



Educational Patient-Caregiver Forum - Winston-Salem, NC **Page 1 of 44**

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Bayard L. Powell, MD: I want to thank the MDS Foundation for inviting me to be here today. Can you guys hear me okay? You have passed the first test. You found your way in here and so therefore you're definitely smart enough to understand my slides. I don't have any problem with that. I apologize to those you had any problems.

Just to summarize upfront, there's not nearly enough new treatment options for MDS and we're all working toward trying to find more different things, but I'll try to help you understand what's available now as best we can. One of the challenges with MDS is it's a very heterogenous group of diseases. Lots, as you see, know it's syndromes or syndromes. So, it's not really one disease. So unlike something like CML where we can target one abnormality that's common to all people with CML, you don't have that in MDS and it makes it a much more challenging disease. It's also more challenging to discuss or describe because everybody in this room they or their family member of whatever you had has a slightly different disease. It's quite variable from person to person. So, it does make it a bit more challenging.

The handout does have a few slides that I will not show including some those personal advice slide. Ms. Tinsley is going to cover a number of disease related things that I did not want really to overlap and I wanted to allow plenty of time at the end for discussion, but I wanted to include those slides. There's several in there like treating MDS is not for the weak and don't give up, don't give up too early type things. It wasn't a Jim Valvano idea. It was really these slides were made primarily for providers. I think many times providers start treating people and their blood counts get worse. They're going to temporarily get worse with some of these treatments and you just got to stick with it and plow through and give it a chance to work. So, that's really what it was. It was meant as words as encouragement because these are bad diseases with intensive treatment at times.

There are lots of data on Azacitidine. I don't really have any strong commercial bias at all. It was the first. There have been more phase three data with that. So, a lot of the data we'll work on that. I don't want to spend all the day working on data and so I wanted to focus on 1) explain how the data came about and work forward. I have never told and I tell the colleagues, Azacitidine, Vidaza, Decitabine, there's Dacogen. I tell representatives from those companies that I really don't care so much which one providers use. I just want them to use one of them if when it's appropriate. I think the problem we have with MDS is it's an uncommon disease and we need to educate you guys as patients, we need to educate providers of the values of these potential treatments and it's not common enough that people get a lot of experience using them sometimes and so they're sometimes somewhat hesitant to use these drugs and so my goal is to try to get providers to actually treat patients when it's appropriate more than which particular agent they treat them with. I also wanted to just say that welcome to Wake Forest to our conference cancer center. It's a cancer center. We're proud. We just got *US News and World*

Report 20th in the nation. We're delighted about that. We have a wonderful new building here. We have our outpatient clinics here for about eight years, but we just opened in December the inpatient units and this conference center on top of the outpatient center, but the thing we're most proud of is our people and how we hope we interact with patients and families. I hope in spite of having a challenge finding your way up here, I hope you'll find this is a warm welcoming environment. So, welcome and delighted to have you here.

That said, let's talk about MDS and see what we can learn. It's not a real common disease, but it's also not rare. It's 15,000 – 20,000 cases per year in the US. Almost exclusively a disease of adults. Because people live for quite a while with this, at any one time 40,000 to 50,000 cases of active patients with disease. It's more common actually than AML but doesn't get attention and the median survival is highly variable depending on the characteristics what type one has. It is a disease primarily of older patients and I'll show you a slide with that. A little more common in men than women and certainly the incidence increases with age. It is a clonal disorder meaning there's a group of cells that are abnormal in the bone marrow. People present with hypercellular marrow. The marrow is packed full of cells that is ineffective hematopoiesis. So, you're making lots of cells, but you're making the wrong cells and the machinery in the bone marrow is working away, but it's not producing mature cells that go out and do their job and so people will actually present with low blood counts and the low blood counts, yet the bone marrow is very full most of the time and the abnormalities can include anything from just the red cells, red cells, platelets, white cells, any combination of two of those or all three of them and severity of disease is frequently related to how many of those cells aren't involved and people generally present with the signs or symptoms of the absence of one of those cell lines. So, if you're not making your red cells, you present with signs of anemia, fatigue, (inaudible 4:58), etc. If you're not making neutrophils or white cells, good healthy white cells, you present with infections and if you're having the low platelets, you present with bruising and bleeding or hemorrhage of some sort. The dominant features are those of ineffective hematopoiesis. The majority of patients who die from MDS or a complication of MDS die from signs of those lack of good healthy cells especially infection and bleeding which are very common to the ones people die from with acute myeloid leukemia. Anywhere from a third to a half of patients who have progressed to acute myeloid leukemia and that depends on the subtype you have and we'll talk a little bit about that in a few minutes here.

Many patients are somewhat asymptomatic at the beginning and for those patients there may be discovered just during routine blood tests. Depending on the severity of the disease they may not need any treatment right away, but they need to be followed because they can progress to more aggressive types of MDS over time. You get to the point they may need transfusions or other more aggressive support. Things that people present to with are the ones I just talked to you about. Fatigue and shortness of breath and the anemia, recurrent infections and easy bruising and bleeding.

This shows the age and as I said it's a disease of older people, so very uncommon in people under the age of 50 as you see here. You're going to see a little more common in the mid-50s and once one... the majority of patients present up in the range of 70, 75, 80 years of age. So, this disease much more common so the number of cases per 100,000 people as you see here really goes up as one gets older.

I won't talk too much about classifications extensively. We'll talk a little bit more about that, but there are two different classification systems. You'll see the FAB and the WHO. I have a couple extra slides in your hand out there for that, but you'll see that refractory anemia basically, WHO divide them up in more subcategories than the old FAB and the old FAB included something called refractory anemia excess blasts and transformation. That's now actually being classified as an acute myeloid leukemia because it behaved much more like acute myeloid leukemia than it did like in MDS. What we do know is from some of the data, some of these patients did respond to our chemotherapy drugs and therefore you can use it for some of the same drugs, the Dacogen and the Vidaza can be effective in some patients with AML with low blast counts, but that's a different issue, but those folks are included in some of the studies we'll talk about.

Patients are stratified in the risk groups and the IPSS scoring system and of the technical things I think trying to get some understanding of this and the handouts includes the tables that will help you with that, figuring out what one's risk is and these scoring systems there's the IPSS scoring system and then there's the revised on that came out relatively recently. There are other ones. MD Anderson has their own, etc., but the IPSS is quite good as I'll show you and advise people in the risk groups and those risks look at both survival and one's risk of transforming to AML. The overall prognostic is based on three real factors: the number of cytopenias, red cells, platelets, neutrophils, two of the three, three of the four, three of three, etc.; the blast percentage which is probably the most dominate feature; and then the chromosomes are the genetics of the MDS cells.

So, this is the IPSS scoring system and this is the number of points one gets for these variables. So, the blast percentage normal is less than five or less. The points you get for that. The chromosome abnormalities, you can see them listed down here, the ones that are included, the good, the intermediate and the poor and then the number of cell lines and these show what they use as the cutoff for cytopenias. That's a little different than some of the other scoring systems, but those are the cutoff. So, you take the number of points here, add those together and fit them into whether you're in the low, Intermediate 1, Intermediate 2 and high and then you look down and see what's the average survival and then what's the risk of transfer... what's the time at which half the people have transformed to AML and that's quite long for the low. As you see, it gets quite short for the people in the really, really high risk group. So, it does really divide people in the risk groups and you see here in the graphic form the risk of dying of any cause for the low risk for the patients in this age group, this is not that high of a risk. Intermediate 1, Intermediate 2 and the really high risk is very, very dangerous to people. Likewise for progression to AML. This is really freedom from progression to AML. It's kind of a backwards slide, but it really

shows these people have progressed to AML fairly quickly. These much more slowly and many of these never progressed to AML. So, it shows that those risk groups do actually divide people into numbers that count and it also drives decisions about who gets treated. You also look and see that probably the number one factor if you had to look at one factor among these that really divides people up is the blast percentage and this looks at survival basis versus the number of blasts one has in their bone marrow.

Q1: Excuse me. (Inaudible 10:11).

Bayard L. Powell, MD: Yeah. I think I... Actually, let's see if we can go back here. This one might go back better. So, if one has in the low... is has normal numbers of blasts, this is survival curve and you see this many, many years out and for this older group of patients it... needless to say is not too bad, but if you get down here and you have... this is all refractory anemia excess blasts and transformation group in the past they really had AML, survival is much shorter and the Intermediate 2 risk, the people already be 2, refractory excess blast 2 with 11 to 20 percent for a very high risk of dying. Does that make sense?

Q1: (inaudible 10:57).

Bayard L. Powell, MD: Thank you. I appreciate it.

So, the revised system just basically takes the same thing and divides it into... divides up the abnormality. So, you have your cytogenetics, you have the percent blasts. Those are all still included and now divides up the red cells, the platelets and neutrophil as separate things as opposed to just how many of them are involved. It puts scoring system in those and divides it up... and divides it now into additional point system and then there's additional categories here. There's a very low, a low, intermediate, high and very high and it gives you, once again, the median survival time, but also the time it takes... median time it takes for a fourth of patients to progress to AML and those are in there... the ones that I give you handout so you would have time to go through those, but if you read things online, sir, you'll see a lot of data about the prognostic factors.

So, let's get into treatment which we were really talking about here today. Want to select the treatments appropriate for a particular patient. Your goals are to minimize the toxicity. You don't want to make people worse. If someone's asymptomatic, it's a little bit hard to improve their quality of life. So, you need to make sure if you're doing that it's for a good reason. Ideally, we'd like to improve people's blood counts especially decrease their transfusion requirements. You also want to increase their neutrophils. You can't improve their risk... decrease their risk of infection. You would definitely want to try to improve people's quality of life as I said earlier and you really want to prolong survival. I mean, we all have that as a goal for any treatment we do.

This is really busy and I have it in your handout, but I just want you to understand there are criteria for what's a complete remission, what's a partial remission and we'll look at improvement and you can refer back to these. It just shows original version, a modified version that recognizes that when you're actively treating someone the dysplasia frequently doesn't go away because the chemotherapy drugs themselves can cause some dysplasia and that maintaining something for greater than eight weeks is difficult when you have someone in active therapy. So, you want to sustain for at least four weeks and you need to take into account if the blood counts are low because you're treating someone that's different than if they're low from the disease and so at least try to take them into account and I don't want to spend too much time on that today except for you to have these references or else when you're looking at responses you can figure out how they're measuring those responses.

Improvement is also important in treatment of MDS because you frequently don't get a complete remission and this looks at measures of improvement of the red cells, the platelets and the neutrophils.

One of the first treatments is transfusion for people with anemia or thrombocytopenia, antibiotics for infections, chelation agents for people that develop iron overload for multiple transfusions. As many of you know, when you get... one of the downsides of multiple transfusions is over time iron builds up in your system. Iron builds up in your system. It can be hard on multiple organs including the heart, liver, sometimes the kidneys. So, there's concern about that and there's also some interest that some of the new chelation agents may actually have some effect on the MDS and so there's a trial now going on that looks at combining Azacitidine with one of the new chelation agents to see if that actually improves the responsiveness to treatment. Also some evidence that controlling people's iron levels and keeping them under control may actually decrease their risk infection. So, there are multiple benefits to that, but the biggest one is to avoid the iron overload in patients and then the growth factors, the erythropoietin factors. Most of you probably know those as either the trade names Aranesp or Procrit, but those are used to stimulate specifically red cells and sometimes we add on one of the white cell growth factors to try to improve the number of white cells, but primarily to actually increase the responsiveness of the red cells. So, you can... I'll show you some data in a few minutes.

Treatment with these growth factors has not demonstrated improvement in people's survival in clear cut studies or reduced the risk of transformation to AML, but it certainly has had impact on people's quality of life not needing as many transfusions, feeling much better, decreased risk of infection. So, there's definitely an upside. It's hard in these studies to show improved survival.

So, the erythropoietin growth factors improved anemia somewhere between 15 and 20 percent of patients with MDS. The benefit occurs mostly in people who are not severely transfusion dependent. So, the people who have kind of moderate levels of anemia tend to do best. If you add GCSF to erythropoietin, you may improve the response rate and there are some accurate predictors, I'll show you in a minute, of how might respond. The biggest ones are the

erythropoietin level, your own innate what your body is already producing to try to stimulate red cells and also the amount of transfusions that you're already requiring and what this really says here is if your body is already making a ton erythropoietin giving more... the erythropoietin is like a cattle prod for your red cells and it tries to get the red cells going. If your body is already flogging the red cell precursors as hard as it can by making lots erythropoietin, giving more probably isn't going to work. If your body is not really pushing your bone marrow to make more red cells then giving shots of red cell drivers may actually help. Likewise if your bone marrow is so sick that you're making almost no red cells, these things may not be able to work as well as if your body is making a few red cells and this stimulant may create more red cells, but if not working at all sometimes and you're requiring lots of transfusion it may not work.

