Amy DeZern, MD
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(Audio starts at 2:45)

Amy DeZern, MD: Good morning, everyone. Thanks so much for taking time out of your weekend to come and visit with us and other people who are going through something similar to what you're going through. So, I'm Dr. DeZern. I'm in charge of the MDS program and bone marrow failure at Johns Hopkins just a little bit north and really this is for you. I certainly prepared some slides that are academically based and show you some of the data and the way that we think about our patients with MDS, but I'm very approachable for those that are my patients in the room, I think they'll agree I'm happy to just be interrupted and talk about anything that you want to talk about. So, questions were sent in which we do appreciate and my presentation includes those answers, I think, but I have the list of questions at the end and please don't at all hesitate to just push your microphone, the red light will come and then we'll be able to hear you and can ask anything that would be helpful. So, I'm going to go through some things this morning just to give us some context.

So, it's been a really, really big exciting week for MDS especially for clinicians and researchers. Just to give you a flavor what's going across the hall is the MDS 2015 International Symposium. It was put together to bring all the experts in the field and there's been some very exciting research. A few days before that there was something called the Edwards P. Evans Foundation which is the fund in memory of someone who had MDS and donated his life savings to research there and so a lot of good science there and at the start of the week, the NHLBI has something called the National MDS Study that I'll tell you about a little bit later on where they're starting to look at the natural history of this disease. So, there's so many people, scientists, physicians, other researchers trying to think about how we can improve things for you guys for MDS patients with this disease.

So today, I'll talk about a few of the changes and to give you a contextual picture of what's going on in the field as well as just what's standard of care because I think that's very important and probably what some of you are experiencing.

So just we always have to start somewhere and so I like to start with what is MDS and I think something that really was highlighted with the scientific endeavors across the hall from researchers is the truly heterogeneous nature of these disorders. Certainly, you may have heard from your doctors that these are clonal disorders, but even though we use the umbrella term of MDS, it really encompasses quite a lot of distinct diseases that have different presentations almost as different as the way each of you are as patients and that's something that as scientists we're really trying to hone down on so that we make sure we get the right treatment for the right subtype of disease and the right patient. It's becoming more common currently. We think it's

somewhere between 15,000 and 25,000 new cases per year. The reason I say it's becoming more common actually has a lot to do with the way the SEER database has started to capture it. So, at least in the United States the way people are being categorized in terms of their disease so that we can keep track of them.

So, the median age is somewhere between 60 and 70 and it's a little bit more common in males than it is in females. It really is a bone marrow failure disorder and this is, again, a bit of an umbrella term, but I think it's probably important in terms of how you guys think about yourself and what's going on. Because the bone marrow is not working appropriately people can be predisposed to infections or bleeding and then about one in three do tend to transform towards acute myeloid leukemia and I'm sure that's something that some of you have on your minds or you're worried about for your loved ones because that's something that we should talk about and then lastly best supportive care has always been the hallmark of treatment and I do highlight this to you because as doctors we recognize that to patients that sounds different in different ways, but it's a really important part of your disease and how you're treated and it's something you should always feel very comfortable talking to your providers about. The only potential cure, though, for this is a stem cell transplant and I am a transplanter in part and so we can talk about that towards the end as well.

So, what's really exciting is this is what I've been telling you is being talked about across the hall as we speak is the evolving diagnostics and it's trying to hone in on these subtypes to make them more distinct with new technologies and newer techniques. So, we'll talk about the International Prognostic Scoring System or the IPSS. It got revised in 2012 which was a pretty big change from 1997 which is what we still use in part. The WHO is the World Health Organization and something that eagerly anticipated is they're about to make some major changes. It's going to be presented at our national meeting in December and then come out in publication form in the early part of 2016 and I think it's really going to change, again, the way we classify MDS and this concept of molecular profiling may not be something you're as familiar with thinking about, but I think we should talk about it so you have an understanding of some of these tests that your providers are sending for you and the other thing that we do have to own as a field is there actually haven't been any new drugs in the United States approved by the FDA since 2006 and that's something that people like me and clinical trialists all over the United States are really working towards so that we can have some other available therapies for people who are suffering with MDS.

