's 1 (800) 637-0839. So if you need anything, just call the MDS Foundation. I have a couple of name tags, but everyone has a name tag. Right? Okay. Alright then. Thank you.

Erica D. Warlick, MD: Technical difficulties here. Welcome everybody. It's wonderful to be here. While we're getting some of the technical difficulties sorted out it's moving the slides up there but not on my computer.

Well again, welcome. My name is Erica Warlick. I recognize a lot of faces here. I am an assistant professor at the University of Minnesota and my focus really is on Myelodysplastic Syndrome

and how do we best treat it. So, I thought what I would do for you today is go over a little bit of the history of MDS and kind of walk you through where treatment was when we first diagnosed or first sorted out what MDS was and what our treatment is now and hopefully where we're going in the future. Please also feel free just to jump in with questions as we're going and if I don't see your hand, just speak up because we want to make this as interactive as possible and if you can't hear me, also just waive. Okay. I'll try to speak louder. I'm glad you're sitting in the front.

So, what we're going to start with if I can get the slides to move forward is a brief description of MDS. Then we will look at identifying kind of the history of MDS, how we first described it then how we all decided to name it because it's hard to figure out a treatment for something until you know a name for something, treatment and then what are some current therapies that we have for MDS now.

So, what is MDS? We know that the bone marrow is our blood cell factory and this factory makes our red cells, our white cells, our platelets for the life of us, but what happens in MDS is that these cells, these stem cells that make all the blood cells don't work right. There's a mutation or some abnormality that causes them to just not develop normally and then not grow up normally. We know that people have low blood counts and we know that there is a risk of transformation to acute leukemia and all of these things are kind of the hallmark of what myelodysplastic syndrome is. So, this is my face view of what MDS is and what happens is in the bone marrow, we have these stem cells that has either some mutation, some molecular change, something that's messed up in that causes it not to work right. So in early MDS or lower grade MDS, we see a bone marrow that's packed with cells. There's a ton of cell activity. The bone marrow is trying. The factory is trying to keep up, but the cells just aren't growing up. They're not developing normally. So when you lok in the bone marrow, you see a bone marrow typically that's filled with cells, but when you look in the blood the counts are low and people are needing transfusions. Now in more advanced disease which is at the lower part of the screen, what happens is the cells keep proliferating and they're still not growing up, but now they're not dying off normally either and that's where we start to see the progression to acute leukemia.

So, how did we first learn about MDS and how was it first described? Well, back in the 1800s the concept of anemia was recognized. In the 1920s, that's when the bone marrow biopsy was first developed and then kind of in the '20s and beyond the concept of a preleukemia was sorted out and specifically in 1923 there was an Italian physician who described kind of a weird bone marrow disorder where the cells looked bizarre, weirdly shaped and people were anemic and had low blood counts and sometimes people ended up dying of it.

So, how was MDS first described? Now in the 1920s and the 1930s, researchers figured out how to treat some of the patients with pernicious anemia, which we now know is due to vitamin B12 deficiency with liver. So, that was kind of the first thing. You were anemic, your doctor said, "Okay. You need to eat liver," and this was really the first description of anemia that came from

a nutritional deficiency and liver has a lot of B12 and other things in it. So, it really helped boost the blood counts and this was really the first description refractory anemia.

So a little bit more about the history. What's in a name and so in in 1938 researchers from New York City noticed there were kind of two different categories of folks who had anemia. There were the folks who developed refractory anemia out of the blue and we now call these folks de novo MDS and de novo just means out of the blue and then they also saw that there was a subset of patients that developed anemia after being exposed to environmental toxins such as benzene and now we call this therapy related or treatment related myelodysplastic syndrome. In the '40s and the '70s, through the '70s, preleukemic anemia became the more common term for anemia that progressed onto acute leukemia and finally in the '70s to the '90s, a bunch of pathologists got together and they made up this thing called the French American British Pathology Classification in Myelodysplastic Syndrome and these categories ranged from refractory anemia to refractory anemia with excess blasts and based on these categorizations, they were able to sort out that there were three groups of people. There were the people who had low risk disease that survived about four to five years. There were the people that were kind of in the middle who survived about a year and then the higher risk folks really only survived a couple of months.

So, doctors once they know a name to something they like to try to risk stratify people because that's really how we sort out how to treat folks and so in 1997 this publication came out looking at this thing called the IPSS or the International Prognostic Scoring System and some of your doctors may have gone over this with you because this is really the benchmark of how we decide how to treat people and what this study did it took thousands of patients who didn't have any treatment. So, were just diagnosed, no treatment and then looked at all the variables of their MDS and sorted out which ones helped to predict how people did and what they came up with is that how many blasts, those really immature cells in the bone marrow, so the percentage of blasts when people were diagnosed, what their blood counts were, did they just have anemia or did they have anemia and thrombocytopenia and then what were their cytogenetics and I don't know if that's a word that you guys have heard of before, but when a bone marrow is done the pathologists actually look at the chromosomes within those bone marrow cells and they can sometimes be very complex or they can sometimes be normal like the rest of your cells and the category that those cytogenetics are in help predict prognosis as well. So, they took all these features, put them together and came up actually with an easy point system for the docs to calculate and what this does is it puts people in a low, an Intermediate 1, an Intermediate 2 and then a high risk category and as you can see the survival, again, is very different depending on which category you fall into and, again, the survival outcomes here are based on patients who never had any therapy. So, this is very different than once you've started on a therapy because hopefully the therapy changes these numbers. More recently just in 2012, they even updated this risk stratifying system further looking at a lot more chromosomal changes, looking at the blast percentage a little bit finer and so we now even have better prediction models than this.

So again, we like to name things more and this is a very busy slide, but you can see that MDS is complicated and you've all probably been told the different MDS diagnosis that you have or that your loved one has and they give it a big fancy long name, but those names range from having just anemia or thrombocytopenia all the way up to having increased blasts to where you're bordering on acute leukemia or having a specific chromosomal abnormality called the 5Q- MDS.

So, this is a lot of naming, a lot of risk stratifying and why is this important? Why do we need this classification? Well as you all probably know, MDS is not one disease. It's not one disorder. It is such a wide spectrum and I have patients in clinic who were diagnosed 15 years ago and I'm glad nobody gave them therapy because they've done well for 15 years. I have patients who were diagnosed a year ago and who we desperately needed to do therapy. So, it's hard to know from the beginning which group people are going to fall into. Are you going to be the really aggressive MDS or are you going to be the really undulant MDS that doesn't need therapy and until recently we really only had supportive treatments, either supportive treatments or a transplant and those have vastly different risks to them. So, risk stratifying people from when they're diagnosed is really helpful for the docs to figure out okay who do we just leave alone and who do we intervene upon.

So, let's talk a little bit about the treatment and where we were and where we are now. So, supportive treatments are common for everybody and that's something we want to do regardless, but decades ago that's all we had. So, transfusions, giving liver to people, growth factors to try to stimulate the red cells and the white cells and then curative therapy and it was really in the '80s and '90s that bone marrow transplant or stem cell transplant was first developed. A very high risk procedure and it was really used for young folks at that point. So, the majority of people who have MDS are over the age of 60 and so it really wasn't an option when stem cell transplant was first developed. So, we do transfusions, but transfusions don't fix things. They help fix the symptoms and hopefully make people feel better and have more energy, but it doesn't fix what's going on in the factory and transfusions, there are limitations. Some people develop antibodies towards transfusions. So, it's hard to find a good match. If you have too many transfusions, you start getting too much iron in your body and that can deposit in organs. It can cause liver problems. It can cause kidney problems, heart problems. So, nothing we do is without risk and possible toxicity. So, there are a lot of things to pay attention to even if the focus is solely on supportive care and then we have these things called growth factors, red blood cell stimulators. There's this product called Aranesp or Procrit to which many of you have probably heard of and basically in a regular body system what happens is if the kidney senses that you are anemic, the kidney senses a low blood volume. It kicks out this hormone called erythropoietin and that erythropoietin stimulates the bone marrow to try to make more red cells. Well if your bone marrow is not working and it's getting a high level of this erythropoietin already, giving shots from the clinic are not going to help, but if for some reason the kidney is not putting out that erythropoietin to stimulate the bone marrow then a trial of these agents can be helpful and for some people it can make the difference between needing transfusions every week to maybe needing transfusions once a month and that would be a big impact on quality of life. The other

growth factor we have is to stimulate white cells and typically we don't use a white cell booster in folks who have MDS unless you have an active infection or you're getting repeated active infections, but it's there to use when we need it and now actually more recently we actually have a platelet stimulator, too. It hasn't been studied as much in MDS. It's been studied more in this entity called ITP where the body is kind of breaking down the platelets that are there, but I think that's coming as well. So, kind of good that we have just little shots that we can give or with the platelet stimulator there's actually one that's a pill that actually can stimulate some of this blood cell production.