So, this is a scoring system and you see all of us in medicine love scoring systems because these gives us guidance. If you take the erythropoietin levels and you measure and it's less than 100 then that's 2 plus... that's positive points. If it's 100 to 500 that's one positive point. If it's already over 500 that's a big negative. That means chance of response is much less. Likewise if you're requiring two units... less than two units per month that's a positive. If you're requiring greater than two or two that's a negative and you add that up and come up with a scoring system and so your response rate if you have a high score, a +1 or greater than +1 is 74 percent, 23 percent if you're in the middle and 7 percent down here. So, you can imagine in this group down here the likelihood of responding to one of those drugs, which are expensive and inconvenient is very low and so we try to check erythropoietin levels on people and look at how many transfusion they're requiring before you make a decision about using those drugs. These drugs really only affect the red cells. They don't do anything for the white cells or the platelets.

Yes, ma'am.

Q2: When we go in for our CBC, how do we know that they're measuring that?

Bayard L. Powell, MD: This would be a simple one time measure your doctor would do before they made a decision to use erythropoietin agents. Not everyone does that, but I would encourage people to do it because these are expensive drugs and it is inconvenient to go get a shot once a week if it's not going to help. The alternative approach is to start the shots, escalate the dose quickly and if you're not responding after a period of 4 or 6, 8 weeks then you realize it's not working, but this is a good way to predict whose most likely to respond and certainly if one is thinking of using one of these treatments versus some alternative treatment this might allow you to make that decision. So, it's not part of your routine blood counts. That's a good question.

The next drug that some people think kind of next in line is Lenalidomide because it's a pill and it's a lot more convenient for people. So, there was a trial with people that have a particular abnormality called 5Q-. So, people are missing chromosome 5Q and looked at that particular drug. Lenalidomide was given daily for either daily or daily for 21 days out of 28 days. Respond rates was quite high in making people transfusion independent. So, these people were requiring

transfusions in general. Seventy-six percent became transfusion independent after about almost six months. Eight percent had a 50 percent improvement. So, an overall response rate of 75 percent and in addition this chromosome abnormality disappeared in almost half of these patients. The duration of this was almost a year and but a lot of people had to have some dose adjustments. So starting on this pill is very good. It can actually decrease your platelets and your white cells. So, your physician has to follow your blood counts very closely when you start it. So, you people frequently become transfusion independent. Average time is almost a year, but I've had a couple patients that lasted well over two years and some three or four years. So, it's a very effective treatment in a select group of people, but it's only the patients with the 5Q abnormality. If you have the 5Q abnormality and additional chromosome abnormalities, you don't do quite as well as if you just have the 5Q by itself. This is a subset of patients for which we have very effective treatment in helping their anemia.

The use of the same drug in people that don't have this chromosome abnormality that had low to intermediate risk disease and were transfusion dependent, there was 26 percent of people that became transfusion independent. I think it was somewhere around 32 percent that either had that or improvement and it lasted about 41 weeks. Dose reduction was less frequent than the people with the 5Q, but it still required some dose adjustments. So, people had to follow you closely when they started.

Anybody in the room on Lenalidomide? Also known as Revlimid? No Revlimid users here.

So, the next set of drugs and which is kind of the backbone of treatment of MDS right now is the DNA methyltransferase inhibitors also known as Azacitidine or Decitabine and this was kind of the landmark trial... This was the landmark trial that really established these drugs as a standard of care for MDS led by Dr. Lou Silverman of Mt. Sinai in New York. The study was done in the 1990s, published here in 2001, subsequent publications, but this study looked at very interesting... I'll spend a little time on this. People were randomized to kind of standard supportive care order to get the Azacitidine or Vidaza. It was a subcu shot at that time. As many of you know, it can now be given either subcu or as an IV. It was given for seven days in a row and repeated every 28 days for four cycles and then they looked at people with bone marrows after two cycles and after four cycles the people in supportive care arm there was some exit strategies. If you had evidence that you progressed and you could go over to the treatment arm. If you were having stable disease you stayed on the control arm and the people who was responding they don't treat for a while longer. Others did not continue treatment. So, there was a bunch of slides from this. So, this is the supportive care arm not to be confused with the subcutaneous arm. The supportive care arm, there were 92 patients and nobody really responded. There were five percent of people that had improvement, but if you looked at people that got... were randomized to get the drug, there were seven percent of complete responses, 16 percent people that had partial responses which is really quite good in this disease and 37 percent improved. So overall, 60 percent of people had improvement their disease with this drug. So, 60 percent versus 5 percent is very, very encouraging and it's also encouraging to patients who

progressed on this arm, but crossed over. There were 49 patients. So, 10 percent had complete response, four percent partial for colo and 36 percent improved. So, a total of 37 percent actually benefited once they crossed over which is encouraging. So, it wasn't just that the people with worse disease are in this arm, but the ones that progressed on this were able to go over and get treatment and still respond.

Transfusion independence occurred in 44 percent of all patients. They got the Azacitidine and 43 percent of those that were in the high risk group. So, this shows this wasn't just the people in the good risk groups, but the ones who were in the bad risk groups also responded and similarly with platelet transfusion independence, over half of the people had platelet transfusion independence in the overall group and almost half in the high risk group although they're relatively small numbers.

And this shows the time to AML transformation. Patients actually were much less likely to transform to AML. This is the group that did not get the Azacitidine and the survival was also improved and self-analysis showed the survival actually was improved in the Azacitidine arm.

So, this looks at if you're in the low risk group you benefited. So, this is the two low risk categories. This is the no treatment and the treatment. If you're in high risk, this is the treatment and no treatment. So, it was interesting because it went across the risk groups. It also affected platelets and red cells. So, it was very exciting because it improved all aspects of people's disease and made things look better. One of those slides that I took out that says don't give up too early. It's related to this because the number of cycles it took to improve. Of those who responded, 21 percent of the responders happened in the first two cycles, another 43. So, a total of 64 percent or so after four cycles and 92... 93 percent after six cycles and a small number after more than six. So, it's one of those diseases where you want to see things at least stabilize with the first few cycles, but don't get discouraged, don't give up if don't work after two cycles or so and really the first response averages around three cycles. The earliest inkling of a response and then the maximum response did really not occur till after four to six cycles in many patients. So, it's one of those things that you encourage people not to give up too early.

And this is one of my favorite slides in all of our business because this is what we as physicians, we as patients and we as family members dream about which is a study that improves their disease and improves their survival, but also improves their quality of life. So, in addition to Dr. Silverman and Dr. Kornbluth did a companion study went with this where they were measuring a number of measures of peoples' quality of life and what you see here and this looks just at the people that were on the supported care arm. So, these were people that started off on the supported care arm and their physical functioning was trending down. When they progressed, they were put on the treatment arm and their physical function trended up which is very important and this looks like a small thing, but this is a highly significant improvement here in this measure. So, those that can function was getting worse off treatment, got better with treatment. This is the group, the same group of patients. Their fatigue was getting worse. They

switched over to the treatment and they got better and likewise their shortness of breath probably from their anemia was getting worse and then it got better. So, this is the dream for any of us in this room. People live longer and they live better and that's good for us. Now obviously, cures is the ultimate dream and that's something we have to tackle in this disease but yet to succeed on this disease, but this is a very good summation slide for this study. There are side effects as you might imagine. Nausea is very common when this drug was used. The drugs that we all think about now the Ondansetron or Zofran type drugs didn't exist back then and I will say that those drugs are magical with this particular treatment. It was amazing. We had people that would... we had participants since early studies and we had patients we had to admit to the hospital for nausea and vomiting with those drugs and when Zofran and ENZAMET and Kytril and those drugs came along which are one your doctor uses came along it almost completely eradicated nausea and vomiting with this disease. It really is magical to see how much impact it has had. So if you're getting any of these treatments and you're not getting an antiemetic, one of those antimetics and you're having symptoms, please let your doctor know because it is phenomenal how much difference it's made in the nausea and vomiting that happen to people. It does temporarily make peoples' blood counts worse. So, this is the control arm. Forty-five percent. They will temporarily make peoples' blood counts worse. The white count will go down, red cells will go down, platelets will go down. So, you have to think about you're knocking off the bad cells over time, but you're having some collateral damage in the process and some good cells are going away as well and then once you get rid of the bad stuff, it lets the good things come back and I always use the analogy in acute leukemia similar in MDS is it's like having a garden that's overgrown by weeds and you got to get rid of all the weeds. Kind of just get all under and then let the good seed cells grow back. It's not quite that simplistic with either disease, certainly not with MDS, but you do have some suppression of your good cells in the process of allowing time for the bad... of getting rid of the bad cells, so the good ones can come back. There's also something called differentiation or maturation that occurs with some of these drugs and what that means is I tell people it's like capital punishment versus rehabilitation and so a lot of our chemotherapy we use for cancer is capital punishment. We're trying to kill cells. With Azacitidine and Decitabine, some of the other drugs, we're trying to actually differentiate cells or take the bad cells and rehabilitate them into good cells and how much we're up and so there's some of that going on as well. All of that takes some time and there's some temporary worsening of cells while you're awaiting for the good cells to mature and grow back.

There was also a follow up study just looked at survival and just wanted you to be aware of that more than anything else. It looked at a high risk population with a high IPSS scores and people with excess blasts, randomized patients. It was a randomized people to get treatment or get standard of care. Multiple countries, 112 investigators and they saw a 24 month survival with the Azacitidine versus 15 months with supportive care and the overall a benefit of a 9.4 months difference. The hazard ratio is something we look at a lot that but the risk of having... of dying from your disease is .58 is high as if you didn't get the treatment. So, the extended benefit was 74 percent there and the two year survival was 51 percent. This is a very high risk group with a very poor survival without treatment. So, the two year survival is only 26 percent in the control

folks and it doubled that basically in the people that get treatment. So, some supported data and this just shows you when people do respond the cycles it took to respond in the previous study. Once again, two cycles or less, two to four, four to six and greater than six and the first cell line to respond many times... you'll see the blast percent go down in the bone marrow, but the first cells that generally will recover will be the platelets often followed by the white cells and red cells around the same time, but the platelets were generally the first ones you see respond.

Decitabine which is the sister drug. They're in the same family of drugs. Also is an active drug in MDS. I won't go through any study dissected. I just wanted you to understand one study. You can see similar things with other studies and other drugs. It's approved for people with MDS, of various subsets. There was a study that looked at it. The original study that got approved looked at it as an IV every eight hours, which as you might imagine is pretty inconvenient if you're trying to work or if you're an outpatient or if you're retired trying to play golf or go to your journal club or whatever, you book club. You can't do that very much with few eight hours on three days. You just literally can't get it as an outpatient, so but the original study looked at supportive care versus inpatient therapy. Once again, response rates much higher than supportive care and the median time of response was a little bit shorter with Decitabine. The duration response a little bit shorter, but in similar territory overlaps there and the median time to progression to AML for those that did progress was longer. Was not a survival benefit proven in this study which is one of the differences, but certainly hints that it's a very active drug. Once again, similar toxicities and the blood counts got worse. People had similar infections, risk, etc. So, some of the data with Decitabine. That was very convenient. Subsequent data has looked at it using it as a... and almost everyone uses it now is an outpatient regimen which is 20 milligrams for each for daily for five days. So, for five days in a row as an outpatient instead of every eight hours which is really not doable as an outpatient. Repeat every 28 days. So, similar patterns as the Azacitidine and the response rates looking at that you see here about overall response rate is 32 percent of patients with improvement 51 percent. So, data fairly similar to the Azacitidine data in response rates.

The time to a first response and then the time to best response is a little bit earlier in the data with Decitabine although the patient populations are a little bit different as well. So, it's hard to judge that except that you may see slightly quicker responses with Decitabine with patients. So, it may not take quite as many cycles to reach your end point. So the outpatient now is five days every 28 days, overall response rate 32 percent and among the responded patients, 82 percent of them had some response by the end of cycle two. The cytopenias is very common. A third of patients had delays in their treatment and about 20 percent up in the hospital and two-thirds of those were hospitalized at some time during their treatment, but about a fifth of the cycles of people end up in the hospital from complications of the cytopenias.