So, this is just a picture of the epidemiology and it gives you a flavor that there is an increasing incidence with age and like most things that's what we tend to think about and I already gave you the median ages between 60 and 70. So what's important is there's no specific clinical features which distinguish MDS from other causes of pancytopenia which is just the medical word for low blood counts. So, low white cells, low red cells and low platelets and sometimes that can mean that for the patient it's a little bit of an uphill battle in the early part of their low blood counts as they go from their internist probably to a gastroenterologist to make sure it's not

the gut onto a hematologist and maybe then an oncologist to make sure the diagnosis is correct. The labs that are sent are often, but not always prompted by signs or symptoms, things that you as the patient are feeling. This can be fatigue which is usually a manifestation of anemia, infections the manifestation of having low, good infection fighting white cells, the neutrophils and then bleeding. If somebody has really low platelets they tend to be at increased risk for having bleeding troubles either in the urine or the bowels or some other way.

So this is again this picture of bone marrow failure. I partly like it because it's a colorful picture, but something that is important for patients is that you really figure out that you're in the right circle here and this is an important part of getting your diagnosis and working through with your doctor that you really do fall into this big blue circle here and not any of the other smaller circles that might be another type of bone marrow failure disorder that you may have heard about or read about on the Internet but might not truly be the diagnosis that you have.

So, we were talking about these signs and symptoms and this is a lot about how you're feeling and you're living it every day. I can put them on a slide, but you really know what is the symptom and the manifestation of your MDS. The anemia. Sometimes you just feel tired and you just want to take a nap and your family is like, "Why are you so tired all the time?" and you really are just that tired and it's okay to own that and your physician should own it too and occasionally I do encourage my patients to be more active, but by and large I think we really know that you're really tired. Some people look pale and not as much themselves and after the winter that we've been having maybe that contributes a little bit, too, but it's very important. The shortness of breath and the decreased exercise tolerance can be really problematic even if it's just going up the stairs in your house when you just don't feel like yourself and then things that can be more serious and things you should be really good about talking to your providers about is if your heart's not getting enough red blood cells to carry enough oxygen, you can really put a stress on that heart and it's something to be very careful about. So, angina is just the medical word for chest pain. If you're not feeling like yourself in your chest when you are anemic that's a real reason to go find your doctor. In terms of neutropenia, we're talking about infection and a lot of the ways that people do end up coming to see me is it's sort of this classic story they had pneumonia, they had bronchitis, they had a Z-Pak, they had another Z-Pak.

I tend to talk fast. It's my nature. So, I'm going to work on that, but just back to the infections, some of these repeated courses of antibiotics is a reason that somebody needs to check the blood counts and make sure that there's not a reason that someone's predisposed to the infections and the platelets we've talked about. You may have heard the medical term petechiae which is just the little red dots when you don't have enough platelets that we see on a patient's skin usually on the legs or the arms, sometimes other places and then easy bruising or bleeding.

So then let's talk about the diagnostics. I know you're all here because you probably or someone you love has a diagnosis of MDS, but it's important, I think, for the patient to really understand how that diagnosis was arrived at. So, we've talked about the peripheral blood counts and

hematologists love counts and I know as MDS patients it can be very easy to either ignore them or to keep a spreadsheet and graph every one and I have patients of different types and it just depends on if you're a data person or less than a data person and whatever you're more comfortable with is how you should do it. I do tend to love the spreadsheets and what we really love is when patients have a sense of where their counts were, but either way is fine. Of course, the bone marrow biopsy and I know that that's an unpleasant part of the diagnosis and everything that you have to deal with after this, but it's very important for us as doctors to take good care of you and to prognosticate your risk and make good treatment choices which is why we do it, not to make you suffer too many times. I showed you that big colorful picture of other possible causes of bone marrow failure that can mimic MDS and these are some of the other tests that you probably have had done over the course of your work up, but once we establish a diagnosis of MDS, we do want to determine the subtype and be able to prognosticate for the patient, but a cautionary tale though is it's still about you as the patient and we can put these graphs up and we all do it, but it really is about you.