Take things into the twenty-first century and that is really where all the excitement came in treating MDS. So in 2004, a drug called Azacitidine was approved by the FDA. In 2005, a drug called Lenalidomide or Revlimid was approved and then in 2006, a sister drug to Azacitidine called Decitabine or Dacogen was approved and this is when things became a little bit more challenging for docs and patients because now we had to figure out okay, so what are our goals? Before all we had was liver or maybe some growth factors to try to improve the blood counts, but we didn't really have anything that could change the MDS. Now, we have not only transplant, but we have three other new drugs. So, it's really trying to figure out what the goals of the patient and their family are. Is your goal to be cured and be open to the risk of a transplant or is your goal to have as much as outpatient therapy as possible to try to keep the MDS under control for as long as possible, but knowing that eventually at some point we won't be able to control it.

So, again, we have supportive goals. We have what I call disease modifying goals. We want to shift that prediction from the IPSS in terms of how long people will survive or curative therapy.

So, Azacitidine, the first drug that I talked about being FDA approved is something that we call epigenetic therapy and that's kind of a fancy term, but basically what it means is that in MDS what happens in that factory. So, we all have cells and in each cell and these stem cells, we have this thing called the chromosome and that's DNA which is the blueprint of that cell. It tells that cell what to do for as long as it's in your body. So, what happens in MDS is that that blueprint gets a lot of extra gunk on it basically and it makes it not work and it makes those stem cells grow up and look funny and not work right. So, what this epigenetic therapy does is it tries to remove the gunk from the blueprint and it's pretty cool because just removing this gunk can make those stem cells work right and make more functioning cells and so this was the first study in MDS aside from a transplant that showed improved survival. It showed a decrease in the chance of progression to acute leukemia. It showed an improved quality of life and the cool thing is that it actually worked in folks who had high risk MDS as well as low risk MDS. So, this is really the first breakthrough treatment. Now, it has some drawbacks in that it's a chronic therapy, but it can be a real game changer in terms of MDS. It's a slower acting chemo. So, if you think my analogy is always the atomic bomb approach versus the steal fighter and Azacitidine is really the stealth fighter. It gets into that DNA, that blueprint level and gets rid of all that gunk. So, you can't do that quickly and so this is the slower acting chemo and the goal is to fix those mutations,

fix those abnormalities that are within that blueprint, but it is a chronic therapy. Typically once you start it, you keep going as long as it's improving things. So as long as you're not having a lot of side effects, as long as it's improving your blood counts, maybe diminishing your transfusion requirements. It's a chronic therapy that's usually given once a month although we tend to alter things a little bit just to make it more amenable to people's quality of life as well.

Typically how it's given is seven days in a row, once a month. So, yup…

Q1: Is that the same thing as Vidaza?

Erica D. Warlick, MD: Yes. Sorry. I should use the trade name as well. So, Vidaza. And the standard dosing is seven days in a row for one week out of each month. Now we, obviously, change things. A lot of infusion centers aren't open on the weekends. So, sometimes it's five days one week, two days the next week and sometimes we reduce the dose depending on how people are tolerating it, but that's kind of the basic approach. It can be given as an IV or a shot under the skin and a lot of docs, I think, leave that up to the patient's preference. Both of them have similar outcomes.

Common side effects. With any chemo the counts get worse before they get better. So, things go down. You'll probably need more transfusions up front, but then eventually by typically the third or fourth cycle, we'll start to see responses. So, three to four months before you know for sure if it's going to work and there are some people who show a hint that it's working at about three to four months, but you really need to push it to six months to see and for some people it doesn't work and then it's a discussion with the doc and you on whether or not you want to keep going and trying or whether or not you say, "Well, I just don't think this is making a big difference." It can cause some fatigue. It can cause some fevers. Some people get some gut issues, but overall, this is a pretty well tolerated drug. At least in my experience seeing my patients go through this I've given this chemo drug to people as old as 86 was my oldest patient and she actually did amazingly well and was still living at home alone. So, I think it's a good option for folks. The overall responses are about 35 to 50 percent, mostly improved blood counts, but some people will get a diminishing percent of their blasts. Some people will get cytogenetic remissions where we can't see those chromosome changes anymore and for those who respond it definitely improves survival and it delays that transformation to acute leukemia and improves people's quality of life. So, that's a pretty amazing step forward for MDS treatment.

So, when I look at this I look at the benefits that it can be done as an outpatient, it's well tolerated. It improves a lot of those things that we just talked about in terms of survival and the responses can be seen and even high risk MDS. The drawbacks, obviously, are that it's a chronic therapy, but if it's working you keep doing it and for some people you want to travel, you want to do things. So, there's a lot of coordination, but the coordination can be done and centers across the country and across the world, actually, use this. So, don't let chronic therapy keep you from doing the things you want to do and that you love to do, but it's not a cure. So at some point it

will stop working and it's hard to know when that will be. If it's a year or I've seen patients on it as long as three or four years. So, it's hard to know until you just start. Questions about Vidaza?

Q2: How does that compare to Decitabine?

Erica D. Warlick, MD: So, Decitabine or Dacogen is kind of the sister drug to this. Interestingly, the studies that have looked at outcomes with Dacogen haven't shown the survival benefit, but I don't think that's because the drug is inferior. I think it's because of the way the clinical trial was developed and unfortunately at this point I don't think they're ever going to do a head to head Decitabine versus Azacitidine. So, I think Decitabine is a good option. I think the treatments are quite similar and in fact in folks who don't respond to Vidaza, about a quarter of people will respond to Decitabine if you try that second line. So, I think it's another good option. In most institutions you'll find kind of start with one or the other. They kind of have their own institutional preferences. That answer?

Q3: I have a question. I was taking Vidaza for two years and it seemed to stop working and now I just get transfusions. Is there anything beyond the Vidaza?

Erica D. Warlick, MD: So, one option would be to try switching to the sister drug, the Dacogen. It's not a huge percentage of people who respond, but some people do and if you're still pretty fit I think it's worthwhile giving it a try. Some people actually add on another drug called Lenalidomide, which we are going to talk about next to the Vidaza and for some people just adding that drug kind of gives the response back. So, we can talk more details, too, afterwards if you want.

Q4: Can you spell that?

Erica D. Warlick, MD: Which one?

Q4: The second. Not Vidaza, but the other one.

Erica D. Warlick, MD: The Dacogen?

Q4: Yeah.

Erica D. Warlick, MD: D-A-C-O-G-E-N. You're testing my spelling bee abilities.

So, the other drug that came along was a drug called Lenalidomide or Revlimid and this was really the first chromosome specific therapy. So in MDS, there is this entity called 5Q- syndrome and this typically occurs in middle aged women where there's refractory anemia, but other blood counts are okay and usually there's an isolated 5Q deletion in those chromosomes, that blueprint and the clinical course actually is pretty benign. Most people… I have a patient in my clinic who

was diagnosed, I think, in 2001 and she really didn't need any therapy until last year. So, that's a long time. Thirteen years of just observing.

So, what they found was this drug called Lenalidomide or Revlimid and now this drug is actually used for numerous types of bone marrow cancers, but what they found is that in this subset of patients with the 5Q- who needed transfusions of red cells, about 70 percent of patients would be become transfusion independent using this drug and it's a pill. It's a pill you take either every day or three weeks out of the month. It's pretty amazing. So this was first noted and published in the *New England Journal of Medicine* which is kind of our biggest medical journal and the benefits of this is that a huge response rate. So, to go from needing transfusions on a regular basis to not needing them at all, it's pretty amazing. I have another patient who started on this, I think, four years ago and she's been on this drug now dose reduced taking it just every other day four years, no transfusions. She only comes to see me one every six months now instead of once a month. So, pretty amazing. You had a question.

Q5: I'm jumping ahead, but is this MDS, is this a genetic weakness for this in the family or this not?

Erica D. Warlick, MD: So, complicated question. Typically, no. Typically it develops. There's some mutation in your bone marrow, in your bone marrow stem cell that makes it develop. Now in this MDS study that I'm going to tell you about in a little bit, we have seen some clustering of a couple of families that have a high frequency of either MDS or AML or other blood cancers, but I would say that is the exception to the rule and not the rule. So, it's typically not something that you need to worry about passing onto your family members, but I think it's important to tell your family members, "Hey, you need to keep up with your medical care and you need to have your regular checkups," and they should check your blood counts and if they're a little off then their doc should know that you have a history of MDS in the family.

Q6: So, is this 5Q… Is the Lenalidomide used exclusively for MDS patients with the 5Q?

Erica D. Warlick, MD: That's how it was started and that's really how it was FDA approved. Now, they have done studies of folks who don't have the 5Q- and the response rates are about 30 percent. So, it's not nearly as good. Now if you have complex changes in the bone marrow that include a 5Q, the response rates are about 50 percent. So, it's definitely an agent that can be used more for just than the isolated 5Q. Yup.

Q7: When (inaudible 29:58) take Revlimid?

Erica D. Warlick, MD: How many? There's not… Oh, here? Does anyone want to show their hands? I see one person in the back. Two. Three. Four. So, a handful. It's not the most… the 5Q- is not the most common form of MDS. So, I'm not surprised that's only a handful folks here, but the folks who have it it's a really good treatment option.