So, Azacitidine now is used either IV or subcu, schedule people use seven days in a row, five days in a row, five days skip the weekend because your doctor's office is not open on the weekends and do it on the next Monday-Tuesday. So, five plus two regimen, a combination of

other drugs. Rhinostat is one example. Decitabine IV there are some data with it subcu although it's approved for IV use. Daily for five days combinations. One of the big questions are they cross resistant. If you progress on one of these drugs, can you go to the other one? The drugs are from the very same family of drugs. There's a lot of overlap. Never been a very good study looking at it. If you progress on one can you get the other one? Is there a strategy if you take one...? Is it better to take one first and the other one second or the other way around? There's no data to really support that. Response rates are fairly low if you fail one of these drugs and you get the other one, but I frequently try it in my patients. I've had a few patients over time progress not scientific at all. I would suggest that I'll see if Ms. Tinsley has other ideas. My impression that among my patients has switched one of these drugs to the other the response rate is probably 10 percent or thereabout. So, somewhere in that range. It's not a real high percent, but I do sometimes try because you don't have lot of the options. Ideally, one would do it if you had a clinical trial, access to a clinical trial, you would do that first before you switched on these drugs or either you would switch to the other drug in some combination, but there is a lot of overlap in the two drugs and if one's not working the other one may well not work as well. While I mentioned briefly immunosuppressive agent, antithymocyte globulin or Cyclosporine are the two most common used. Responses have been modest. There's been no improved survival. As a whole, there's something called serum sickness you can get from these agents that you can suppress with steroids and these are the things that predict one's likelihood of response. It's not a very commonly used thing, but there's a subset of patients that may benefit from use of these immunosuppressive agents. They are not without toxicity either to be honest and they certainly have side effects.

So finally then we'll stop and have plenty of time for questions. I want to go over the NCCN guidelines. This is the guidelines for treatment and just very, very briefly walk through this. It's much of what we talked about. So, somebody has clinically significant cytopenias. So, they have some symptom and in supportive care options. Are they symptomatic from anemia point of view? If they have the deletion of chromosome five, we'll go to the next page, but we're going to try Lenalidomide because it's very effective in that subgroup of patients. If they did not have that or if they have that plus other abnormalities then you really want to look at what their erythropoietin level is. If it's really high, they probably aren't going to respond. We got to look at some other things. If it's low then we look at those other predictors and we think they're respond and that's likely going to be our first course for a supportive of treatment. This is people with low and Intermediate 1 risk disease. If they have low platelets, low neutrophils or low white cells then you have to think about either Azacitidine, Decitabine or maybe the immunosuppressive therapy if they have things to predict they would respond that we just looked at or ideally a clinical trial if you have access to one. If disease progresses there's no response then you really got to look at the clinical trial and you got to look at the bone marrow transplant or stem cell transplant as an option if that's an option for patients. We didn't talk about that much and I'll mention that at the end the indication for stem cell transplant.

So, this is the next page of that. So once again if they have the 5Q, you want Lenalidomide. If they don't respond then you go to these pathways. If they do respond, you keep them on it. If they don't have the 5Q abnormalities, you did the erythropoietin measure. If they're low, you give them the erythropoietin plus or minus the GCSL. If they don't respond then you fall down to this pathway. If they have a probability of responding to the immunosuppressive agents, you make that... this is a group you might try the hemoglobin or Cyclosporine. That's once again, a small percentage of population. If they don't respond you go to the pathway below. If they're EPO is high or they fail here or they fail here, then we come down and if they have a high probability to respond to immunosuppression you might do that. If it's low or if they fail that then you look at the Azacitidine or Decitabine. You look at possibly Lenalidomide if they have low risk disease or ideally a clinical trial and once again if they don't respond you move on down the pathway. If they're in a higher risk disease then you really have to... if they're in a Intermediate 2 and a high risk where their average... median survival is very short the patient... if you're in that group and you're a candidate for a bone marrow transplant. So, what are the issues for a bone marrow transplant? First of all you have to be in relatively good shape. It's a good physical condition. You can actually tolerate the rigors of that treatment. In general, most of the institutions have cutoffs, age cutoffs, at some point. Since is a disease of older patients that makes it a challenge. Our intuitional cutoff may need to go off if your group is participating and use 75 as a rough cutoff, but that's factored in age. Some places use 65 or 70, but we've gone up now to 75 with a few exceptions even above that. Do you have a donor? Can we find a good donor that matches you? Will your insurance pay for it because these transplants are anywhere from... they're close to \$100,000 to \$200,000 depending on what type of transplant. You can't do the type of transplant where you get your own marrow back in general because then you're just giving you back your diseased cells. So, you have to do one where you get someone else... a so-called allogeneic transplant. It may be a reduced intensity allogeneic or a sub myelo ablative whatever terminology people or nonmyelo ablative whatever term you have or full allogeneic transplant, but there are lots of factors there, but if you're in a high risk group you and your physician want to look at this option and say am I a candidate for that? You can then choose not to do it, but you at least want to look at the option if you're in a high or Intermediate 2 risk group. If the answer is yes, then you look at that option. If you relapse or end up not getting it then you go to either Azacitidine, Decitabine or a clinical trial. If you're not going to go transplant route then Azacitidine or Decitabine is the approach, other high intensity treatment or some clinical trial, but there are really not a lot of other proven... there's no other proven agents here. These are the ones that... and the reason they approved they preferred Azacitidine is because that was the one that has survival data to support it. So, that's the... and there's more phase three data there. If you're not a candidate, once again, then you go down this similar route and then you have clinical trials out here.

So current treatment options. Supportive care, transfusions, treatment option for everybody one option is not to take any treatments. I don't want to go that route. I suspect most people who are not interested in treatment didn't show up here today probably and people will factor that out, but if you're interested in treatment there's supportive care, transfusions, etc. If you have very

low risk disease that's very appropriate. You may wait until you have some symptomatic low blood counts or if you're having other problems before you look at treatment. So, that's an appropriate thing. As you start requiring more transfusions over time you may want to think about other approaches. If you have like the 5Q abnormality, you would go directly to Lenalidomide early on because it's so effective. Growth factor is primarily for people who are anemic where your main complication is you're anemic. That's the most common single finding or blood line to be involved is anemia and if you have just that then Erythropoietin is the treatment of choice. Lenalidomide is a factor, once again, for the people with the 5Q-, but even some of the others, there's that 26 percent improvement rate. Once you have excess blasts in general Lenalidomide is not an idea. So if you're in that group that has refractory anemia excess blasts either a 1 or a 2, you probably need something more intense than Lenalidomide. It doesn't have a big impact on the blast portion. You got Azacitidine and Decitabine. We talked about both of those. Agents in development. They're not nearly enough of those. People are looking at combining a variety of things with Azacitidine and Decitabine. We're looking other agents. I know the Azacitidine people are looking at an oral preparation. There are some studies out there looking at that. Clofarabine is another drug that people have looked at in MDS. Low dose Cytarabine which is a drug we use in AML or so called ARC is an old agent that was used many years ago. It's kind of considered a standard one compared to but not as effective as Azacitidine or Decitabine. Almost certainly not as effective as either one of these. So, you probably would not use as your early choice.

So, looking at oral agents trying to find new combinations. The challenge here as I said in my introduction is that there's not a single target we're looking at MDS. So, everybody's disease is a little bit different and certainly subgroups could be divided into even smaller subgroups that have different chromosome abnormalities. The nice thing about CML which is kind of our golden child in the heme malignancies because you could target the BCR able, that abnormality with chromosome 9, 22 or other... had a BCRL able complex and you could develop drugs that target that. Levac (sp? 42:24) or Imatinib and then all the four or five drugs that have come after that target that one target because everybody with that disease has that abnormality and so you could work on that. There's so many different subsets of people with chromosome abnormalities. I didn't put this slide in there, but the number of different little pieces of pie with chromosome abnormalities with MDS, you don't have a single target and it makes it much harder to come up with those agents and then for people that are in spry or healthy, are interested. You do have to before you move to transplant get your blast percentage down to normal range. If you move to transplant while you still have excess blasts, the likelihood of success is much lower. So, you want to get that blast percentage down if you have excess blasts, but if you're in a high risk group either Intermediate 2 or high intermediate or the high, you want to really think about transplant as an option if you're in good enough shape to tolerate that.

Questions. That's a lot of information. Hopefully not too technical, but I wanted to make sure that we address your questions. So, I want to give you people enough time to try to ask me questions and I'm glad to try to tackle individual ones. I won't be able to review your medical

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record at the moment and tell you about things, but I'm more than glad to take any that you have a question you're interested in asking.

Q3: Do you have any results on how long Vidaza works? If you're in that 60 percent that works then what do you think... how long do you think it's going to last?

Bayard L. Powell, MD: I'm very glad you asked that. One of the slides in there that's in your deck shows I think the average time on paper that people were getting is somewhere around 46 or 47 weeks. So, right at a year is kind of the average time, but a lot of the early data, the original study, the landmark study, actually gave people two cycles after a best response and the backed off. Some subsequent studies looked to continue it. One slide that I didn't keep in there that I should have I mentioned to you guys it is important and I feel very, very strongly about that that one to not stop those drugs once you had a good response. If you stop it, I think Dr. Silverman's experience and my experience, many people's experience that I've talked to is that if you stop those drugs the disease will come back. So, you're really with Azacitidine, with Decitabine, you're suppressing the malignant clone, but you've not eradicated it. You've not cured it, so you don't want to stop. You want to keep giving the drug. Now, I will say that with some patients their blood counts will get to a point their blood counts are not recovering, they're low, and in those patients, you need to check the bone marrow from time to time. If the bone marrow is emptied out and there are no cells there then it could be that the blood counts are low because you are getting your treatment a little too often or you're getting too intensive treatment. So, it could be low just from the treatment. If there're abnormal cells in there then you still need to get your treatment on schedule, but if one's blood counts aren't fully recovering between cycles, there are a lot patients that I didn't stretch out their treatment. You can take one of two approaches. You can either stretch it to every five weeks or every six weeks instead of every four weeks or you could reduce the duration. You could go from seven days down to five or five down to four or three. So, you can adjust it to people's to allow their counts time to recover. You don't want to adjust it so far out that you give a chance for the malignant cells to grow back. So, you're walking a fine line and treatment of MDS, in my opinion, one man's opinion at least is it's still a fair amount of the art of medicine and we don't have exact guidelines for every single patient. There are guidelines for how to adjust, but you do have to take into account people's ability to recover between cycles and you don't want to treat them so intensely that you've emptied out their bone marrow and they don't have any blood cells. You frequently have to give to people once they've had a response they get out six or eight cycles is you frequently have to give people some additional time in between or either cut back the dose. You can cut back the dose itself. I tend to cut back the number of days or either extend the interval between treatments.

Q3: That's with him and me I did it... I started in January and we... I go to Dr. Radford and we decided that after the sixth treatment we would go six weeks and last week was week five and it jumped. So, it worked.

Bayard L. Powell, MD: And really do have to... many times it's a bit of a nuisance for the patients, but many times to really make those decisions you have to look at the bone marrow and see what it looks like. Once again, if it's all emptied out then you may be over treating people a little bit and you may need to back off and give it a time for the normal seeds to grow back. If... and you also have to follow their blood counts really closely for a short period of time and see. Watch the pattern. Did their counts go down on week three, week four? So, you may have to get weekly blood counts for a little while and just see when they recovered and because there are some patients that you say I'm going to give them more time to recover and they'll get to week five and week six and they'll actually start going down further and those people you probably waited too long, but it is a still a fair amount of the art of medicine and trying to adjust things around and try to get it right for that individual patient. It always scares us a little bit when we start doing too much of that because you're always afraid you're going to give the abnormal clonal cells a chance to rear its head and come back up, but I agree with that completely and I think that's the (inaudible 47:43) one has to take. I don't feel strongly about decreasing the dose or the duration verses lengthening a little bit. I just don't think you want to go too far out. You don't want to get out where you treat every 10 or eight weeks or something because then you really are giving the abnormal cells a chance to grow.

Q4: At what point do you begin Vidaza?