So, everybody's had a bone marrow biopsy. We won't, dwell on it, but I think sometimes it might be nice for you to realize exactly where we're going because at least in me I can certainly some days feel my hip bones than other days, but we really are trying to go right into that marrow space to get a good sample for you and then I thought some of you probably haven't had the opportunity to see why we do it or what it looks like under the microscope. So, just to give you a flavor, these are pictures of what we look at when we take that pull out of your hip to look under the microscope and this is the first place that we really start in terms of trying to diagnose Myelodysplastic Syndrome. These are cells that don't look quite right. So, these look like a big gmesh and globby and not correct and they should look a lot more like this and so this is that word 'dysplasia' which is just ugly looking cells under the microscope and sometimes and some people read their own bone marrow biopsy reports and some people don't, but this is called dysgranulopoiesis which is just a really annoying, fancy word for funny looking white cells and those do look funny and not appropriate. These are funny looking red cells and, again, when you're looking at you reports you might see words like megaloblastiod and I use the word soccer ball sometimes. Do you see how this all looks chunky and not too smooth? That's some of the problem and these are big and globby and don't look normal right here. They shouldn't have so many lobes and be so squooshed together. That's very bizarre looking.

Q1: Point to a normal one.

Amy DeZern, MD: I realize that would help and the most normal ones are these smaller ones right here. That's probably the best example.

Q2: Purple is normal?

Amy DeZern, MD: Purple is normal. It's just part of the stain. We only have a few colors to stain in the lab. It's usually pink, purple and blue, but when we look at it they don't look normal.

Q3: (inaudible 16:12) normal would be spheroid with relatively smooth (inaudible 16:18).

Amy DeZern, MD: Yes, that's a very good way of explaining it. I will go back though because the one thing that's not normal and that we don't like to see and I know this is exactly spheroid towards what you're asking, but this is that ominous blast. Can you see how the inside purple is much bigger on the outside blue is very small? That's a leukemia cell and that's not a good thing and those do also tend to be more round.

Q4: (inaudible 16:42)

Amy DeZern, MD: Blasts are early cells that are more like leukemia.

Q5: (inaudible 16:49)

Amy DeZern, MD: There's no pointer here and this only comes up periodically, but it's that cell.

Q6: (inaudible 16:59)

Amy DeZern, MD: This one right here. Alright. And then the megacaryocytes are the grandmothers or the grandfathers of the platelets and this one is pretty normal. Usually like to see three of these round ones. This one only has one. This one has two, and this one has way too many and so, again, these are the funny looking grandmother or grandfathers of the platelets that cause us a problem.

So then there's the concept of karyotype and some of you guys may be accustomed… I don't know but of hearing about a deletion of 5Q or a chance in your karyotype for normal and normal men are 46XY, the Ys being what makes them a male and normal women are 46XX. This is just a picture of a karyotype. I wanted you to see what we look at when we look at the chromosomes under the microscope and quite often in your packets you may have a printout of it so you can see your own karyotype and this happens to be a normal woman. I just wanted you to see what…

Q7: Is (inaudible 18:09)

Amy DeZern, MD: Of course. Yeah.

Q8: I have the deadly deletion of the short arm of 3.

Amy DeZern, MD: And you look wonderful.

Q8: Well, thanks to Johns Hopkins and Rick Jones. My new birthday is September 5. I had a bone marrow transplant in Hopkins September 5 and I had every complication known to man.

They brought every doctor in the house. They wanted to see me with press and here I am. Okay. So, does anybody know what might cause a deletion like that? In my case, I believe it was secondary to an experimental treatment I had a Sloan Kettering that had radioactivity in it, but does it sometimes just happen and why is it so deadly?

Amy DeZern, MD: Well, so speaking about chromos or karyotype in general. So, something that I think's always important for a patient to hear is when you have MDS these are acquired cytogenetic changes. This isn't something you were born with and it's not something that affects your whole body. It's specific to the bone marrow and the stem cells in the blood. The reasons it happens are different…

Q8: I never understood that. Thank you.