Q8: They don't give it to other people that don't have the 5Q?

Erica D. Warlick, MD: They do. So, and in other studies about 30 percent of folks who don't have the 5Q will have a response. Now, there are some studies that combine the Revlimid along with Vidaza and that's not necessarily used for folks who have… who only have the 5Q, but the FDA approval was based on low risk MDS that had the 5Q- and needed red cell transfusions and as with anything in medicine the docs try to carry it over to other patient populations and other folks especially when people haven't responded or have progressed on kind of the standard first line therapy. It's an expensive pill. It's thousands and thousands of dollars a month.

Q9: Doctor, my husband does have a genetic related… an established MDS. Are you or anyone who (inaudible) doing a specialized study for the subgroup?

Erica D. Warlick, MD: Yup. Yup. We're actually doing… We're looking at a couple of families that are in our MDS study right now and trying to see if we can find the genetic link between all of those. So, we have a lot of studies going underway looking into that.

Q9: So, could my husband (inaudible 31:52) sign up or do you…?

Erica D. Warlick, MD: Yeah. We can definitely touch base afterward and get some details. That would be great. The more we learn about it the more we can help come up with new treatments.

Q10: Why is that pill specifically so much money?

Erica D. Warlick, MD: Why don't you ask the drug companies about that? Any of these new drugs that come out to the market by the time they get to market they have… I mean, the drug companies have spent probably billions of dollars developing… finding the lab studies then the animal models then the early phase studies. These studies are expensive. I mean, they're hundreds of thousands of dollars just to do one study. So there's a lot of investment from the drug companies in this drugs. So, that's why I think they start out so expensive, why they stay so expensive for so long. That's a whole patent issue and… It's incredibly complicated.

Q11: What does (inaudible 32:51)?

Erica D. Warlick, MD: About 2005 – 2006, but I will say there are a lot of drug companies sponsored help. So, the drug companies have a lot of patient assistance programs. So, there's a lot of resources out there. The one other challenge that is with the drug benefits and Medicare is that a lot of drugs if you're getting g an infusion in clinic are billed through one part of the insurance and if you're getting a pill it's considered outpatient medicine and it's billed through another part of the insurance that the pharmacy benefit which often isn't as good. So, that's something that a lot of us are trying to work with Congress to change because chemo is chemo.

So whether you're taking it as a pill at home versus coming in for an infusion that's whole lot more expensive. It makes more sense to charge it under the same kind of umbrella because it will before the drug… or for the insurance if they would charge it that was as opposed to making people to go into for clinic. But that's a whole other tips that we can probably spend an hour on.

Q12: Well, I found that Revlimid and (inaudible 34:03) took for less than a month and I broke out in a rash all the way down into my back (inaudible 34:09) and that (inaudible 34:12).

Erica D. Warlick, MD: Yeah. So, I'd say probably about a third of people will get some skin rash. Now, I have had a couple of folks who got isolated skin rashes that we used a little steroid cream on and eventually it went away, but if you get a whole over body skin rash, I think your body is saying I'm alerting to this. I probably shouldn't be taking it. So, that is a little bit of a drawback. The other drawback is that it does cause some neutropenia. So, it can drop white cell count and make you at a little bit higher risk for infection. So, this is a drug I typically recommend in folks who don't already have neutropenia, that low white count because it really can make things worse kind of profoundly so.

So, what about a cure? In stem cell transplant is the one thing that we know that can cure MDS. What we know is that the response rates aren't perfect though. About 40 percent of patients depending on some of the features of MDS can have a cure from a transplant. The ability to use this as an option really depends on the age of the person, but even not so much the age, the fitness of the person. If you have a lot of other medical comorbidities and then finding a donor. So as people age, their siblings usually age and as siblings age sometimes their siblings aren't an option for a donor. So luckily, we do have other donor options. We have umbilical cord blood, which these cords are just sitting in a bank waiting to be used and we have the adult unrelated donor pool. You probably heard of Be the Match or marrow.org. So, millions of people have signed up to be a possible donor. When the transplants are first developed, they used what's used myeloablative treatment where they wiped out the marrow completely and that's pretty toxic as you get older. So, that's really why when transplants are first developed it was for younger patients, but now we have this thing called the mini or we call it reduced intensity transplant. So, that really extends the age that we can do a transplant, but before we talk about all the (inaudible 36:33) of transplant, first things first. What is a stem cell? So, you'll hear I had a bone marrow transplant or I had a stem cell transplant or I had a cord blood transplant and people get confused sometimes thinking that it's different things, but it's all really the same thing just where we got the stem cells from and if you go back to the beginning of the talk, we talked about why MDS develops and it's because there's an abnormality or a mutation in the stem cell in the bone marrow. So, the only way to fix it completely is to get rid of those mutated stem cells and give you new ones. So, that's kind of the whole basis of a transplant and a transplant has two parts. The first is something called conditioning where we give chemotherapy and radiation to try to clean out the bone marrow, really try to minimize the MDS that's there, but also diminish the immune system of the person getting the transplant so that their immune system doesn't reject the stem cells when they're given and then the next part is the transplant. It's not a surgery. It's

not a huge big procedure. It's actually just hanging a bunch of cells, stem cells, just like a red blood cell transfusion. Those stem cells go in through an IV. They go into the blood and then they make their way to the bone marrow and it's like planting new seeds. You have the new stem cell seeds that will then grow and start making the blood cells.

So, the way that a transplant is a cure is that if you think about any cancer. So, we all have an immune system in our body and cancers develop because they've somehow evaded our immune system. So, our immune system doesn't recognize them and get rid of it and that's how MDS develops. So, a transplant is basically trying to wipe out the MDS with chemo, but then giving a new immune system that can go in and get rid of the other microscopic MDS cells that are left behind.

So, it sounds like a good thing. Right? You wipe out the MDS. You give a new immune system. The new immune system can get rid of the remaining MDS and it sounds pretty straightforward and easy. So, why don't we do it for everybody? Well as we talked a little bit about not everyone has a donor option. Even though we have adult unrelated donors, we have cord blood. Now, we're starting to do something called haplo identical transplants. That's a new approach around the country. There are a lot of donor options, but still not everyone has one. Not everyone's fit. So, regardless of age, there may be heart issues or kidney issues or liver issues that just make it too dangerous to do a transplant and it's not a guarantee. So, the cure rates kind of range from about 30 percent up to 70 percent and a lot of that depends on are there complex chromosome changes in the bone marrow, have you had a lot of infections before? Have you had a lot of iron overload? A lot of features go into who gets cured and who doesn't and the risks are high. So, depending on the type of conditioning you get for your transplant the chance of dying of a complication can be upwards of sometimes 20 to 30 percent and that's a real risk and for some people their MDS is not causing that many problems. So, why take the risk of a 20 to 30 percent chance of dying of a complication when the MDS isn't causing much in the way of problems? And you can get side effects. So, you can get organ dysfunction. Your kidneys may get injured. Your liver may get injured. You may have a heart issue, a heart event from it and the big thing we worry about is the new immune system recognizing the recipient, the patient who received the transplant, as foreign and attacking that and that's something called graft versus host disease and it's something we can treat, but sometimes the immune system is incredibly powerful and every drug that we have sometimes can't get it under control. That's a small subset of patients who get a transplant, but it happens and then people actually can die of that transplant related complication. So, it's a very specific decision-making process that goes into deciding whether or not to have a transplant and that's where coming up with the goals of care really are important because if you don't have that established then it's hard to weigh all the risks and benefits of these different treatments.

So, the way that I look at making decisions is looking at the risk of the patient, the risk of the MDS and then trying to and look at the goals and then trying to figure out where to go from there.

So, first we talk about goals of therapy and whether or not someone is a transplant candidate and that decision can come from whether the doc thinks that the patient is fit enough to get a transplant or whether the patient really wants to do that. I mean, some people come in and say, "Nope. Don't want to go that route. I want to be at my home doing outpatient therapy as long as possible. I understand that the MDS is going to impact my life, but I don't want to spend my time in the hospital," and other people say, "You know what? I want to do anything possible to get this MDS to go away," and so it's really a joint effort deciding is someone a transplant candidate and if they're not and they have higher risk MDS and it's causing problems, they're needing transfusions, they're getting infections then going ahead with treatment really makes sense. Azacitidine or Decitabine or Lenalidomide kind of depending on what characteristics of MDS they have. If they are a transplant candidate and they're higher risk then doing everything we need to move on to get to transplant. We know that patients do better with transplant if their MDS is under good control. So, some patients will need some therapy prior to going onto the transplant and that can be the Azacitidine, the Vidaza. Sometimes we treat people as if it's acute leukemia and give that aggressive of therapy. So, there are a lot of different decisions and options that go into getting someone ready to go onto a transplant.