That's a very good question. Any time... Question if you didn't hear that. What point does one begin Vidaza? I'm not sure the microphone carried, but what point do you begin Vidaza or Dacogen or who want to be generic here Azacitidine or Decitabine. Once again, a little bit of a judgment call, but I think in general one would say as you're going through those guidelines there if you don't have an option for one of the less intensive treatments, I think any time someone has an excess of the blast cells to me that's a 'gimme'. Once you have an excess of blast cells you need some treatment because if you don't you're a very high risk progressing to acute leukemia. When people become cytopenic with things other than red cells, you need to think strongly about that. So when they become... their neutrophils or the infection fighting cells get low or when their platelets are low you need to think about it. I generally when people's platelets are falling don't want to wait till they get all the way down to 10, - 15,000 where they have bleeding risks. When they get low and they're obviously falling, somewhere in the 40, - 50,000 range, I start thinking seriously about treatment because that gives you a little buffer knowing that they're going to fall further when you treat them and it may decrease the need for transfusion, but when the platelets are getting low, the neutrophils are getting low when one of these other treatments is not working more when you're number of transfusions starts to exceed a couple times a month then, I think, seriously about that because then you start worrying about iron buildup over time and then any time someone has excess blasts, I think of all those as indicators for treatment. If someone is going along and their hemoglobin is eight or nine, they're not really having trouble with infections, their platelets are 70, - 80,000 and nothing is getting worse, you can watch those people closely. You don't want to see them back every three to six months. You want to watch them a little more closely than that, but if you watch them closely

you can wait till something's getting worse, but as things start to get worse if one's in the Intermediate 2, high risk groups that we looked at those people need treatment and if you look at those last couple slides from NCCN, they'll say those folks go to treatment. They need treatment because if you're in that risk group where you're highly likely to transform to AML or if you're average survival is a year or two or less then you definitely want to get some treatment in those group. I think also you have to take into account if someone's kind of on that edge and they're a candidate for very aggressive treatment like how to (inaudible 50:26) stem cell transplant or a bone marrow transplant and you think they're in that group where they're in good shape now and if you wait too long they might not be a candidate for that then those folks you might think about treatment, but in general people that you think about transplant are already in the high risk group. That's along answer to a short question.

Q5: I also understand that once you start that treatment that as long as it's working you continue to take it.

Bayard L. Powell, MD: Correct.

Q5: It's not that you take it for a while, you get better and you stop the treatment.

Bayard L. Powell, MD: Correct. You do want to keep taking it as long as it's working and to follow up on both of your questions on that one. One of the reasons you want to keep taking it is because once you stop it and the disease progresses it's sometimes much more difficult to get it back to respond again for whatever reason. If you're working in the laboratory and you're trying to develop a model for resistance to chemotherapy, what you do is you expose people to it, you stop it for a while, let the bad cells start growing and then expose again and do that several times and when you do that the cells become resistant. So stopping and starting is not a great idea. If you got it knocked down, you want to keep it knocked down. Next question.

Q6: What are you saying in familial tendencies for myelodysplasia?

Bayard L. Powell, MD: It's interesting because classically MDS is not thought to be a disease that runs in families, certainly not strongly runs in families. So, I don't really think of that much in the range of like breast cancer or some of the colon cancers that you think of. You think of MDS as a drug... a disease that we don't really know what caused it with a few exceptions. Some of the exposure things including exposure to some other chemotherapy drugs for other diseases, but as far as a family, I don't think people need to alert their family and data don't backup any real familial... Well now, we do sometimes see people where two or three people in the family have it. That's probably just really bad luck or exposure to similar agents or something, but there's nothing that makes us think it runs in families. I think somebody else in the back had a question unless you have another question. You have a microphone, you can do two for one.

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Q7: Dr. Powell, I'm wondering if you are on the Azacitidine and you start to respond to treatment and you're on the younger age like the early 50s, but you're in the high risk group. So, how long should you continue on the Azacitidine before you look at bone marrow transplant?

Bayard L. Powell, MD: Excellent question. As a matter of fact I just saw a patient at the end of the day yesterday who fits... no HIPAA issue here that fits pretty much the criteria you just said. So, young person in MDS world is less than 70 or certainly less than 65, but relatively healthy person who would be a transplant candidate and they may have 10 – 15 percent blasts, so they can't go directly to transplant, but they need a transplant and you know it. To me, the treatment with Azacitidine and Decitabine are bridges to get to transplant. So what you want to do is treat, get your response, get you down to where you're a transplant candidate. So, your blast percentage are in a normal range. You're now a transplant candidate and as soon as you can move the better because those are... You do not want to ride that horse as long as you can till the horse falls over because then you may not be able to recapture that and move to transplant. You want to move to transplant while you can or if you already have additional complications. So if transplant's in your future as soon as you're eligible for that everything can move forward. You want to move forward. You don't want to take a chance of your disease progressing before you do that although it is tempting because transplants say scary move as well. The temptation is I'm doing really well, why do I want to push my luck? You don't want to miss that opportunity if you've gotten it. Does that answer your question?

Q7: Perfect.

Bayard L. Powell, MD: That's an excellent question and that actually comes up. Yes, sir.

Q8: I've read about the cell therapy and how effective it is on leukemia, but you visualize the cell therapy could ever be used on MDS?

Bayard L. Powell, MD: I assume you just mean it's on the manipulated cells where the cells kind of attack the abnormal cells.

Q7: They reprogram the (inaudible 55:09).

Bayard L. Powell, MD: I never say never. I hope so. I think the challenge once again with MDS is the disease is so variable from patient to patient that it's going to be a bit challenging to do that and certainly if one's trying to use your own cells identifying normal cells to reprogram and do that may be a challenge. We need to find very good ways to identify own cell... but find a way manipulate cells give them back is almost like trying to do the reduced intensity transplants in some ways and there may well be a role and there may well be a role for subsets of MDS. It's going to hard find a treatment like that that hits a wide subset of our patients, I think, and it's going to be a lot. Yes, sir. If you want to go ahead, I'll just repeat the question.

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Q8: To get to stem cell transplant, you have to have... be in remission and if you've already done intense chemo and you're doing the Vidaza and you're still high risk but considered clinically stable are there other chemotherapies to get you into remission if others haven't worked for you?

Bayard L. Powell, MD: So by remission for transplant, I really mean you do not want an excess of blasts. You do not have to have full recovery of your platelets or your red cells or neutrophils. You just need to be able to get rid of the blasts. So in general if one can't do that with Azacitidine, Decitabine, then there are other agents people can try. You can treat it like an acute myeloid leukemia and do the AML treatments. If you already done those then you just you keep going down that kind of AML road and also that happens sometimes. You just can't... It seems like if you have just a few blasts the AML treatments which deal with folks with lots of blasts should work, but it doesn't always work that way. It just depends on whether those few blasts are sensitive to your treatments or not, but you really go down the acute myeloid leukemia pathway and try drugs that increasingly work for that and go to different levels and intensities just like you would a refractory AML try to get a blast percent low enough that you can do that, but that is a challenge. I saw a patient for him that's been a challenge and throughout. I do the Azacitidine or Decitabine one and then if there's something you can add to that, but if you're short of some clinical trial, you really kind of rapidly move toward the AML because the main reason you wouldn't do that is because you can't get rid of the blasts that soon. That's very frustrating though.

Q9: When you talk about stem cell transplants, could you talk to the percent of people with MDS that make it. I was told it was only 20 percent that make it.

Bayard L. Powell, MD: That make it to transplant.

Q9: No, that make it through transplant. They get to that six year mark or that five year mark.

Bayard L. Powell, MD: I don't know the exact number there, but the five year mark, I would have guessed more in the 30 – 35 percent range. It may be 20 percent at five years, but somebody else may know that number. I don't know that number off the top of my head because I'm not a transplant doctor, but I would have guessed more in the 30 – 35 percent range, but it's... transplants not... a transplant in elder population in people with a relatively stubborn refractory disease is still a challenge and there's that from toxicity of the transplant which may approximate 10 – 15 percent or so and just the disease comes back in spite of that because you saw even on the NCCN guidelines they had a treatment for what to do when people failed the transplant. Twenty percent may be right. It just seems a little bit low to me. I would have guessed more... I don't know. Do you have any ideas? I think 30 – 35 would have been more what I would have thought. Let's work our way around and then I'm going to have to shut up before our next speaker strangles me.

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Q10: I was told I have had a transplant for my MDS and I was intermediate risk and I was given a 50/50 chance for a cure. I'm a year and a half out now. I don't know if... my blasts never got above five percent, so I did not have to get put into remission and maybe that has something to do... I don't know that...

Bayard L. Powell, MD: Having not had excess blasts probably does improve your odds a little bit, but that seems reasonable. Go ahead. That's good.

Q10: I was just going to say I don't... I haven't seen statistics based upon survival and blasts at the time of transplant. They may be out there. I just had not seen that.

Bayard L. Powell, MD: It would be nice to know and I don't know the answer to that if people had excess blasts and gone in remission if those... you would guess that those people might be a little more resistant to treatment than the ones that never had an excess of blasts with your case which might account for that slightly better prognosis. I'm almost wondering if the 20 percent relates to people who people start looking at transplant some of whom never actually get all the way to transplant. I don't know that.

Q11: Hi. My name is (Attendee). I've been here for about five years. I've been through all the treatment. I've had a bone marrow transplant three years ago and I primarily came today to make myself available to anybody that would like to talk about this wonderful place, these doctors, Dr. Ellis, Dr. Herb (? 1:00:48). How about if I speak up? Could everybody hear me?

Bayard L. Powell, MD: You should not push anything. It should just be green.

Q11: That's why I came to help for anybody. This is a great place and the doctors are wonderful. Anybody who's new to this disorder, I already know the words are difficult. They're all more than one or two syllables, but over time I would suggest you learn and get educated with this. There are ways to deal with the problems and I would like to talk to you about them. I've incorporated a wellness program. I exercise even though it was difficult. I changed my eating habits. I did a lot of different things. When I had my transplant. I exercise for one hour every day. I watch what I ate. My health come back. The side effects with chemo and although they may not have worked they work for me. I felt really good about it and I helped as many people as I can and I just wanted to let everybody know, but my question to you real quick. You talked a little bit about the immunosuppressive part of the system and (inaudible 1:02:21) therapy (inaudible 1:02:22), but is there anything in here anything you can give me where I can look up and study that a little further?

Bayard L. Powell, MD: Yeah. The immunosuppressive therapy I was talking about was really not post-transplant immunosuppressive although they're some of the similar drugs. There are really ways to... There's a group of patients in whom it seems that their immune system is what's driving the MDS. Very different than many of the other patients and that subgroup

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seemed to respond to just immunosuppressive therapy. There's some references that we can get for you for that. Okay. Shall we move on? I think if there... One question in the back and if somebody else has a question, I can meet with you outside right after. I don't want you to miss the next talk. So quickly, go ahead.

Q12: I noticed a lot of the statistics that are on these charts are rather old and dated. Where can you get more current information because some of them are eight years old? Well, certainly things have changed in eight years.

Bayard L. Powell, MD: Well, I wish I could say you're absolutely correct. We wish things had changed more and that's why I start off by saying the problem is that these drugs were developed... they're kind of established track record. There's lots of people doing it, but there are not studies going on with MDS now, not very many large studies going on with people looking for new agents and improvement, but people aren't going to do updated studies with these drugs because they're approved, they have a track record. So, they're dated and they're still unfortunately the best we have and the best data we have. Now, the data probably are better with those drugs than the data I showed because we all have a lot more experience. Many of the people that are using these out in the community didn't have any experience and we spend a lot of time trying to teach the community how best to use these drugs because is an art, it's not a science and I take phone calls every week from referring physicians who I'm trying to give some advice to how best to use or at least give them my opinion on how best to use it.

Q12: Doctors pool their thoughts into one central area where they can get more current statistics.

Bayard L. Powell, MD: (inaudible 1:04:21) but people don't actually send in pooled data on patients they treat unless they're in a clinical trial. First of all, they're not allowed to do it. We can't really collect research data on people that are not on studies and secondly there's not really a sense of a need with these drugs because they have enough of a track record now. Hopefully, there will be new agents coming and we'll have a new comparison, but there's not been anything to come and supplant Azacitidine or Decitabine. They're still the standards of care. Next question and then we have one more I think.

Q13: Okay. Quickly. How are excess blasts monitored? Is that just bone (inaudible 1:04:57).

Bayard L. Powell, MD: You have to look at the bone marrow. You cannot monitor any way other than a bone marrow. Unfortunately, for your behind there is no other mechanism to monitor that other than the bone marrow. You wish there was. I know.

Q14: How would you define a response to the Erythropoietin?

Bayard L. Powell, MD: How did they define it?

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Q14: No. How would you define the response?

Bayard L. Powell, MD: Improvement in your red cells and they're actually in those response criteria that I gave you in your handout. It really is your improved your red cells, so you don't need transfusions anymore or at least there's a 50 percent decrease in transfusions.

Q14: But could the response be that the fact that you're stable, too?

Bayard L. Powell, MD: Yes. Stable if you're... but stable means you're not needing transfusion. If you're still needing the same number of transfusion you were needing before you got it, I think most of us would not consider that a response to Erythropoietin. Now, you could say it would have gotten worse if I hadn't gotten it, but I don't think any of us would consider a response. You want to see it such that you're not needing as many transfusions as you were or hopefully not needing them at all.