Amy DeZern, MD: The reasons it's different in different people and we know things that do cause these changes and so she's talking about having lost that part. So, see the darker part in the middle, that's sort of separates the short arm from the long arm and I guess part of that was missing before for you and there can be any kind of changes here. It sounds like yours was related to radiation. Some people's is related to chemotherapy, but the majority of people and really the vast majority it's not something they did. It's not something somebody did to them. It's unfortunately very bad luck and, again, it doesn't affect the whole body. It's just specific to those cells that kind of took a turn, became bad actors and the bone marrow alone.

Alright. So, the reason looking under the microscope knowing a peripheral set of blood counts and then looking at the chromosome all has to do with prognostication which is how we help you get a flavor for your disease, but also how we pick your treatments and I mentioned that we have an older scoring system from 1997 which we still use very much in terms of clinical practice and especially in clinical trials. It's called the IPSS. So, this is the most common way that people get stratified for MDS. Some of you may have stratified yourself. You can find it on the Internet just by Googling and really it's pretty simple. The way it was defined and the math behind it, I think, was quite complex, but it's not hard to do. You have a score value depending on what's going on. So, we looking the marrow and we see how many blasts are there and we get a set of points and then we look at the karyotype and doctors know what karyotypes are more concerning and what karyotypes are less concerning and that gets a point value and then the cytopenias depending on if you really don't have any blood counts that are abnormal, you don't get any points or if you have two lines. So either the reds and the whites or the whites and the platelets or the platelets and the reds, just two of those, or three of them, you get more points and then you fall into a specific set of values.

What I want you to take home from this is really not this picture, but I want you to see this. So, the reason this was important and doctors do find it helpful rightly or wrongly to put patients in categories in our head because it helps us pick treatments and helps us know how to guide expectations for our patients, but a lot of patients come in my office and they've either heard

from a doctor or they somehow read themselves and are very scared because they've seen these curves and they realize that these are the number of patients who are still alive and the number of years after their diagnosis and so on the X axis is years since diagnosis and these curves look rather steep even to me who does this for a living, but what I want you to remember and to take home and not feel upset about is none of these patients were treated. That's not patients like you. You are invested in your health and you're going to advocate for yourselves and your doctors are going to advocate for you. So, this is just a way to classify patients. Just realize the patients that made up these curves didn't get treated.

Q9: Not treated is because of age, no insurance, too late?

Amy DeZern, MD: Not reasons like that. These patients were even though it was published in 1997, the patients had been observed in the 1980s and 1990s and predominately in Europe where there's a very different healthcare system and so this is very good natural history data, but it shouldn't be construed as something that's just horrible and I think that a lot of times people come and they just have heard this number that I'm only going to be alive for 3.5 years because that's what some curve says and we can modify that to a point and that's very important.

Q10: I think this is a real issue because when you search online that's what you find and there is absolutely nothing to correct it because I'm French, so I check also the French sites and it's much more balanced. So, do we have to wait the new WHO classification to our different outcomes?

Amy DeZern, MD: No and it's a complicated question and I hear what you're saying which is why I wanted to present it to you this way. I think we have to own this and it is important… I find it very useful clinically in our discussions and our treatments, but just remember you're you and not a person on that line because things are different now. So really, the next step was the IPSS-R. We're very exciting in our nomenclature. It's the IPSS Revised and this came in 2012 trying to give some more granularity and better control of that. The patients are still untreated though and so that's important just to remember, but the way it defined what your risk category was helps separate patients and I'll show you in the curves, but the changes that were made is they changed those blast categories. You may have recalled is was just less than five, five to 10 and greater than 10 and then really high. So, they made a lot more categories to help think about that. They refined those chromosome changes and instead of having a lot of specific abnormalities preset the way they were they actually spaced them out because as science gains knowledge, we know that some of these things that we thought were bad actors maybe are modified in other ways and it's not quite as deleterious as we might think.