So, once we've decided that we're going to go in that direction, we need to find a donor. So, we look at brothers and sisters because as I said we have a lot of other treatment options or a lot of other donor source options and then every patient undergoes a pretty extensive week of clinical testing to make sure that all their organs are fit to withstand the transplant. For the transplant itself, depending on which institution you go to some places do them outpatient if they're the mini transplant. Other places do them in the hospital. If you're in the hospital, it's usually a three to four week stay in the hospital and then very close follow up in the bone marrow transplant clinic afterwards and if people get to that two year mark and it hasn't come back then you can actually say that they're cured, which that's a really cool visit.

So aside from those things that we talked about, what's new on the horizon and how do we get to better treatments? The first thing is to look at clinical trials and that's really looking every doc who's studying this at institutions are trying to come up with new therapies building upon standard therapies or maybe coming up with something brand new and so this is really the future to getting better therapies that maybe we can cure this or control this for a lot longer and we can avoid transplant. I mean, that would be ideal. So one option that we have here at the University of Minnesota and actually this is open at Mayo as well. We have this Minnesota partnership grant where we have combined Decitabine or Dacogen along with a drug called Vorinostat which is another one of those stealth fighters that kind of gets the gunk out of the blueprint and then we've added some immune therapy with these things called natural killer cells. It sounds kind of aggressive, but these are cells that we all have in our bodies and they are very good viral infection fighters and cancer fighters and we know from a lot of studies looking at MDS patients is that their natural killer cells don't work so well. So if we can do a therapy that builds upon a standard platform and then adds additional therapies maybe we can do better and so at this point

we have treated I think we're on our sixth patient right now and this is a study that I'm in charge of and of those six patients the first three had kind of the worst of the worst MDS. They had MDS that developed from therapy from other cancers. So, one had a different type of leukemia, one had CLL and breast cancer and they got the MDS from the chemotherapy for the other cancers and these people actually got a near cytogenetic complete remission meaning the blast percentage went down, all those bad chromosomal changes were gone when we looked in their bone marrow and they went on to go get their transplant. These were in patients who had never had treatment before for their MDS. So, we were pretty impressed and pretty surprised actually because if you remember back with the Azacitidine it takes a good three to four months before we see a response. Well in these folks, we actually saw responses after the first and the second cycle. So, it worked a lot faster than we were thinking. The last couple patients actually had MDS that progressed on the Azacitidine therapy and their response wasn't as good, but again we only have five patients who we have outcomes data on yet and the responses look pretty good. So, I'm very excited for this as an option.

Q13: So, (inaudible 46:46) on a nine months clinical trial using Vidaza and Vorinostat and just recently had a bone marrow and the results were almost too good. That is the blasts were greatly reduced, but it looks as if some of the other lines may be affected now and we're not sure whether the platelets are down and the white blood cells and it's been two or three months since the last of the nine month, but I haven't heard about the new therapy with natural killer cells. Is that something that can be taken after the clinical trial or is this in addition to it?

Erica D. Warlick, MD: It would be in the context of getting onto a new trial, but if you've already had the combination of the Vorinostat and Azacitidine it probably doesn't make sense to go to this because it's just the immune therapy that's being added and unfortunately I think that would actually be an exclusion being the prior Vorinostat. Sorry.

Q14: How long have they been doing this?

Erica D. Warlick, MD: We started this I think it's been about a year and a half.

So, what about other treatments? What happens when the Azacitidine doesn't work or the Dacogen doesn't work? So one of the combinations that's being studied a lot is combine the Lenalidomide and the Azacitidine, oral Azacitidine. So, the pill version of that is in clinical trials now and hopefully that will be coming soon because then that's another drug that you just don't have to come into the clinic for which would be great especially if we can get the Medicare pharmacy benefit stuff fixed. The Azacitidine along with these things called histone deacetylase inhibitors which is the Vorinostat, valproic acid which is actually a seizure drug is one of these agents as well. Rigosertib is a very fancy oral multi-kinase inhibitor and this is in early phase trials and then there's another drug that's been around for a while called Clofarabine and there are some oral trials in that and this is just a handful of what's out there. I mean, if you look at the clincialtrials.gov website, you'll see hundreds and probably thousands of trials that are around

the country and that's a good place to go if you're looking for something different. You can search by states, you can search by what phase of the trial. You can search by supportive care versus intervention. I mean, there are a lot of different ways that you can search. So, there are hundreds and thousands of trials out there.

Q15: Is this stuff up here in your book?

Erica D. Warlick, MD: I don't know if it's in the book, but I'm sure we could easily get copies of the slides.

?: We're videotaping and audiotaping (inaudible)

Erica D. Warlick, MD: So, that is great. And then the other study that I'm really excited about and proud about is this study that was based on a big national grant that Dr. Julie Ross who's a professor here was awarded and this is the first study of its kind that looks at newly diagnosed patients with MDS in Minnesota and tracks people over time. So, the goal of this study was to recruit 500 patients and how it works is the Cancer Registry actually alerts us when there's a new MDS case diagnosed. We contact the doctor of that patient to see if it's appropriate to contact the patient. If the doc gives the okay then we contact the patient and have a big long discussion with them. We send out a questionnaire that's about 30 pages. People sometimes send in a saliva sample. They may agree to having part of their bone marrow biopsy that diagnosed the MDS used in the study and then we watch people over four years. Now, I will tell you it's not in real time. So, I actually have the joy of reviewing all the medical records for the patients that are in the study and it's not in real time. It's about a year or two later. I'm reviewing some patients who were diagnosed in 2011 and 2012, but it's pretty amazing. We're able to pull a ton of information from the chart and from the questionnaire and from family history and then I assign those risk scoring standpoints. I look at what's happened in terms of treatments, look at the responses and the hope is that we can figure out why do some patients go onto acute leukemia, why do some patients not. Are there some genetic abnormalities that put people in a better risk or a less good risk and how can we change things? So, we look for risk factors specifically in Minnesota and then again looking to see if there are risk factors of why people progress onto AML and then we collect the DNA and some of you may be involved in the study and have agreed to have subsequent bone marrow biopsies, a pellet of the DNA taken, and those things are immensely important because especially in folks who have progression from lower grade MDS to higher grade MDS to acute leukemia. If we have a snapshot in time of what's going on in the bone marrow to each of those time points then we may be able to figure out what happened that made it go to the more advanced stage or to the AML and then is there some drug that we have that could intervene and stop that. So, it's really exciting in terms of the possible information we can get.

This is kind of detailing a lot of the stuff I already talked about.

So to date, we have 520 MDS patients who've completed the survey, 78 percent of those folks have given spit samples that give kind of the germ line DNA or the germ line blueprint. We have several folks who have given additional blood samples, who've given additional bone marrow biopsy samples and then we have almost 700 noneffective Minnesota residents who have filled out the same survey. So, where I see this going is over the next probably two to five years we're going to be able to continue to follow these patients, continue to get more information and hopefully we'll come up with some good descriptions of the biology of MDS and maybe first of all maybe we can prevent it but then how can we prevent it from progressing to more advanced stages.

Q16: Question. In treating the MDS, are there key points where you would do biopsies?

Erica D. Warlick, MD: So, I think if you ask five different hematologists you'll probably get five different answers. I look at first the goals of treatment. So if I have a patient who I'm trying to get to transplant and we want to see what to see what the response to therapy is to see if they're ready to go to transplant then I'm going to have kind of scheduled times where I would do a bone marrow biopsy and then if someone gets a transplant we have kind of scheduled times we do a biopsy afterwards. If the goal with the patient is to get the MDS under control and keep it under control for as long as possible, I honestly let the blood counts guide my decision for the timing of the biopsy. If the blood counts normalize with the Vidaza then I don't see a reason to do a biopsy because the blood is already telling me what's going on in the factory. If I see the counts get better but then drop well then I'm going to look in the bone marrow again because it could be that the dosing of the Vidaza is too much and it's just suppressing the good stuff that's in the marrow or it could be that the MDS is progressing and I can't tell that by the blood. So, that's when I go to look at the bone marrow.

Q16: When do you consider it under control?

Erica D. Warlick, MD: No longer needing transfusions.

Q16: Well, when don't you need a transfusion again? Is there a number in the red cells?

Erica D. Warlick, MD: So typically what I will use if it's a really young person which doesn't happen that often who has no other medical issues, I actually use 7.5 to try to minimize, but as people get older they can't tolerate 7.5. So usually, I use eight. If people had any cardiac events, have had a heart attack in the past then I sometimes actually consider nine as my threshold. So it really depends on the specific person. For platelets if patients aren't on any blood thinners, if they haven't had bleeding issues then 10,000 is the number threshold I use. If patients are on blood thinners for something else then I use 50,000. If they've had bleeding, say, they've had a bleed behind the eye or bleeding in the stool or the urine then we boost up that threshold as well. So, eight for hemoglobin and 10 for platelets are kind of the standard, but then you adjust those, at least my standard, but then you adjust those based on the patient and what experiences they've

had and so for me if someone goes from having red cells every two weeks and is always dipping below that eight and now they're staying at nine or 10 and they haven't needed transfusions, well then I'd say the drug's probably working and I wouldn't do a biopsy unless the patient really wanted to know for sure looking at the marrow or if things got better and then they got worse again. Every place is different though. I have patients that go to Mayo because they do their biopsies a little bit differently and they have a scheduled biopsy every year. There are pros and cons to that. A benefit is maybe you'll catch something early before it's causing problems. The con is maybe you'll see something that isn't clinical significant and doesn't change what you do. So, I think there's a lot of interpretation and probably just a lot of difference in docs' opinions about that.