Q14: And then the other question I had is on the neutrophils, is there ways to bring up the neutrophils?

Bayard L. Powell, MD: You could try the G-CSF. That sometimes worked if people are less than 500 and having recurrent infections that may be worth a try and there are patients who treated with the G-CSF or even GM-CSF. Either one of the...

Q14: What exactly the GSF...

Bayard L. Powell, MD: G-CSF, growth colony-stimulating factor. So, the G is granulocytic. So, the G or the G is granulocytic monocytic macrophage. GM is granulocyte stimulating and so it stimulates the granulocytes which are the infection fighting cells that matter. So, the G is granulocyte and there's colony stimulating factors is CSL. Does that make sense?

Q14: It does, but so that would be taken in combination with the erythropoietin.

Bayard L. Powell, MD: You would do it in... What I described was using in addition to Erythropoietin to stimulate the red cells. It actually improves the response to red cells because there's some crossover but it can actually be used to stimulate neutrophils in patients. There's some concern that it might also stimulate the blast cells although they're not really any data to back that up for the G-CSF. One last question there and I'm going to run because I'm jumping into my colleague's time here.

Q15: We have two autoimmune conditions here polymyalgia rheumatica along with the MSD. We haven't had really much treatment for either once except the Prednisone for and how does the Prednisone affect the polymyalgia rheumatica... I mean, the MSD.



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Bayard L. Powell, MD: The Prednisone certainly the right drug for the polymyalgia rheumatica. It probably does not have a big impact on the MDS. It may actually increase your white count, but it really just takes the white cells you have and gets more of them out into the bloodstream instead of hiding in the bone marrow, but it does not have an adverse effect. If you're on Prednisone long term, it can and your neutrophils are low your white cells are low, it could actually make you a little more prone to infection, but it probably does not have a big impact on the MDS.

Okay. I'm passing the torch.

(Applause)



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Sara Tinsley: I want to thank you all for attending today. Some of the things that I'm going to present will be just reputation, but you can ask questions as we go along if you have more questions that come up or you don't understand some of the terminology. I know when I started working with MDS patients and they started talking about cytogenetics and molecular profiles, it just hit my head and went right back out. So if you have a need for further explanation or want to try to understand that part of the disease better, we can go there today and I want to thank the MDS Foundation for sponsoring that and you all have this *Building Blocks of Hope*. I think there was a book that was given out and much of this information is including in that. There's also an online version of this. So, this was developed by the International Nursing Leadership Board and it was really spearheaded by Sandy Curtain and this is all of the people who contributed to the book, making the book and I'm the last person on the list there with the last name of Tinsley.

So, this is what you can find in your booklet: How you understand the diagnosis of MDS, how it's diagnosed, what are the common side effects of the treatment and what can you as a patient do about those side effects to help ease your toleration or improve your toleration of the treatment, what happens when you get blood transfusions repeatedly and what can you do about it or how can you minimize adverse side effects of blood transfusions and should you receive iron chelation therapy? That is one of those hotly debated topics. At the MDS Foundation when they do the international presentation there was an actual debate about between two physicians as to whether you should use iron chelation or not and they went over the pros and cons of iron chelation and you can find that actually on the MDS website, I believe, and how do you select a bone marrow transplant center? That's all in there and then as (Attendee) pointed out to me, what can you do keep yourself healthy because you didn't go out and choose to have Myelodysplastic Syndrome. It just kind of happens for the most part. It's a normal part or abnormal part of aging as your bone marrow gets older and it's reproducing cells, people's cells go bad and older people develop Myelodysplastic Syndrome.

So, what can you do to change the MDS? Well, a lot of it is thing that you would normally do to keep yourself healthy. Exercise, eat right, get enough rest, get your hydration in. That way you have control over the things you can control and then the MDS, you educate yourself about it and go to physicians who are experts in taking care of MDS. So, that's what the last part of this is about about how you can take control of the things that you can take control of.

So, like you saw previously with Dr. Powell who did an excellent job about understanding the disease, there's a little bit of the International Prognostic Scoring System score and the revised risk category, how to look at your treatments, what are you treatment options depending on the level of disease that you have and we use that IPSS and the IPSS Revised like a staging system. How many of you when you told a family member or a friend that you had MDS they asked if it metastasized? Did anybody have that? I get that question sometimes in clinic if a person's newly diagnosed with MDS if their disease had metastasized and it's mainly because their friends who had solid tumors like breast cancer or other types of solid cancers. When it moves from one place to another. Well, with MDS it's in your bone marrow, so it's all over. So, some of that can be

challenging like how to explain the diagnosis to your family members and friends, how to ask for help and how you can partner with... how you can become a partner with your healthcare provider in your journey with the MDS.

So, Myelodysplastic Syndromes, as you know, these are a group of bone marrow cancers. We do consider this a cancer and it's the... it comes from a clonal cell. That's how it gets distinguished as a cancer. It's one cell that's gone bad and made lots of other bad cells and it comes from a certain line in your bone marrow. You have the hematopoietic stem cell and it's the myeloid line. We have myeloid and lymphoid. So, we're talking about the myeloid line of your stem cells that has gone bad in your bone marrow cells and it's a hematologic stem cell malignancy. So, a bone marrow cancer and it's not just one disease as he spoke to you about. It's very many different kinds of diseases with lots of different bone marrow... Well, the bone marrow can look different, but what leads to that looking abnormal are these clonal abnormalities which really start inside the nucleus in the cell where those chromosomes go bad and so each of you may have a different chromosomal abnormality that leads... that gives rise this bad cell and so that's why we think of it as not just one disease, but different diseases as a bone marrow that we clump all together and call Myelodysplastic Syndrome like he talked about some people have 5Q- MDS. Well, we know that there's a certain percentage of MDS patients that is the unique characteristic of their MDS, the 5Q- and it behaves a specific way and it responds to a specific drug very well, the Lenalidomide. We can't say that we know that for all the other types of Myelodysplastic Syndrome that is... that's there. We have the 20Q deletion. We have Trisomy's. We have extra copies chromosomes. So, that's how we know it's more than one different clonal disorder. Like he was talking about CML is a pretty easy to understand disease because it has one chromosomal abnormality and that's 9 and 22 are translocated. In MDS, it's a group of different disorders. So, that's why it's more difficult to come up with one treatment that one size fits all and then depending on what your disease characteristics looks like that's what dictates your treatment.

So, what happens in MDS? Those... This is like a smear and these are all the cells that are crowded in there and then this is a magnification of the same thing and what this is illustrating as that the cells are abnormal in not only shape. So, they're formed abnormally, but their size... the size is abnormal. If you look at a CBC with differential one of the keys to a patient that might have Myelodysplastic Syndrome when you look at the CBC with differential and you'll see there's MCV. The MCV is looking at the mean cell volume. That means if it's really high that that person's red cells are big and so size and shape, MCV that's high is one of the keys that someone could have Myelodysplastic Syndrome. Other things can cause that like vitamin deficiency, vitamin B12. So, that's one of the things that we check to make sure that the anemia is not just related to iron B12 deficiency. If they have a MCV and they have anemia, we check a B12, but when you look at the bone marrow cells not just looking at the differential on your CBC, you see dysplasia of the cells and that just means that the size and shape are abnormal and they also don't grow up and mature normally and that's what we call ineffective hematopoiesis. That's the big term for it, but it just means they don't mature and then function normally. Ineffective hematopoiesis. And then what you see in the peripheral blood, this marrow, this

smear, is all crowded with cells, but they don't grow up normally. So, what you see in the peripheral blood is anemia or a low hemoglobin or thrombocytopenia, a low platelet count or you can have either high white count or low white counts. So, a lot of people have like neutropenia and within the different subtypes of Myelodysplastic Syndrome you know there's that variable risk meaning each person's risk is not the same of a disease transforming to acute leukemia and that's what a lot of patients fear is that they're going to develop AML or acute myeloid leukemia because remember that there's a myeloid stem cell disorder, but in general even if the person doesn't transform into acute leukemia as the disease is there for a longer amount of time it functions less effectively and so patients will have progressive cytopenias or another way to say that is like someone will present with a hemoglobin of 10 and over years you'll see that hemoglobin starting to slide or the platelet count changing or have like a borderline low white blood cell count, but with time it can get lower and when those blood counts are changing then that's a trigger for us to recheck the bone marrow a lot of times. It's time for a bone marrow biopsy and really the only way that you can check for those chromosome problems is by looking at the aspirate of the bone marrow cells. That's where you get that specimen and they do karyotyping where they let the cells naturally divide and then they look at the chromosomes to see if there's any chromosomal problems in the cells that are growing out of your bone marrow. The other way they can check for those chromosomal abnormalities is a test called FISH and you have to tell them what you're FISHing for. So, we're fishing for MDS changes and so they can do FISH on the peripheral blood, but usually that's one on your bone marrow sample also.

So, this is looking at all blood cells begin as hematopoietic stem cells like we said before and remember I said you have... yours is coming from the myeloid lineage versus a lymphoid lineage because if you look at your differential where it tells you what type of white blood cells you have if you ever look at your blood work, which I'm sure you do, is in your differential it will tell you myelocytes, metamyelocyte, sometimes you can see blasts. That's usually not a good sign if you can see a lot of blasts out in your differential, but you also can see lymphocytes and so they come from this lineage, but then you can see how these turn into your other normal functioning cell. You have your red blood cells here, your platelets and these are different types of white blood cells. So, those are the three lines that come from your myeloid progenitor cells. Mainly these white blood cells, your red blood cells and your platelets. So, that's how we know it comes from a myeloid lineage and then something happens in your bone marrow back here or maybe with this stem cell and then these start to lower. So, that's what this is illustrating and peripheral cytopenias.

How do we diagnose it? Well, you have to look at a peripheral blood count. You also want to check your reticulocyte count. I have a lot of people asking me what a retic count is. It's mainly seeing how you're making more red blood cells. That's what a retic count tells you. If you're anemic your retic count should be high because your body is trying to make more red cells or it's retic'ing a lot. Then you're going to look a bone marrow biopsy with an aspiration. You really want to pull if you have your pathology reports from your bone marrow biopsy, which I would encourage you. I try to print those for my patients and go over them with them. I know a lot of

times we're limited with the amount of time we can spend, but the more familiar you are with it then you can start to understand it if you look at it over and over again, but you really want to look. It'll tell you the percentage of blasts. So, the less blasts you have the better. Less than five percent is normal. So, more than five percent blasts in your bone marrow is increased blasts. You want to look at the cellularity like Dr. Powel said. Most patients with MDS have a hypercellular marrow where there's more cells in the bone marrow than you would expect for your age and you can tell what your cellularity should be by subtracting your age from 100. That's how cellular your bone marrow should be. So if you're 60, you should have a cellularity in your bone marrow of 40. So, if you get a bone marrow biopsy report back and it says the cellularity is 60 or 70 percent that's hypercellular. If it's lower than that than its hypocellular. So, just things we look at when we look at bone marrow biopsy reports and then you want to see if they describe dysplasia. They'll say nuclear budding or they'll use different dysplastic type terms to describe how their cells look abnormal in comparison to a normal cell.

This is really, really important. You cannot know what your risk is as evolving into acute leukemia or what your stage of MDS is without knowing what your cytogenetics are and that means those chromosomal problems that go along with your disease. So, a lot of people when we do it it doesn't tell us anything because you have normal cytogenetics, but that's good when you're talking about MDS if you have normal cytogenetics. There's also if you remember in the IPSS, they classify them as good, intermediate or poor. So, you would want to know what your cytogenetics look like. Iron stain tells you if you have too much iron stored in your bone marrow, which you will get if you've had lots of blood transfusions you'll have increased iron stores and then the other thing is this reticulant stain. This tells you if your bone marrow is fibrosed and that means your bone marrow is scarred up and the more fibrosed your marrow gets which can be an element that complicates your MDS is if it's got fibrosis as well. It doesn't function as well and then remember we were talking about that B12 and folate. These can make your cells look abnormal. So, you want to check all these other things. Hemolysis, that means you're looking to see if the red cells are being destroyed by your own immune system and there's tests that we use for that. Your hormone levels affect your bone marrow. So, we do check your thyroid stimulating hormone. We check testosterone levels in men and then you want to look at your kidneys because that erythropoietin that we were talking about comes from the kidneys. Your kidneys are what make your erythropoietin. It's a hormone and it tells your bone marrow to make red blood cells. So, if you have some kidney problems then you might not be making enough erythropoietin and that can be complicating your anemia.