The depth of cytopenias is really important clinically and this, again, the revised version really incorporated clinical relevant cut points as opposed to those preset just you have one cytopenia or you have three and that's how you get your points. It put in some other features, age, performance status and I think this is what your question was getting at. Why did patients not get

treated? We do have to really look at the patient in front of us and age is really, in my opinion, something to think about and know about but it's a lot more about performance status because a 70 year old who spends most of the day in bed versus a 70 year old who's out running three – four errands a day is quite different and then because there's different risk categories as opposed to the four that I showed you before, there was for sure an improved predictive power and that's really the reason it was done and so you can see that it split things out again in these curves, but still these patients are untreated and you can see, unfortunately, it didn't come out quite as well as I hoped. There's actually five lines there, but nonetheless there's a really big range between patients who have very low risk disease and very high risk disease and we still have to be very cognizant of this low line here which is right here, but you can also be way up here and do just fine and so just remember it's important to categorize yourself. Your doctors are going to want to categories you and feel like they have some context for it, but you're still you and you should be aware of this, but it doesn't mean just because you get bad news and you fall into the high risk category that you should just throw in the towel or anything like that.

So then really where science is going and I would say 80 percent of the meeting I've been attended was really related to a lot of these specific things. There was a good paper that came out in the *New England Journal* in 2011 by Dr. Behar and Dr. Ebert, some of our good colleagues up on Boston at Dana-Farber that really described a different set of mutations. So, it's not that karyotype and those kind of mutations that I've been talking to you about, but it's what we call sematic mutations which just means, again, mutations that you weren't born with. Ones you're born with are called germline and sematic mutations are acquired and these acquired mutations are seen in more than half of patients who tend to have a normal karyotype so the normal chromosomes, but still can have a modification of that disease risk and in this particular paper tough there's been many more there were five genes in particular that were very predictive of how a patient was going to do. Unfortunately, they all suggested a poor prognosis but something you're really I think going to be hearing more about in your doctor's office is that we need to check for these. These are not disease defining and they aren't a reason at this point to change therapy, but it's information that we need and we want so that we can work with a patient going forward as science changes and we have this ability to gain more information about their disease.

So, this is a picture that seems, again, colorful and confusing, but it actually has a lot of point and this is the way I hope you feel very excited and hopeful as I do because we're able to find the different pathways that these mutations fall in and these are all potential pathways that could be targeted and may be specific for drug therapies and the size of the circle is related to what percentage of patients tend to have these mutations. So, the bigger the circle, the more patients have been described to have them and so down here in this epigenetic dysregulation picture the most common mutations are TET2 and DNMT3A and ASXL1 and those really are falling out to be very common for patients with MDS and we already have in the leukemia world a targeted drug for these IDH mutations and so it's uncommon in MDS in particular to have the IDH mutations, but it happens…

Q11: (inaudible 29:59)

Amy DeZern, MD: No, it's by an Agios company. It's AGI221, but the point is that science is coming along. We're able to improve the diagnosis and there are going to be better therapies specific for the disease that each patient has. I think we're still a little ways out from it, but I hope you feel excited and, again, hopeful that there's a lot of promise here.

Q12: Can I ask a question? On that slide, UPenn, they're working on CAR T-cells. Is there any possibility that a target could be found to make a CAR T-cell work against MDS?

Amy DeZern, MD: So, the person working on it it at Penn is a good colleague named Saar Gill. So, where car T-cells have had…

Q12: What's his name?

Amy DeZern, MD: Saar Gill. G-I-L-L. The where CAR T-cells have had the most promise is actually in ALL which is a lymphoid disease. MDS and AML are myeloid diseases and for some specific scientific reasons it's a bit more challenging to target a CAR T-cell that way, but it's an area of active investigation and a technology that people are quite eager to try and bring into the clinic.