Q17: Is there a sort of progression not of the disease, but is it typical for MDS without any of the chromosomal abnormalities start, say, with a red blood cell abnormalities and then next it's platelets and then white blood cells or can they all start simultaneously?

Erica D. Warlick, MD: Every combination. So, some people come in and all of their counts are low. White counts low, platelets are low, hemoglobin is low. Some people come in and it's just their hemoglobin and the patient that I was talking about earlier who's had the 5Q- MDS for about 14 years. She start with just mild anemia, but then it progressed to having neutropenia and we did a marrow and there were some new chromosome changes that kind of explained why there had been that progression. So, there definitely can be progression but I don't think any one person tends to follow the same pattern.

Q18: Is there any treatment for low platelet counts?

Erica D. Warlick, MD: So, there are some new platelet boosters that have come out. Promacta is one of them and I'm blanking on the other trade name, but one is a shot and one is a pill. They haven't been studied as much in MDS. They been studied more in this thing called ITP which is your body's immune system destroying the platelets, but there are some early phase studies in MDS and so that's definitely something that's kind of new and coming. Some of the drawbacks that they've seen are that it can cause some fibrosis in the marrow for a small subset of patients. So, that's why I think waiting until the big trials in MDS are published is going to be helpful because we don't want to do anything that could cause progression of the MDS or worsening, but I think if that becomes the only option and people are refractory to platelet transfusions which can happen then I think that's something that's very reasonable to talk about trying.

Q19: I went and I had blood drawn every three weeks and get a shot of Aranesp and my counts seemed to fluctuate in the beginning (inaudible 59:35) my history and going back to 8/29 (inaudible) 1.9 and on 10/3 it was 4.1 and on this (inaudible) down to 2.5. My hemoglobin was about 10, 9.9. The platelets that's what stayed pretty much (inaudible 59:58). My neutrophils fluctuated (inaudible) and my white blood cell counts (inaudible) 1.9 (inaudible) and dramatic change that I don't know. Does that…?

Erica D. Warlick, MD: I mean, that can happen. The cells in our body live for different durations of time. So, platelets usually live for about seven days. Red cells, normally produced red cells, live for about three months. Now obviously in MDS they're not normal so that lifespan is shorter, but the neutrophils only live about six hours. So, that's why you can actually see some pretty wide fluctuations sometimes. If you've been exposed to some virus that you weren't symptomatic from that can be enough for your neutrophils to kind of go up a little bit to try to fight it. So, those are kind of a little bit wide swings, but I'm not surprised that you're seeing some variation.

Q19: Basically, there are therapies (inaudible 1:01:06)

Erica D. Warlick, MD: Well, yeah. I mean, the Aranesp is really only impacting the red cells. So, it's not doing anything… There's no medical reason that it should be doing anything to the white cells or the platelets. So, if the goal is to get the counts all back to normal not obviously knowing all the specific details of your case then Azacitidine would be an option, but again it really goes into the goals and if the goals are to do no harm and to improve things then I typically wait until the white count or the platelets are getting to a lower standpoint where we need to intervene because the Azacitidine once you start it it's a chronic therapy and so it's really trying to sort out what the goals are and how much is the MDS causing a problem or could the therapy cause a problem?

Q19: I'm getting this for my hemoglobin. That's what they started it for. (Inaudible 1:02:10)

Erica D. Warlick, MD: So, that would be one thing to talk about with your doc and say well what are your thoughts on the rest of my counts and when should we make the decision to do additional therapy?

Q20: My husband he had both those shots for five days in a row every month. So from what I understand is Vidaza helps your hemoglobin and… No, the Aranesp and the Vidaza (inaudible 1:02:42) is trying to hold back as MDS. Is that correct?

Erica D. Warlick, MD: Yeah. The Aranesp is trying to boost up the red cells, but the goal of the Vidaza is really to improve all the blood counts.

Q20: Yeah. Well, they stay good for a while, but now they're really low and he wants to put him on (inaudible 1:02:58).

Erica D. Warlick, MD: Revlimid.

Q20: Yeah and now you say if your blood counts are very low.

Erica D. Warlick, MD: So if the neutrophils are really low. I tend to have caution.

Q20: (inaudible 1:03:07)

Erica D. Warlick, MD: Yeah. I tend to have caution with those because the neutrophils get better or get worse before they get better. It doesn't mean that it won't work.

Q20: So, it could still work.

Erica D. Warlick, MD: It could still work.

Q20: Does that bring up the red blood cells or…?

Erica D. Warlick, MD: The hope would be that improves all the blood counts. I mean, any of the treatments that we use that are not Aranesp or the growth factors, any of those the goal is to improve all of the blood counts, but the hard part is sometimes the counts get worse before they get better.

Q20: Yeah. His are really low, but he just couldn't start that and you just said it's probably not good if they're really low.

Erica D. Warlick, MD: So, I use caution in those folks and it doesn't mean that it's a never. Even though we have a lot of options now, they're still not perfect. I mean, having three or four different drugs is far away from the arsenal of therapies we want to have. So sometimes you weigh the risks and the benefits and that's how I decide my treatment. We look at to treat or not to treat. Is the MDS causing problems or would the treatment cause more problems and I think that's a good example that the MDS is probably causing some problems and so it may be worth the risk of the treatment to see if you can improve things, but then paying close attention and if the counts aren't getting better then not continuing a treatment that doesn't seem to be helping things.

Q20: (inaudible 1:04:30)

Erica D. Warlick, MD: So just to summarize things as you heard from patients and everything given their stories, MDS is complicated. It's not one disease and it's hard to sort out when to treat and really balancing the risk of the disease versus the risk of the treatment, choosing your treatments based on the patient how fit they are, what their age is, what their goals are because the goals are really the crux of the matter in my mind and it's individualized and it can be very challenging and it changes over time.

So, I will stop there and open it up for more questions.

Q21: Talk a little about chromosomal changes, mutations, etc. Some people with MDS have several genes missing or are mutated. Others may just have one. Can you talk about that (inaudible 1:05:33)?

Erica D. Warlick, MD: So the first thing that we look at when a bone marrow biopsy is done, we look at those blasts. We look at which blood counts are low and then we look at the cytogenetics. So, the chromosomes, 46 is the number that everyone's supposed to have. XY in a man, XX in a woman and so sometimes the chromosomes in the bone marrow are normal and that happens probably in about a third of the cases of MDS. Sometimes they're abnormal meaning there could be a deletion of a chromosome, an entire chromosome or a deletion of one of the arms of the chromosome and sometimes people have lines of mutations, lines of deletions within their description. So, they could have 10 different changes, 15 different changes, but what we know is that even in the folks who have normal chromosomes there are probably finer what we call molecular changes that we don't pick up with the standard chromosome assessment and so even those good risk normal chromosome MDS patients there're probably a lot of mutations that we're not catching. So over the last couple of years, there has been a lot more work looking at the molecular changes and there are these new molecular profiles that are being developed. They are more research based at this point and they're not used across the spectrum. There is actually a company called Genoptix that has developed a 22 gene molecular profile for MDS and for AML based on a lot of the work that's actually been published in the *New England Journal of Medicine* highlighting specific molecular mutations that really impact prognosis in MDS and so that's something that's coming, but it's not something that's routinely used and I think it's the molecular changes as we learn more about those finding drugs that target those molecular changes specifically are going to be helpful in changing the therapy for MDS. Now, the challenge is if you have 10 mutations if you don't fix all of them the MDS… I mean, the cells get smart and they work their way around it. So, it's really going to be needing to understand all of the different mutations and then how do we impact those mutations from many angles to fix things. So, it's complicated and I don't think it'll be… like you may have heard of CML. It's a leukemia that patients have a chronic leukemia where we have pills that are targeted to the one mutation that causes that type of leukemia but it's one mutation and there are now six different treatments that target that one mutation but in AML and MDS it's going to be much more complicated because a lot of patients have numerous mutations.

Q22: Can you speak to benzene and chromosomal mutations?

Erica D. Warlick, MD: So, benzene exposure can lead to abnormalities often of seven or five or just complex changes and I'd say benzene exposure is kind of similar in my mind to therapy related MDS that people can get from chemo. So, chemotherapy for breast cancer has specific drugs called Topo II Inhibitors that cause specific abnormalities that we see in MDS. There are other drugs, Cytoxan, lymphoma therapies or an auto transplant the patients can get can cause abnormalities of five and seven. Those are kind of the classic changes, but you can see just complex changes where they have four or five, six different abnormalities.

Q23: They have for RARST and (inaudible 1:09:23). Can you address that a little?