And then this is, again, looking at the different subtypes. There's a lot of... the French American British, World Health Organization and then the World Health Organization 2008 and these are just the different subtypes of Myelodysplastic Syndrome. Does anyone know their subtype? You have refractory anemia with excess blasts, Type 2. So, that means your blasts are more than 10 percent, 15 percent. Right. Someone has refractory anemia. Does anyone have 5Q- MDS? You did? You don't now because you got a bone marrow donor cells and they have probably normal cytogenetics now. Right?

Q16: Yeah. (inaudible 1:26:39).

Sara Tinsley: Anybody else know their subtype? You would find that... You know yours?

Q17: RA.

Sara Tinsley: RA, refractory anemia. So, there's certain... Yes? A question?

Q18: No, no, no, no, no.

Q19: Sideroblasts. RA with sideroblasts.

Sara Tinsley: What are ring sideroblasts? It's a cell, a red cell and what they see on the outside of it is a sideroblast. It's a little ring of iron. So, certain subtypes like the refractory anemia, refractory anemia with ring sideroblasts are usually a lower grade as long as the blasts are not increased. So, they respond differently than refractory anemia, but excess blasts is more aggressive. So, that's how we kind of break those down. Thank you for sharing. I hope I didn't make people... I figure if you didn't want to tell me, you wouldn't tell me.

We see... I probably see this the most in our clinic, the clinic that I have. Refractory cytopenia with multilineage dysplasia and if you say that to a person and they haven't studied up on it, it's like you're talking Martian to them. Right? Like did you say something to me that I'm supposed to understand? But that just means that they have lower blood counts and that it's more than one line of cell that looks abnormal in their bone marrow. Refractory cytopenia with multilineage dysplasia and then Dr. List will take it one step further and just say RCMD and then that really confuses everybody. So, it is a learning curve. It took me a long time to understand it all and I still don't understand it all because they keep improving on the science and hopefully that will translate into new treatment options. So, these are the ways that we stage patients with Myelodysplastic Syndrome. The IPSS and the IPSS revised and it's really to help us determine what we think your survival will be and what the appropriate treatment is for your Myelodysplastic Syndrome and this is, again, just more saying the same thing again for just driving it home. The percentage of blasts is very important. Chromosomes in your bone marrow are also very important because we know there's some really bad players and usually the 5Q- is a good player. If you have that that's favorable. Also deletion Y and deletion 20Q and the Q and the P just refer to the long arm or the short arm of the chromosome. P is little for petite and Q is the long arm. So, that's how you can remember that and remember that looks like an X when you're looking at chromosomes.

Yes, ma'am.

Q20: What about Trisomy 8?

Sara Tinsley: Trisomy 8. With different diseases, it means different things. I don't remember if it falls into the favorable or unfavorable, but it should be in your book. I think it's favorable, but I would have to look it up again and I do have patients that I've followed since 2004 who have 20Q deletion that all I do is look at their bloodwork every three months or every couple months because they've been so stable. So really, the type of MDS you have does really help you kind of plan for what you need to do and what to anticipate and then really selecting treatment like the 20Q deletion person that I've been following for years and years as long as his blood count stays stable, I don't repeat his bone marrow because I'm not going to do anything. If he starts to drop his platelets more than that's when we'll check his marrow again.

So, this is the International Working Group for Prognosis of MDS. This is the manuscript that describe the IPSS revised and there is a phone app for this that I've downloaded to my phone and if you have your information, you could go on there and figure out what your IPSS Revised score is. These are facts that...

Yes, ma'am?

Q20: If you knew the IPSS score five years ago and the chart just progressively going down in every area...

Sara Tinsley: You mean your blood counts?

Q20: Yes. Should you insist on a bone marrow... another bone marrow test? Would that show something different or did that stay the same as the five years previously?

Sara Tinsley: It can change and that's why we do the bone marrow biopsy because the chromosomes, you can't really get that information in a better way or the percentage of blasts in your bone marrow without looking at the bone marrow again. So, you can't change. You can go from having normal cytogenetics to the clone will expand to the point that you can see what the chromosomal abnormality is that's leading to your disease.

Q20: Does it (inaudible 1:32:12).

Sara Tinsley: It should be a decision you make together I think. So if your blood counts are declining and you're needing transfusions and things seem to be changing, sometimes the doctors think that patients don't want bone marrow biopsies because they hurt, but if it will give you more information to be able to determine if you're in need of a specific type of treatment that is one of the triggers, really, for rechecking the marrow and determining if you need a new treatment is when things start changing.

Any other questions? No. Okay.

So, we do consider it incurable. The average age is 73 for diagnosis. Allogeneic stem cells transplant is the only potential cure. Leading cause of death is the disease itself even if you don't... If patients don't progress to acute myelogenous leukemia, infections and bleeding are the leading causes of death which are the same as what a person with leukemia. That's the leading causes of death for them and then we hit that other point already.

So, we individualize treatments based on... These are treatment triggers. Progressive or symptomatic cytopenias which is what you are alluding to lowering of your blood counts that you can see in a CBC. If you were not requiring transfusions and suddenly you start to require transfusions and the frequency of transfusions increases that may be a time to recheck the marrow and consider treatment. The doctors that I work with, there's about 18 doctors in our group. Not all of them are MDS experts and as you can imagine, they all have a little different flavor of how they treat patients and some of them would not start a treatment if the person was getting transfused like once a month or once every couple months. Another one might consider treatment. So, it is really is highly variable, but definitely increasing blasts and high risk disease and that also means not just the blast percentage, but if the chromosomes in the bone marrow are changing and you're requiring... they call it clonal evolution, but it means that the inside the chromosome where... inside the nucleus of the cell where the... those chromosomes tell your cells how to make more chromosomes or more cells that it's becoming more bizarre. There's like additions and deletions and it's just not normal. So, if that's happening that also translates in aggressive disease and you can only get that type of Infomraiton from a bone marrow aspirate, the dividing cell.

Yes, ma'am.

Q21: I was diagnosed from a bone marrow biopsy late in 2004. Only had one translocation. It was not specific. It was 111. Two thousand seven, same thing, but by 2010 I had developed (inaudible 1:35:35) three more translocations.

Sara Tinsley: So, you had clonal evolution.

Q21: I did have progression and of course they came increased symptoms.

Sara Tinsley: Did everybody hear that? She was describing perfectly like clonal evolution.

Q21: Yes. In 2004, I have a family history. I'm the third of my siblings and my father to have this disease. In 2004 because of increased bleeding and some other immune issues, I saw a hematologist, had a biopsy and indeed I have translocation that pointed to myelodysplasia and we decided that I wasn't symptomatic of it and bruising leave it alone and I was able to with bruising precautions do well until 20.... I guess it wasn't... I had another just follow-up biopsy in 2007 or 2008. There were no more changes and I was stable, but by 2010, I was getting short

of breath and I was having worse bruising. My ANC just... that's your acid neutrophil count had dropped down next to nothing and I'm an ER nurse, so that affected my work and so another biopsy showed that I had indeed gotten further translocations and that's when (inaudible 1:37:03) immuno therapy.

Sara Tinsley: So, you had to do something different.

Q21: Yeah.

Sara Tinsley: Symptoms and the changes in your bone marrow cells.

Q21: Yes.

Sara Tinsley: Thank you very much. I think I saw another hand somewhere. Did someone else have a question? No.

So, performance status good versus poor performance status. Comorbidities. That's a fancy way of saying do you have other illnesses like hypertension, diabetes, heart disease. Whether you have low, intermediate versus intermediate 2 or high risk disease. Low and Intermediate 1, the goals of therapy are different. You want to improve your ability to make your cells and decrease your transfusion requirement. When you have intermediate or high disease, you're really wanting to make sure that you live longer. So, the goal of that therapy is to improve your survival and do you have primary versus secondary MDS. Primary means you developed it, it just happened to you. Secondary means that you got treatment for some other kind of cancer and that's how you developed your Myelodysplastic Syndrome and then cytogenetics, deletion 5Q. Complex karyotype refers to if you do a bone marrow aspirate, you do the cytogenetics. You look at the cytogenetic report. If there's three chromosomal abnormalities that's called complex and that's always a bad thing and then lifestyle.

So, you heard about our treatment options, supportive care, Lenalidomide, Azacitidine, Decitabine. These are chemotherapies. Clofarabine, Cytarabine and Etoposide, bone marrow transplant and then we do have a variety of investigational agents. We have probably four or five clinical trials at Moffet where we have patients enrolled. Some of these are new agents. Some of these are established drugs that we're adding something to it like Lenalidomide plus something else to see if we can improve on the response with just Lenalidomide by itself, but we do have limited treatment options for that have been approved by the Food and Drug Administration. So, that's why he was saying you want to make sure you're not... that you're giving it a good try before you give up on it because if you have three treatments that are approved, you want to make sure you gave them enough cycles to effect an response.

Yes, ma'am.

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Q22: The Vidaza is for white platelets. Is that correct? To improve the white platelet count?

Sara Tinsley: Vidaza is... it has different goals. Like if you're getting it to for low risk disease like refractory anemia or refractory anemia with ring sideroblasts or even one of the other ones that's a lower Intermediate 1. It usually can improve platelet count and can improve the red blood cells. It rarely helps neutrophils although it can. It's not as good at improving white blood cell count.

Q22: What comes first generally? Transfusions or going on Vidaza? Do you have transfusions just for the red blood cells or also for the white platelets and at what point would you go on the... I don't understand the...

Sara Tinsley: At what you point you started treatment and what you're trying to do?

Q22: If you had first go on transfusions or you go on the medication to avoid transfusions.

Sara Tinsley: That's a good question. There's three lines of cells in your bone marrow mainly. The white blood cells, but we really look at the neutrophil count which is a type of white blood cell. So, the neutrophils if they're low that puts you at really increased risk for infection. The second thing that we really look at is the red blood cells and we don't really look at red blood cell on the CBC, we look at hemoglobin. So when your hemoglobin is getting less than eight usually most people use eight or seven, seven grams per deciliter and you're having symptoms of anemia like fatigue, shortness of breath, difficulty doing your normal activities because you're so tired then that's the trigger for getting a transfusion and then for platelets, that's the third line of cells that are made in your bone marrow. Platelets help you keep you from bleeding. So if you have a low platelet count, you're at increased risk for having a major bleed and usually we wait till your platelets get really low before we transfuse. Like a normal platelet count is 143,000. When your platelets... most places when they get to 10,000 or less is when you give a transfusion, 10,000 or less, unless you have active bleeding then we'll use 20,000 as a cutoff. So really when you start Vidaza, you can start it if you have low risk disease to try to improve the number of transfusions you receive or the number of... with blood or platelets if you're getting those. Sometimes it can help neutrophils, but not usually... that doesn't really help that much usually and then but if you have high risk disease you're really trying to decrease the percentage of blasts even if the person keeps getting transfusions because blasts will eventually convert to AML and then you need more intensive therapy. So, there're different reasons for starting.

Q23: In terms of the blood tests, what sort of variance is there in measures? Because our son is the patient here and he'll report that this numbers are stable and then somebody will have a blood test and his platelet count has dropped 18 and they'll wait a couple of weeks and they'll be back up into the 40s or whatever for him is normal now. Can that be a variance in the test itself or does that actually indicate that there's something happening?

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Sara Tinsley: It is the lab, the same lab every time or a different lab?

Q23: The same lab.

Sara Tinsley: If it's happening regularly, it might be really pretty cyclic. It might really truly reflect a change in platelet count.

Q23: (inaudible 1:44:02) variance in that sort of a test.

Sara Tinsley: It's usually 10 percent plus or minus 10 percent. It shouldn't be that much unless you're going from one place to another, but something that can really happen with especially platelet counts is platelets can clump. So if that's happening I would have them check for platelet clumping and there's a special tube that they can put it in to rule out platelet clumping or have them do a smear like a manual dip and they'll see the platelets are clumped.

Q23: Thank you.

Sara Tinsley: You're welcome. Any other questions? Yes.

Q24: I'm curious bone marrow transplants. I just know that (inaudible 1:44:40), but what can you tell me about of any progress in the last couple of years with the ease of transplant, bone marrow transplant surgery. Has there been anything new?

Sara Tinsley: Are you talking about getting the stem cells from the donor or are you talking about the recipient?

Q24: Well, I guess both. Both. I've read, for example, that umbilical cord is a great source, but I don't know if anything's come out of that. I've read that Israel and France they've come up with ways to make the process shorter and more successful. I also understand that MDS is cancer is on the low end of the totem pole for research, but bone marrow transplants can help a lot of people out with other ailments.

Sara Tinsley: The biggest... I don't work in transplant. They separate hematology from transplant, but I did work in transplant before. So, I know the big changes that I've seen is that they have changed the way that they harvest the stem cells which has, I think, improved... It's improved for the donors, but also for the recipients as far as viability of cells and like graph versus host disease. So, they used to take people to the operating room and do bone marrow harvests. I used to do that. Sweat, sweat, sweat because it's like doing a bone marrow biopsy and you just pull up a lot of aspirate and then you pass it off, but now they collect the stem cells from the donor usually getting peripherally primed stem cells. I know that sounds very technical, but they give them growth factors like they get those stem cells out in the peripheral blood and then they put two IVs in them and put them on a machine and collect the stem cells that way. So,

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that's been an improvement, but also there are antibiotics have improved. Patients used to die from aspergillus infections and now we have antifungals. There's Fluconazole and Posaconazole. That's been a big improvement and also the drugs for combatting graft versus host disease, but as far as umbilical cord, I know the big drawback with umbilical cord transplants is they've had problems with engraftment meaning that if you have a big person and you have a limited number of cells then when they try to give those cells sometimes the bone marrow will not function. You won't have enough dose of stem cells to have a functioning bone marrow. That's one of the big problems. Okay. You're welcome.

Q25: Are they getting away from radiation because I know that radiation used to be a big part of the preparation protocol, but that's (inaudible 1:47:50).

Sara Tinsley: Right. We used to Vitoxin and total body radiation. She's asking are they still using radiation for transplant. I don't know at other centers just because I haven't kept up with it but I do know that they're not using Cytosan and total body radiation like they used to at Moffet, but they're using other chemotherapies for their treatment.

Q25: (inaudible 1:49:15) not recommend radiation.

Sara Tinsley: I think the big concern with radiation therapy now is other cancers or even MDS as far as dose of radiation.

So, these are other therapies under investigation. You can look at those. I know at Moffet, we've Arlotnib. We also... I think we have one of these... We have several and we also have used Eltrombopag which is used for... really for patients who have immune thrombocytopenia purpura or low platelets from immune mediated crosses. That's what the drug was approved for but we're using it in a clinical trial to see if it will help patients who have MDS who the main manifestation of their MDS is thrombocytopenia.

Q26: Where do we find that number or is that only out on the website? Do we know?

Sara Tinsley: I don't know if this is in the book. Also if you go to clinicaltrials.gov and you type in MDS you can find that on the Internet like other places and different agents that are in trials for treating MDS.

Q26: And these are clinical trials (inaudible 1:49:44) clinical trials.

Sara Tinsley: These are like agents, but all the agents that have letters and numbers are clinical trials. Although some of them like Eltrombopag is FDA approved, but not approved for use in MDS. So, that's why we're testing it. That's what the trial part is, but... Do you have a question? Is it not in there? I know down here at the bottom this *Clinical Journal of Oncology and Nursing*, this... if this is our supplement, we did a... International Leadership Board did a supplement

specifically on MDS and that's available on the website, but it's difficult to get to, but that's... CJON is for the references for that.

So, we went over this. Allogeneic stem cell transplant or bone marrow transplant is the only potential cure. We really shouldn't... There used to be this age bias in treating patients, but if a person is physically fit age alone shouldn't exclude you from treatments, active therapies, and remember it takes four to six months of continued treatment to know whether our treatments are going to work or not. The Vidaza or Azacitidine, the Decitabine, Lenalidomide, they take time to work and the blood counts especially in those first two to three months get worse before they get better and you just have to proactively manage your side effects or get your healthcare team involved in managing those and then this is illustrating why time is required. Before your treatment begins, your blood counts drop because the MDS is progressing and the normal blood cells are crowded out by abnormal stem cells in your bone marrow right here and then when your treatment starts the treatment cleans the marrow. He was talking about this, Dr. Powell, and your blood counts drop further, so they get worse. During this period, I see patients and even healthcare providers who are not experienced in taking care of MDS patients start to freak out thinking that therapy is failing, but this is what you expect and this is looking at an absolute neutrophil count on someone who started a therapy and you can see it went from okay to not okay, but that's what we would anticipate and then as you begin to respond, the bone marrow gets cleaned up and starts making these healthy blood cells and then it comes back up. This is the absolute neutrophil count recovering and then as the response continues you should see pretty much stability in the blood counts. The one thing I can say is sometimes and Dr. Powell described this also. After a person's been on Azacitidine or Decitabine for six cycles or eight cycles, the marrow can start to get kind of tired and it can get too cleaned out. It can be kind of empty and not be reflective of the disease. If the blood counts drop, we usually will check a bone marrow again and if it's an empty bone marrow, there's just not a lot of cells there then that tells you you need to adjust what you're doing. I have a patient that I've been following with lymphoma who developed therapy related high risk MDS. So, it was very sad and she has like four rows of chromosome problems and she had like 13 percent blasts. So, she's in trouble and we've treated her with four cycles and her counts were terrible, but when we looked at her bone marrow it was just almost like a person who didn't have a bone marrow. There weren't very many marrow elements left. So what we did with her, I just saw her Friday, yesterday, we changed her therapy not... we changed the dose. We went from 75 milligrams per meter squared to 50 milligrams for meter squared. We went from every four weeks to every five weeks and we changed the duration from seven days a week to five days a week. So, we did a 50 times five every five and she went from having neutropenia requiring blood, low platelets to almost a normal CBC. So, that's where it gets like... there's a little art involved in whether the person's marrow is getting wiped out or the disease is progressing. The only way you can really tell that is looking in the marrow again. So, and it's not the same... That's... I've never done that before in another patient and I worked with one of the MDS doctors I work with in coming up with the treatment plan that fit that patient. I was very happy because I've known her for 10 years to see her blood counts look so good.

Yes?

So, we stopped at this and the challenge is getting through the first few cycles and you want to at least give it four to six cycles before you say this isn't working at all. If you're doing it for the reason of high risk disease you would want to check a bone marrow to see if you decreased the percentage of blasts in the marrow or sometimes you can get a change in those chromosomes, too. Like you might have more normal chromosomes and not as many abnormal ones with the treatment, too.

So, time is required for the best response minimum of four to six months. We said all this before. You can get dose modifications delay. Supportive care. This is defined differently by different healthcare centers. I think... We think of supportive care as blood, platelets, checking your neutrophil count, really teaching patients about what to do when they're neutropenic, washing your hands well, not eating out, not going in crowds, not digging in your garden and really monitoring for signs or symptoms of an infection. If you have a fever and you're neutropenic it can be life threatening. So, you need to be evaluated by a healthcare provider so they can get a full set of vital signs, listen to your heart and lungs, make sure you don't have any problems going on in your bowels.

Yes, ma'am.

Q27: A quick question here. As the season is approaching, the weather is about to change, what do you recommend as far as being around crowds or flu vaccines or things of that nature?

Sara Tinsley: Did you all hear that question? She said what would we recommend for neutropenic patients specifically?

Q27: Well, just meant the overall... used to be with the season changing and potential for infections or in crowds and so forth.

Sara Tinsley: Most of the patients I take care of we talked... I talk to them about using those hand sanitizers. If they soil their hands or they're in a place like... money is very contaminated with bacteria, doorknobs, things like that, washing your hands frequently, not eating out. If they go to the movies, I have them go during times when it's not busy. The lady I was talking to you about that I've been taking care of since 2004, she asked me yesterday if she could go pull weeds and I'm like, "You want to go pull weeds really?" You have normal blood counts now, but so I said, "Get someone else to pull the weeds for you. Find someone else to empty the kitty litter," and if there's a lot of flu going around during that season, just to try to stay... advise sick contacts to not come around. I know that's hard, but it can be life threatening especially the viral things. We have antibiotics, but the viral things sometimes there's not a lot you can do and we don't recommend live vaccines to neutropenic patients, but the flu shot that's a dead vaccine, it's

not live then we do recommend that for our patients. The different doctors I work with don't all have the same recommendations though. So, you would want to check with your doctor.

Yes, ma'am.

Q28: I've had (inaudible 1:58:52) my ANC is low. It's 400 and I carry with me my weekly blood results, my last visit's doctor report and I have a face mask that I carry in my purse with me all the time because if you're even in a room like this and somebody starts coughing, you got to be able to react immediately.

Sara Tinsley: Thank you. And I think just being educated on what your blood counts look like really knowing where you are, if you're neutropenic, if you're not neutropenic and then this is illustrating a person... This is Sandy Curtain, one of her patient's responses. The hemoglobin is the pink line, platelets are the yellow line and then the white blood cell count, I think, is the blue line. So, you can see this is the cycle one, cycle two, cycle three and cycle four and you can see right around cycle three what happened with those platelets. They dropped... they jumped way up and this is sometimes how you know a person's having a response is the counts will go from being low to really high. You can see... I think you were asking me, someone was asking me, about the white blood cells. It really doesn't normally help the white blood cells that much, the Azacitidine, but the platelets went up and then the hemoglobin there and of course when the get a transfusion that'll make it look higher and then come down and then come down and this is where they went to a transplant. So, this was used as a bridge to get the person to transplant.

And then this is another patient of labs graph of Sandy Curtain. She's the one who really put... was the spearhead for your *Building Blocks of Hope* book there and this is a patient she's been following for over 10 years who's on Lenalidomide. I have a similar patient that's been on Lenalidomide since we had the clinical trial at Moffet and she still has a beautiful response and you can see this is the hemoglobin here. So, this is what really went up and has stayed up and the platelets kind of bump around then the white blood cell count kind of stays lower. So, this is what you see if you have the... and what 5Q- and other types of low risk MDS you can see that the hemoglobin will be preserved. You can ever get hemoglobins of 15 and 16, but the other ones are usually a little low but functional like a lower platelet count than the ranges but not needing platelet transfusions and also for the white blood cell count.

So, what can you do to stay healthy? I think you said it beautifully when I was talking to you. These are the things you can control. You don't have control over the MDS, but you have control over certain parts of your life. Eating a balanced diet. There's lots of clinical trials especially in transplant patients. There's not a lot in heme malignancies, but breast cancer, there's a lot of literature supporting the use of exercise that's getting patients through therapy and transplant patients they're using exercise in our transplant patients and there's some clinical trials going on with that. Avoiding infection, avoiding bleeding. Really with the bleeding piece, I would say pay attention to your platelet count. When your platelet count drops less than 50, you don't want to

be taking aspirin or nonsteroidal anti-inflammatories or low molecular weight heparin or things like that unless, of course, you have a heart valve or a stent or something and that's more life threatening, but you really want to be in discussion with your doctor about over the counter drugs, too, that are touted as anti-inflammatories because those usually affect platelet function and put you at an increased risk for having a bleeding event.

Yes?

Q29: Where does wine and alcohol and where does wine is the platelets or (inaudible 2:03:23) red cells or red that... I mean, at what point (inaudible) that turned out to be (inaudible) but now I can't remember the reason he said that.

Sara Tinsley: Wine and alcohol is what she's asking about and I really... I haven't seen any like studies or data specifically addressing wine or alcohol.

Q30: I was the on the Internet the other day and I saw where they have a couple of glasses of wine every day. (Laughing) (inaudible 2:00:00) MDS or (inaudible 20:04:03) but it says a couple of glasses of wine every day.

Q31: it goes down there and continue to enjoy things you love.

Sara Tinsley: I'll have to look this up so that I'll be prepared next time because I think it is a part of a lot peoples' life, you know, wine and alcohol.

Yes.

Q32: There's (inaudible 2:04:025)

Sara Tinsley: Antiplatelet effect.

Q32: (inaudible 2:04:29) it's in volume. I think if you drink a glass of wine at (inaudible 2:04:33) or one week I think it's not going to hurt you but every day but also (inaudible 2:04:40) should be vitamin (inaudible 2:04:42) probably...

Sara Tinsley: Moderation.

Q32: I think the (inaudible 2:04:47).

Sara Tinsley: I do know... we do pay attention to the liver function tests also and so if we think someone has some liver dysfunction, we usually advise them not to be drinking alcohol or taking Tylenol and that goes for Tylenol and Advil. Like if you're neutropenic, you have to really be careful because that could mask an infection and you could be in trouble and not be aware of it.

Q33: Did you say Tylenol you should take?

Sara Tinsley: We usually advise when you neutropenia like severe neutropenia with a neutrophil count less than 500 that you monitor your temperature and use Tylenol with caution because it can mask a fever and the way healthcare providers react to fever is how high it gets. So if you take a Tylenol it might blunt it and you might have some real infection. I would take your temperature first. If you don't have a temperature, take the Tylenol but, I mean, I would ask your doctor how he feels because that's one of those grey areas.