Erica D. Warlick, MD: I don't know the trial specifically. I mean, they haven't reported any of the results yet. The RARST is an interesting entity. So, it's refractory anemia with this thing called ring sideroblasts and thrombocytosis. So, having high levels of platelets instead of sometimes low and that's what we call provisional entity in the pathology classification. We're still trying to figure out is that more like an MDS or is more like a myeloproliferative disorder and so I think there's a lot of research looking at studies for what therapy is going to be the best. There isn't much published on what's out there for RARST in terms of therapies. Sometimes Revlimid has been used and I've had a patient that had a decent response to that, but I think participating in a clinical trial is really crucial because we don't know how best to treat that type of MDS or myeloproliferative disorder.

Q23: When I started my platelets (inaudible 1:10:28). Now they're down to (inaudible 1:10:32).

Erica D. Warlick, MD: That's great. So, it's working for you.

Q23: Yes.

Erica D. Warlick, MD: Which is good.

Q24: I have a question related to Revlimid and also Prednisone. I was on Revlimid for several months and the doctor at Mayo gave it up after a while because he didn't see any real benefits and I think it was about three to four months that I took it. Is that long enough first of all to see any benefits?

Erica D. Warlick, MD: Typically in the initial studies the responses were seen between one to two months. So, I think that's definitely adequate time.

Q24: How about Prednisone? Does that have any affect?

Erica D. Warlick, MD: It's a complicated answer. Sometimes people can have some immune related low blood counts along with MDS and if there's that component then sometimes people can respond to the Prednisone, but I'd say that's a very small subset of patients with MDS.

Q24: Thank you.

Q25: I was wondering if you went through a course of Revlimid, let's say, and it's got you transfusion free for a year and then it stopped working. If you're playing with the other studies for another year or a year and a half, would it help to go back onto Revlimid and see if it would start up again?

Erica D. Warlick, MD: I think if you tolerated it it would be worth a try. Once a drug kind of stops working I worry that it's probably not going to be effective again later, but the MDS could be different from the other treatments that you've had. What we're learning now more with bone marrow cancers is it's not like there's one cancer cell and that's the only one. We call them clones, but there are probably numerous clones within acute leukemia or within MDS and sometimes the treatment gets rid of one of the clones, but then another one emerges. So, I think it's worth a try because maybe you've changed that balance of the different clones of MDS and maybe the one that is there now, the most present, would be sensitive to it and so I think it's worth a try.

Q25: One other question, a sister question, about the Revlimid, but if your doctor has given you a (inaudible 1:13:04) test and you aren't producing any red blood cells at all do all of these possible drugs stimulate the growth when there's none being produced or do they just kill the bad cells that are killing the people who are making red blood cells kill the bad cells and let the red ones that are good live longer?

Erica D. Warlick, MD: The hope is that you're killing the bad stuff and letting the good stem cells in your bone marrow work, but if you're not making any then I think looking in the bone marrow, again, and seeing are there red cell precursors there or are there not because sometimes that happens where we look in the bone marrow and the precursors that make the red cells are gone and that can sometimes actually be an immune type phenomenon where your body kind of attacks those red cell precursors called pure red cell aplasia. So, when things change in the counts that's when I would look in the bone marrow.

Q25: So, just a question, just a comment on the other gentlemen. The (inaudible 1:14:14) study done at Mayo. I was in it for over a year and we started out with 11 people, two dropped out, five responded and became transfusion free and I was one of the ones who it didn't help at all after a full of year of taking that stuff. That's a pretty good response rate though.

Erica D. Warlick, MD: That's really good. I mean, most studies we say if it's a 30 percent response rate, we're happy. So, I mean, that sounds like a pretty good response rate overall.

Q26: Could Prednisone interfere with Revlimid therapy?

Erica D. Warlick, MD: Not necessarily. Where I worry about Prednisone in MDS is if your neutrophils are already low you're at risk for infection. If you add Prednisone which suppresses the immune system further the big thing we worry about when people are neutropenic are fungal infections. So if you add Prednisone on top of that and you're still neutropenic the risk of fungal infections does go up and so that's where I worry not so much that it would have an interaction with the drug, but complication-wise that's what I worry about.

Q26: Because when he was on Revlimid and it was working transfusion free for a year, when he started Prednisone, Revlimid stopped working, but we don't know if it's related when it stops working and other conditions.

Erica D. Warlick, MD: Yeah. I wouldn't look at it. In fact in other disorders that we use Revlimid, multiple myeloma, we actually always have either Prednisone or its sister, Decadron, along with it. So, I don't think that it messed up the Revlimid.

Q27: Question. When we did the matching, genetic match for stem cell transplant, three of my siblings, we were three for three on matching, but we were told that because I had MDS they may be predisposed to also getting it and I wonder what your thoughts are on it genetically or because, you know, as a concern for them and are there any… is there anything to support that or what are your thoughts?

Erica D. Warlick, MD: So, as we talked about before, someone, I think it was you in the back talked about that their family actually has kind of a clustering of MDS. That is definitely the exception to the rule and not the rule though. What I always tell people is if you have a family member that has it you should be vigilant about your health maintenance and seeing your primary doc and getting screening with the blood count maybe once a year, but typically the goal is to find a sibling match and if we were really worried that someone had a predisposition to having MDS we definitely wouldn't want to use them as a donor and so we do look very specifically when we do the donor workup if it's sibling, are their counts normal. We've had patients that we do bone marrow biopsies on because their counts were abnormal and we have sometimes found some festering problems in the bone marrow, but that's rare.

Q28: Stem cell transplants make a difference. If that's not an option, can children of a person who has MDS, if they were to give their blood as part of the transfusion does that have make any difference?

Erica D. Warlick, MD: So, there are some studies not as a transfusion, but as a transplant of using haplo identical stem cells transplants. So, that would be kids. Your kids have half the genes from the parent and… from both parents. So, there actually is a national study right now comparing cord blood to haplo identical transplants. I don't think MDS is included yet. It's in acute leukemia right now, but I know out at Hopkins where I trained that was a big donor source that they used and so haplo transplants, that was kind of where they developed those. So, I think we're going to be going in that direction that there are going to be a lot of other options.

Q28: So the blood that you actually transfuse into a person, the children if they were to give blood that matched…

Erica D. Warlick, MD: But it's the stem cells not the blood. So, just giving a transfusion won't… nope.

Q29: Is MDS cancer?

Erica D. Warlick, MD: Yes.

Q29: It is cancer.

Erica D. Warlick, MD: In 2001 that is when the Cancer Registry started recording it as a cancer and when I think of a definition of a cancer I think of it as a cell that's growing inappropriately and causing problems that can be life threatening. So, in my mind it is a bone marrow cancer and that's how kind of the governing agencies now define it, but a lot of people are surprised by that.

Q29: Yeah because we were told it wasn't and I keep hearing a lot of people say, "Well, I have MDS cancer," and I just need to figure that out.

Erica D. Warlick, MD: Yeah and some of it is… it probably comes from when the doc was trained, too. I mean, if they are a little bit older than me and were trained in the '70s and '80s it wasn't considered a cancer then, but as we learn more about the disease process, we learn that it behaves not differently than any other cancer. So, it really is a cancer of the bone marrow.

Q30: Can you talk a little bit about the (inaudible 1:19:57).

Erica D. Warlick, MD: Yup. So, those are those platelet boosters and, again, they were looked at initially in folks who had idiopathic thrombocytopenia, so ITP which is an immune attack against the platelets. Now, they're starting to do more studies in MDS, but what they have seen in some subset is that some patients have some fibrosis in their marrow, some people get some liver issues and some people they've seen a little bit of an increase in the blasts of the bone marrow. So, I have been using that really in specific cases where people maybe aren't responding to platelet transfusions anymore and really have low platelet counts and kind of reserving it for that category of folks as opposed to their platelets are 30,000 and we want to get them up to normal. So, that's kind of how I've approached it.

Q31: On the chemotherapy you've mentioned that there's a tradeoff against some organ damage. Does that damage go away over time?

Erica D. Warlick, MD: In which chemo? With the transplant or with…

Q31: I was just thinking any chemo.

Erica D. Warlick, MD: Any chemo. Maybe. So, I mean, there are some damage that's reversible that if you take away the offending agent it gets better. With a stem cell transplant, people get chemo and radiation and some people can have damage to the heart, but with good medical

management it gets better. The kidney irritation a lot of times comes from a lot of the drugs that we give after a transplant, so as those drugs get out of the system it can get better. Similarly with Vidaza or those types of agents some people do get some kidney irritation. They get GI irritation and those things can get better, but I have had patients that they they've had some event after getting the chemo and it may not be just the chemo, but it may be everything else that goes along with it. So, did they get a bad bloodstream infection and did they drop their blood pressure and was there a lot of infection and fever going on at that time that led to the heart damage or the kidney damage. In those settings, sometimes it's hard for it to get better. If it's a direct toxicity from the chemo then hopefully over time it gets better. So, that wasn't really a straightforward answer, but unfortunately it's not necessarily always straightforward.

Q32: I have a comment not as much a question. It came to my attention recently that there are larger numbers of people who have had chemo, not for MDS, who later on developed MDS and thinking how ironic it is MDS patients are getting chemo to get cured of MDS. So, I don't want to say it's a vicious circle, but your thoughts on that?

Erica D. Warlick, MD: Yes. So, it is true that we're probably finding more therapy related MDS and I've had a lot of patients who come up to me and say like if I have a patient who has newly diagnosed lymphoma. Well, I just saw the Robin Roberts thing on TV. I don't want to get chemo. That's going to give me a problem down the road and what I always try to bring people back to is we can't worry about the problem… I mean, we need to think about the problem that could happen five to seven years down the road, but we won't get to five to seven years down the road if we don't deal with the problem that's in front of us right now. So, the first thing is dealing with what's in front of you right now and trying to minimize the risk of toxicity going forward, but it's very true, yes, we're giving chemo to fix a problem that may cause problems down the road, but what we know are that there are specific chemo drugs and radiation that cause these problems. So, allocating agents. So, drugs like Melphalan or Cytoxan. Those are drugs… and radiation, those are drugs that can cause specific breaks or abnormalities in chromosome 5 and 7 that can lead to MDS. Topoisomerase inhibitors II which are some the drugs we use sometimes in leukemias but in breast cancer therapy can cause a specific abnormality called 11Q23 which is a type of MDS or AML. So, there are kind of specific drugs that we know can lead to those problems and interestingly the drugs that we use for MDS, first of all, they haven't been studied for more than 20 plus years, so we don't know those long term effects, but we do know that Azacitidine and Decitabine probably aren't going to work long enough that we're worrying about an acute leukemia or something that happens 20 years from now where just kind of a morbid way of thinking about it, but a realistic.

Q33: I have a question on graft versus host. We've been to long periods of high Prednisone with complication damage (inaudible 1:25:11). Is there anything out there or studies being done or something else to work on that?

Erica D. Warlick, MD: Yeah. I mean, there are a lot of graft versus host disease studies that we're looking at especially in the chronic versus host disease because in the acute stuff that happens soon after a transplant it's usually a couple months of therapy and you can get off of it, but it's really the chronic GBH that is an issue and I have patients who are eight years out and we're dealing with steroids. So, there's a new study that's opening up and I can't remember all the drugs that are going to be looked at but there's an immense amount of work looking at how can we find steroid sparing treatments for chronic graft versus host disease? So, those are definitely coming. Velcade is one of the drugs. I think they're looking at… I'm blanking on the other ones. The study is not open yet, so I don't know all the details.

Q33: But for the moment the main one is probably Prednisone.

Erica D. Warlick, MD: Prednisone, Cellcept, Sirolimus, Rituxan in certain types of chronic GBH. Imatinib can actually be used in certain types of chronic GBH. Photopheresis is another thing that's sometimes used. Those are kind of the big ones that are out now, but there is a randomized study that's coming trying to compare different drugs, but it's hard because the whole point of the transplant is to get rid of the MDS and it's wonderful if you get rid of the MDS, but it's really not wonderful if you're left with a chronic complication and so that's something that we feel incredibly bad about, too, because we want to fix all the problems and sometimes we can't or we keep trying new ones, new solutions.

Q34: I'm in that study of today when I got here gave me (inaudible 1:27:19) for both of my doctor because I have polymyalgia. They think that was something to do with the MDS.

Erica D. Warlick, MD: Yeah. That's one of the questions we have because what we're seeing when looking through all the patient's histories is that a lot of people do have some history of some autoimmune something. So, polymyalgia rheumatica, temporal arteritis, rheumatoid arteritis. Some people have CLL which is another type of bone marrow cancer, but we're seeing that link and so we're trying to investigate that a little bit further.

Q34: But then they asked again because I have lung cancer, too, and so (inaudible 1:28:00) different solutions for that.

Erica D. Warlick, MD: Yeah. We're trying to really sort out why are people getting it and if there is some predisposition in folks who have autoimmune problems, is there something we could do prevent it or to do better screening to detect it earlier. So, we're just trying to learn as much as we can about the folks who have developed it.

Q35: Could you speak a little bit about blood transfusions? How often you can keep taking them and taking them and taking them? I have two questions and our grandson has (inaudible 1:28:36) diamond. Have you ever heard of that (inaudible 1:28:38)?

Erica D. Warlick, MD: Well, it's a bone marrow disorder. So, it could be linked. Probably not, but it would be something to investigate and in terms of transfusions, the things that limit transfusions are your donor, your blood type. So, what's available and there are some people who develop antibodies when they've been exposed to transfusions. So, there are some patients that it's incredibly hard to find a pack of red cells that doesn't have the red cell what we call antigens on them that they will react to. So, those are the biggest limiting features and then also iron overload. Monitoring blood ferritin levels is important in people who have low risk MDS who are going to have years and years and years of transfusions. In folks who have very high risk MDS who you're not thinking are going to survive for years and years to see the complications of iron overload. Then those folks it may not make sense to do additional therapies to try to prevent that iron overload because the iron overload therapies actually have complications and side effects, too, and it's really balancing kind of expectations and goals and not putting people at risk for toxicity from a drug that they may not need for five – ten years down the road.

Q35: So in that case you're talking about years and years?

Erica D. Warlick, MD: Yeah. So, I have a patient who was diagnosed in 2001 and she hasn't wanted to do any more aggressive therapies and the therapies we've tried haven't really worked and she gets transfusions every three weeks. Every three weeks for the last 14 years and we have her on a drug called Exjade to try to keep her from having too much iron in her body, but if she were someone who had very aggressive MDS that was bordering on acute leukemia and we couldn't do therapy or for whatever reason the patient didn't want it then there won't be that number of years of iron overload and so then it doesn't make sense ot put someone on a drug that could just cause toxicity.

Q36: Yeah (inaudible 1:30:51) blood transfusion and (inaudible 1:30:55). Will that go away or will I always have it?

Erica D. Warlick, MD: You probably will always have it and it's weird because I have patients who have had transfusions like this one patient since 2000. Never developed an antibody and then I had another patient who one platelet transfusion she developed a ton of antibodies and then we couldn't find platelets and so it is… I don't know why some people develop them so quickly and other people don't. You had a question?

Q37: I have a question. Do we know what causes or allows the progression from MDS to AML and I know it's sort of preliminary, but do we know and I am part of a (inaudible 1:31:42) study. So, I'm just curious what you might know.

Erica D. Warlick, MD: We don't know yet. We're trying to figure out if there is a genetic step-wise path that it takes. In colon cancer they've shown that from a polyp to a cancer there's very specific mutations that happen. We don't know that yet for MDS and it's really studies like this

where we have serial samples and unfortunately looking at patients who went onto AML to really try to find out if there is a step-wise pattern. I'm guessing it's going to be not one pattern that there may be a few different patterns and I think using the work that they've done in acute leukemia and finding… they've looked at the whole genome of the majority of leukemia patients and they've identified all these different mutations and I think if we can extrapolate from that and learn from that information, I think we'll get to the answers sooner, but I think we're still probably 10 years away from… unfortunately. Everything moves really slow because the more we learn the more we realize it's much more complicated than what we thought.

Q37: Could you address a little bit more, too, some of the… you said there were some intracellular things that you test for which aren't commonly…

Erica D. Warlick, MD: Molecular studies. Yup. Looking at specific mutations that we don't pick up on conventional cytogenetics. There's this thing called AXL1, RUNX1, P53. Those were some of the big name ones that have been shown to… if someone has, say, a low risk IPSS score so that International Prognostic Scoring System and they have one these mutations, it gives them the same outcome as if someone who had an Intermediate 1. So, it kind of pushes them up one higher risk score in terms of the risk scoring system if they have a mutation.

Q38: Is fibromyalgia associated with MDS?

Erica D. Warlick, MD: Yeah. I haven't seen that, but there's a lot about fibromyalgia we don't understand as well and is that an immune related phenomenon and so I think as we learn more about fibromyalgia and if it is an immune related phenomenon we may see some correlation.

Q39: I'm sure (inaudible 1:34:16) talked about expectancy after diagnosis like in the past. You didn't show a slide that would talk about presently like at diagnosis. Can you talk a bit about that?

Erica D. Warlick, MD: So, the prognostic scoring systems have been shown to help predict people's survival. They've been shown to help predict survival in patients undergoing certain treatments, but they don't necessarily predict response to the treatment if that makes sense. So with stem cell transplant, people who have a lower risk IPSS tend to do better than folks who have a higher risk, but if you're on of the… I mean, it's hard to tease out… You can't predict who's going to respond still. They have a higher chance of responding and they may have a better survival if they get a transplant, but I still can't say for sure that you are going to be that one that has that response.

Q39: What about (inaudible 1:35:19) transplant to other options?

Erica D. Warlick, MD: Similar with Vidaza it can predict who's going to have an impact IN survival based on their risk score, but it doesn't predict who's going to respond. So, that's where

it's hard and it's hard to give an overall number because everybody has a different duration of response and so what the studies have shown is that Vidaza typically improves the survival by maybe a year and in the folks who are older in the subset analysis, the folks are over the age of 75 their median survival actually wasn't met at two years compared to the folks who didn't get Vidaza. So, the survival benefits can be on the order of years, but it all just depends on if you're one of those ones that responds or not. It's kind of a… it's a messy answer, but… and you had a question in the back.