Q34: I was under the impression Tylenol was not anti-inflammatory.

Sara Tinsley: It is not an anti-inflammatory, but it's called an antipyretic meaning it brings down temperatures. So if we're using our... whether you have an elevated temperature or not to make decisions about whether you have an infection when you're neutropenic it can alter the way we treat you.

Q34: Thank you.

Sara Tinsley: You're welcome.

And then avoid bleeding. Continue to enjoy the things you love and live. Get enough rest. I don't know if any of you have used these before. I am not selling for the company. I just like this and I'm kind of nerdy. It's a Jawbone Up and I'm working on my PhD so when I graduate it tracks if you have an iPhone. You plug it in. They also have wireless now too. It monitors your activity like the number of steps you take. I push this button in at night. I monitors how many hours of sleep I get. It tells me if I get deep sleep, if I get light sleep and I'm really nerdy, so I like collecting all that data, but it helps me to realize sometimes why I feel really bad some days. Well, I only slept like four hours for three days in a row. So, it just... I don't know if any of you are really techie, but...

Q35: What is that called?

Sara Tinsley: This is Jawbone Up and they have an app that goes with it that's free. I think mine was like 120 but now that they have the wireless version, I think they dropped the price to \$80. I think I bought it too soon maybe, but I was thinking... Yes.

Q36: If you're taking Prednisone, it's hard to get four or five, six hours of sleep.

Sara Tinsley: I think so with Prednisone. That's a tough one.

Q37: Did you say that monitors all your steps (inaudible 2:07:57)

Sara Tinsley: It does monitor your steps. It tells you to wear it on your non-dominant arm and to get a more accurate count of your steps and so it'll tell you... and it also has like this little encouragement every day. Like "I've noticed you haven't gotten in your 10,000 steps today" and you can set your own little goals. Would you like to be challenged and then halfway through the day if I've only gotten like 2,000 steps, they're like "Uh, you're behind pace," so I'll have to go take a couple laps around our clinic. So, I find it... I like it, but anyway I thought about doing something like this with a group as a way of managing fatigue. You know, set goals and have groups and... but anyway if you like gadgets...

Q38 What Sarah has is great, but you can get a pedometer for like 20 miles. I count my steps or if you have a smartphone, there's applications...

Sara Tinsley: I think the new smartphones count your steps and you can put in your own.

Q38: Yeah. You count your step, called (inaudible 2:09:04) walk or check your heart rate. They even have one for (inaudible 2:09:11) level.

Sara Tinsley: And hydration, too. It's so important to get enough hydration as far as fatigue and your kidney function. They have My Fitness Pal is a free app and you can download and monitor your calorie intake, your fluid intake. So, just ideas.

Q39: I want to make one comment on alcohol.

Sara Tinsley: He wants to make a comment on alcohol.

Q39: My whole life I drank not excessively, socially. Part of my job as doing (inaudible 2:09:43), so I had cocktails all the time. I really don't drink now, but if you have anemia and alcohol is a depressant. It just doesn't go with and so I mean (inaudible 2:10:00) gave it up because it's a (inaudible 2:10:03). Occasionally, I'll have a glass of wine and there might be some benefit for it, but I think you want to be successful with our disease. There are things to modify and consider giving up and I promote giving up alcohol.

Sara Tinsley: That's probably like there's so many different types of MDS, lots of different opinions.

Q39: That's why I say it's not just (inaudible 2:10:34) might be wrong but it's just me.

Sara Tinsley: I'm not saying yours is bad, I'm just saying different things work.

Alright and then ask for help when needed. This might be a way that someone could actually be a part of your life again that wants to be a part of your life. If you need help, let them know that

you have needs and be an active participant in building hope. This is Healthy Body Healthy Mind. You could go there and check that out and then become an active partner in your care and build your MDS plan. This you can do through the *Building Blocks of Hope*. It's in print. You have the print version. There's also an online version that I use for teaching patients in clinic and helps really to focus on how to live with having this bone marrow disorder. There's an online interactive version and there's going to be a personalized MDS plan coming out that has an interactive patient data entry tool and there's also tools for tracking your progress, pages 85 through 91, and then this is a link to the PDF format if you travel on planes a lot or you like to use your Kindle, you can download it to your Kindle or your iPad and this is contact information for patient outreach and advocacy program and this is just going over what's underneath each tab. Understanding the Disease is under tab one. Seeking Treatment is under tab two. The Quick Tips is under tab three and this is really helpful for managing... monitoring and managing your symptoms. There's tab four on Iron Overload and that's mainly for patients who are getting frequent transfusions and then My MDS Plan is tab five and, again, this is saying you might want to make extra copies before you write on them so you can track it and then you see this and we've been talking all the way through, but if you have anything else you want to talk about.

Yes, ma'am.

Q40: If you have high risk disease is there any benefit going to a particular center for (inaudible 2:13:14)?

Sara Tinsley: She wants to know if you have high risk disease is there any benefit of going to a specific center? I would go to an MDS Center of Excellence. They have those identified.

Q40: So, that's really the only criteria? I mean those centers different than another one as far as...

Sara Tinsley: Well, I'm biased. I'm biased to Moffet, but it has to fit into your life, too. So if there's one closer to you that's a Center of Excellence like I don't know if you live near here or have been treated here.

Q40: I'm at Duke.

Sara Tinsley: You're at Duke. Different centers offer different trials and I've had patients that we've sent to Shands or to MD Anderson because they offered trials that we didn't have that we thought could benefit them. So, the clinicaltrials.gov you could look and look for high risk disease and then try to see if there's a center near you and then they usually provide like information like how to contact them and you could get more information that way and like work a plan.

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Q41: Can I (inaudible 2:14:40) to a question a little bit? I live around here too and you're at a great place. (inaudible 2:14:45) and Duke around here are the best for MDS and some of the other hospitals are great, but they don't specialize and going through this process myself or you're going to a (inaudible 2:14:58). I talk to some significant doctors in Greensboro that were (inaudible 2:15:03) or doctors about ailments and gone all over the country. Now, Dr. Jane Lavera said to me, "(Attendee), go to your best place if you can locally, but the most important thing is get a doctor that cares about you," and if you have that which is (inaudible 2:15:22). In a lot of places that's as important as the facility that specializes in MDS or bone marrow transplants.

Sara Tinsley: If you've exhausted all of your FDA approved options then the clinical trials is the way to go. Anything else? Yes.

Q42: (inaudible 2:15:50) comments don't you think that if you don't like the doctor or you don't like what he's telling you it's okay to find another doctor especially with this disease because not everybody knows everything about it.

Sara Tinsley: Yes. I would definitely if there's... if you're having issues and you're not understanding or you're not eye to eye, a second opinion, a third opinion. I mean, this is your life. We got one shot at this. Anything else? Yes.

Q43: In the (inaudible 2:16:33) or would you recommend a facility (inaudible 2:16:36) is it better before that or is a low level (inaudible 2:16:44).

Q44: Could you repeat that question please?

Q43: The low levels of testosterone. Okay. For low levels of testosterone, would you recommend a patient having... getting the patches or injections?

Sara Tinsley: We have started patients who have anemia who have low testosterone levels that don't have other contraindications for testosterone supplementation. We have started that and it has helped their anemia. You want to be careful if you have like another kind of cancer that could be stimulated by testosterone like if you had problems with prostate issues or prostate cancer or things like that, but that is part of the... That's why we check the thyroid stimulating hormone to see if the thyroid is working properly. If it's not then we put patients on thyroid medication to get their thyroid in the normal range.

Q43: What role does that play in the sort of the red cell production?

Sara Tinsley: A good testosterone level will increase usually your hemoglobin if that's part of the reason that it's low which it can be and that's the other thing we really didn't talk about. Lenalidomide with time can affect your thyroid function tests. So if you're feeling more fatigued and have the same hemoglobin on Lenalidomide then that's one of the things that you would

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want to have rechecked again as your thyroid stimulating hormone to see if that has... you might need thyroid supplementation, but definitely testosterone is one of the things we start patients on also. Men.

Yes, ma'am.

Q45: What's your recommendation taking Vidaza and light constipation? Is a stool softener regularly or what's your...?

Sara Tinsley: I have an usual recommendation I give to patients who are getting Vidaza for the constipation and the sugar free gummy bears have sorbitol in them that if they eat the whole bag they're going to have problems because I have them try those sugar free gummy bears in moderation, but we usually put them on Senokot S if they don't want to do gummy bears if they think they're too adult and it's childish or it can be a real problem though. The constipation is probably one of the biggest side effects I've heard with the Vidaza. Constipation, injection site reactions if they're getting subcu, not that many problems with nausea and vomiting because we do a good job with the antiemetic, but a lot of times different things work well different people. So, some patients use MiraLAX but Senokot S, sugar free gummy bears. Yes?

Q46: What if you don't have a problem with sugar apricots.

Sara Tinsley: Apricots?

Q46: Oh, they work.

Sara Tinsley: I know those Fiber One bars, but I would try a half one if you're not used to a lot of fiber because you might have some discomfort there.

Q46: Thank you.

Sara Tinsley: You're welcome. Anything else?

Q47: Drink water.

Sara Tinsley: Yes, water and I had one patient that's not very... moving very much and I'm like you need to get up and walk a little bit. That will help motility. Motility.

Yes, ma'am.

Q48: I don't (inaudible 2:20:56) recommended like vegetables sort of like eating more vegetables and eating real foods on diets with MDS website the ones that I've been to the research, the holistic food approach. I don't see any of that. Is there any of that available?

Sara Tinsley: They don't have like specific diets other than neutropenic diets like when people are neutropenic and that's usually an area that there's not research. It's just more common sense like well washed fruits and vegetables, fully cooked meat so that people don't get infected from the foods they're eating, but there's... I think that's in your book, too, because I wrote a piece on it "Living Well with MDS" about just a balanced diet. They recommend you get five fruits and vegetables in a day. *The Healthy People 2000* I think has general recommendations. So, there's not one specific for MDS patients.

Q48: There's like a list of fruits that you can take if you are constipated. I haven't had those problems or specific. Have to just... instead of going with gummy bears (inaudible 2:22:13). I just didn't find that when I looked.

Sara Tinsley: I don't think there's a specific one, but I do know that blueberries and the berries are wonderful antioxidants. So, those are always a win/win. Just make sure they're well washed under running water. Yes, ma'am.

Q49: Would you take (inaudible 2:22:38) of juice plus. It helps. It's (inaudible 2:22:45) without getting to your blood cells. It helps create... to build... to help your blood cells because they don't keep your blood cells, but every 180 days and then 120 days they might change. So, eat a good (inaudible 2:22:58).

Sara Tinsley: Are you drinking?

Q49: We're not drinking anything. We're taking whole food nutrition (inaudible 2:23:06) in the (inaudible 2:23:07) and then there are (inaudible 2:23:13) and enzymes and preserve as well as the nutrition. There's 31 studies that (inaudible 2:23:22) that and MD Anderson just did a study on that and cancer and they found it so favorable when they... it was ovarian cancer. The ladies took this supplement as they were going through chemo and their nutrition status and cellular status were so much better than those that did not. So if anybody wants more information on that, I'll be happy to give them some.

Sara Tinsley: Okay. Thank you.

Q50: One question. What about injection site, the soreness...?

Sara Tinsley: The injection site reactions, there's a technique called the Z technique. Do you know if they're using it? I mean, we're a Center of Excellence and I still... There's so many different nurses in the infusion center that it switches out who's given the injection. It's a technique where they use a different needle than what they pulled it up in and change the cap and then it's like this is... has never had the Vidaza in it, the Vidaza is here and then there's air here



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so that there's no drug that's getting on the outside. So, it's... I think it's called air sandwich actually. I said Z initially, but I think that's a different technique for a different injection.

Q50: Is that for pain? Site pain?

Sara Tinsley: For injection site reactions. I've used it. Some patients... I have slides on it. They're not in this group, but I have slides on it, so I usually if a patient's having an injection site reactions, I print that slide and include it with their orders. So,...

Q50: Is it somewhere online we could find that or...?

Sara Tinsley: It should be, but if you give me your E-mail I can E-mail it to you. I know Sandy Kurtin wrote an article or a manuscript with one of the other nurses on the technique like because I think they use it for (inaudible 2:25:28) with multiple myeloma or something like that, but it does help the injection site reactions.

Just about one o'clock. So, we'll finish up early. Thank you very much and it's my pleasure to be here.