Q40: Yeah. It's just an interesting fact, but being tested my husband (inaudible 1:36:25) and we had his family tested and he has a twin brother and so we though, "Oh, we have a perfect match." It was too perfect. It doesn't work.

Erica D. Warlick, MD: We typically don't use a twin brother if they're identical because they're identical and their immune systems are going to be identical. So, the whole point of a transplant is to get a new immune system that matches well but is not identical.

Q41: (inaudible 1:37:00) always… can it occur in a (inaudible 1:37:06) or it more associated with MDS?

Erica D. Warlick, MD: Say that again. Can what be…?

Q42: The (inaudible 1:37:11), the platelets, the (inaudible 1:37:14).

Erica D. Warlick, MD: Oh, myeloproliferative disorder?

Q42: Can it (inaudible 1:37:16) or is it with MDS?

Erica D. Warlick, MD: It definitely can be independent. So, people can just have what we call a myeloproliferative neoplasm where they have too many platelets or they have too many white cells or too many red cells or they have a bone marrow that has a lot of fibrosis in it then the liver and the spleen start making a lot of the blood cells and they get a big liver and spleen. So, they can definitely happen in the absence of MDS. Some patients have kind of this thing called overlap syndrome where they have some dysplasia features, but they also have some of the proliferative features and then they kind of fall into this overlap syndrome. It's kind of a tough term because we don't know which component plays a bigger role in their disease.

Q43: I have a question about one of your early slides where you talked about one of the early treatments was vitamin B12 and the case study started with my mother about 1942 when I first noticed it for… She's had a shot every Saturday morning of vitamin B12 liquid. She lived to be 93 and I was just wondering is there other forms of anemia that don't necessarily turn to MDS and so on?

Erica D. Warlick, MD: Yeah. So, that brings up a really good point. So, that's pernicious anemia where people have kind of actually an antibody attack against the cells that deal with B12 and so giving them B12 actually corrects the anemia. When people are diagnosed with MDS, we rule out all those deficiencies. So, we check B12 levels, we check folate levels and we check thyroid levels because if your thyroid is off, it can affect your blood counts. We check liver numbers because if your liver is not working right that can cause blood problems, too. So, we kind of rule out all those things before we say it's MDS. Now, there are still some patients who their docs do a trial of B12 or do a trial of B6 or a trial of other things just to see if it could help because there's not a lot of downside. I mean, there's not a lot of toxicity you get from a B12 shot or B6, but by definition MDS is abnormality is in the blood counts in the absence of a nutritional deficiency.

Q44: I have one other question too that's been bothering me a little bit. I think my doctor is very experienced. He's an older doctor, but it seems to have control on things and I think he's totally frustrated with me in the sense that he can't improve my condition. My condition is not that bad that my platelet count is usually from 16,000 to 30,000, but he wants to improve it and he's not been successful and let's say that eventually it gets down to 10,000 and he would recommend chemo at that point. Would that be your prognosis, too?

Erica D. Warlick, MD: Yeah and I think it goes back to the goals again. If the goals are to keep it under control as long as possible and deal with it when it's causing problems then yes when the platelets start getting closer down to you needing a transfusion then starting treatment at that time would make sense, but we all get frustrated because we want to fix people and sometimes we realize that we can't necessarily fix the problem, but if we can help with the quality of life along with it then I think we need to give ourselves a beak that sometimes we can't fix a problem and we need to try to work on other parts of a person's life. So, his or your doc's heart's in the right place.

Q44; I know it is. Thank you.

Q45: Do you recommend clinical trials for like you say I was on Vidaza for about (inaudible 1:41:33) infusion. Do you recommend some kind of a clinical trial for (inaudible 1:41:41)?

Erica D. Warlick, MD: I do. I mean, I think clinical trials are how we learn how to make things better in the future and hopefully we make things better for the people who are going through it in the present as well. So, if there's a clinical trial that's appropriate I think it makes sense to at least investigate it. Now, one drawback about clinical trials is that they're a little bit more of a pain in a butt than getting your standard therapy. So, there is extra consents you have to sign. There is sometimes extra blood tests that you have to do. Sometimes extra clinic visits and sometimes it's honestly not convenient to do it. So, it's a little bit more effort on your part and so I think it really is looking at okay does this impact my quality of life but not so much that it's a huge deal or does this really impact my quality of life? I mean, do I have to move someplace for

four months for the treatment? Well, then that doesn't really seem to make a whole lot of sense, but if it doesn't have a really bad impact on how you spend your time then I think it's reasonable to look into.

Q46: What is the difference between MDS and having cancer of the bone? I've heard of people who had another kind of cancer and then they say it moved just to the bones, but is there a difference?

Erica D. Warlick, MD: So in MDS or acute leukemia, it's a cancer of the bone marrow. So, it's not of the bone itself. So, some people can have breast cancer or a lymphoma or kind of any cancer that sets up shop in the bone part of the bone and sometimes cancers like breast cancer and other solid tumors can move into the bone marrow, but it's still not a bone marrow cancer. It's just kind of moving into that space. So, very different.

Q47: I've been diagnosed with MDS with refractory cytopenia multilineage dysplasia. My doctor says it has not reached a point of which any proactive action may… treatment is necessary. We're just in a watch and wait situation. It's a little frustrating because we'd like to get started on something (inaudible 1:44:03) the earlier is better than later. When and how you decide that it's appropriate for treatment?

Erica D. Warlick, MD: So, I go back to that prognostic scoring system and I look at okay, well refractory cytopenias with multilineage dysplasia by definition have less than five percent blasts. So, the blast percentage is low. I look at the chromosome changes depending on what yours were that would put you in a specific category and then looking at the degree of low blood counts in each cell line. If the degree of low blood counts is not that significant, just kind of in general terms then your risk on the prognostic scoring system would be low and even if transplant were considered they've done studies looking at when transplant benefits people and in folks who are in the lower risk category, transplant doesn't benefit until it does advance a little bit. Actually, people have instead of life years gained from transplant actually have life years lost if you do it too soon. So, it's really looking at that risk scoring system and I don't know if your doc went over those details with you, but sometimes that can be helpful because I get that you have something that's going to cause a problem at some point. Why not just deal with it now so that it doesn't cause a problem at some point, but what we have found is that you do really aggressive interventions too soon you may actually make people worse off than watching, but watching is hard.

Q47: The fitness or prefitness, one of the variables, is there something you can do to maintain your fitness for future therapy in the meantime?

Erica D. Warlick, MD: Eating well, exercise, don't smoke, don't drink too much. I mean, I use really basic things, the things that are hard to get us all to do.

Q47: Functional un-fun things.

Erica D. Warlick, MD: Yeah. Pretty much.

Q48: So my dad gets frequent blood fusions, aspirate cells, platelets, sometimes many units over the course of even one week. Besides the iron issues how does that effect of organs, spleen, (inaudible 1:46:30) other things and what is he doing with all those blood cells?

Erica D. Warlick, MD: Well, the other thing that's important to look at and I think when and I don't want to say autopilot but when someone's been getting transfusions every two weeks for a long time, sometimes we forget to look for the other things that could be contributing to why he's not retaining them. So, is his body breaking them down? Is there some component hemolysis? I mean, those things are important to look at because then sometimes it's an immune phenomenon and people need to have some steroids to counteract that hemolysis, but if they're not bleeding and they're not breaking them down then sometimes they are just kind of chewed up in the system and people need them every week because the ones that they get from a transfusion maybe they're all the old red blood cells. You know, it's just a pool of transfusion. So, you're getting these cells that they could be all on their end of their life, they could be all baby red blood cells and they're going to live longer and there's more that we're learning about. So in MDS, it's the bone marrow that's messed up, but there's also an environment that allows that bone marrow to get messed up. So, there could be some environmental things within the MDS patient that predisposes them to more inflammation or whatever that's not just those stem cells that are wrong, but we call it the milieu of the rest of the body.

Q48: Such as inflammation?

Erica D. Warlick, MD: Inflammation. Yeah and we're still learning about that.

They're coming the hook.

?: Before we thank Dr. Warlick which we will do, I would like to give a little bit more of an introduction for her. Many of you in the room I know know her, but some of you don't and we are fortunate that she is the clinician who grew up here in Minnesota, did her medical training her in Minnesota, went away and got some specialized training and came back and so we are happy thrilled to have her as a part of hematology oncology and transplant group here and happy that she takes time to give to patients and people who are coming here. So with great, great pleasure, thank you Dr. Warlick.

(Applause)

?: There's been a little bit of a change in the schedule. What we're going to do next is take a break and have some lunch. So, the lunch will be out in the area where we had breakfast and so

we will move the other presentations to the afternoon if that's okay with our nurse here. Is that alright with you? Sounds good. Any questions right now that have to do with logistics?

Q49: So, we can leave our things here.

?: Yes, we're coming back here. Alright. Thank you everyone and let's go have some lunch.