So, I think I've shown you at this point as well as you know living it is that MDS is really complex. There's a lot of ways to look at it under the microscope to classify it by chromosome and then this extra layer of discrimination or classification with these mutations is really coming along. It is rare, but it's a growing cancer. As our population ages, you saw the increase incidence with age and I think it's going to be an ongoing issue. It's very challenging to diagnose, but still it can be done and that we've talked about why marrow testing is so important and then I think it's important for patients to understand their disease prognosis and the implications that that has for therapy, but as I know I've been sort of reiterating and hitting home is that the IPSS and the IPSS-R are a starting point for risk stratification. They're a very important staring point and some that I use all the time, but it is just that. It's a starting point. So, I think is everyone comfortable with diagnosis at this point?

Q13: Can you go back… I just want to take slide (inaudible 32:29). I'm just asking to go back to a slide.

Amy DeZern, MD: I don't know that these are worth writing down in all fairness just because they all… You can see there's quite a lot and at the meeting there's more than appear to be relevant all the time.

Then we should talk about treatment.

Q14: Before we go to treatment, could you… did you know anything about this Dr. Jose Baselga at Memorial Sloan Kettering?

Amy DeZern, MD: I know him.

Q14: And he's doing tiny snippets of cancer. So, maybe you wouldn't have to have the bone marrow? It said something about lymphoma which I also had and so I'm thinking wow if they could find it lymphoma which they had to do a bone marrow couldn't they do it…?

Amy DeZern, MD: So, something that's helpful. Those mutations that I just showed you can be done in the peripheral blood, but I think what's not going to go away is the first picture I showed you which is the looking at the cells under the microscope. That is still a very powerful tool and Dr. Bersad (sp 33:34) is actually a breast cancer oncologist and so…

Q14: Yeah.

Amy DeZern, MD: And I'm not making light of a bone marrow biopsy but it is a little bit different than a mastectomy or a colon resection and things like that and so I think rightly or wrongly the solid tumor field is a lot more interested in trying to find circulating markers of tumor whereas we are very interested in the blood as an easy organ to sample, of course, with blood counts and, again, those mutations are done in the peripheral blood, not necessarily in the marrow, but I think it's going to be a long time before bone marrow biopsies don't continue to be helpful, I'm sorry to say.

Q15: Very briefly having had four or five, I just wanted to highlight that the pain level varies enormously based on the… my experiences based on the experience of the caregiver. So, go to a place where they do this all the time and their intention.

Q16: I've never experienced pain on one. I've had six and maybe I have spongy bones, but I do my relaxation exercise and my meditation breathing and just relax and I guess I had magic people.

Amy DeZern, MD: I think the first point is actually a fair one. People who do this on a regular basis. I will tell you though sometimes it depends on the day. It depends on if the marrow feels like giving it up or not and it can vary widely, but you should not hesitate to speak to your provider about how awful it may or may not be for you and if there's other ways to provide comfort either before, during or after the procedure and I think there's ways as providers we can do it very safely and rightly or wrongly sometimes we feel… I guess wrongly. Sometimes we are just in a hurry to get the information to help you and maybe we're not as patient about doing the conscious sedation or things like that as we should.

Okay. So, talking about treatment. So one of the reasons I started with diagnosis and working through how we think about putting patients in categories is that there is a difference between lower risk MDS and higher risk MDS and the lower risk categories really still are the low and Intermediate I and then the higher risk we'll get into in a minute, but the goals in lower risk MDS are to improve the marrow function certainly, but really it's focused at decreasing the transfusion needs, decreasing the impact of MDS on the quality of life which I think cannot be underestimated and then establishing a very careful monitoring plan and this is important and somewhat patient specific though there's very good guidance based on some of the risk categorization. There's a much lower risk of transformation to AML in lower risk MDS than in higher risk and so that's something that's on your mind. It's not an impossibility but it's a much lower risk and our treatment goals are not focused as much on that and so a lot of the discussions I have with some of my lower risk MDS patients early in their diagnosis are focused on not defining themselves as a patient because it may be a disease that people are able to live with relatively few interactions with the healthcare system at least early on and I think that's important.

So, this is a complex flowchart, but it's very accurate in terms of how we think about treating in 2015 and you do know I'm from a fairly large academic center. So, you'll see clinical trials on here not infrequently. So, this is obviously a bias, but I think an important thing to consider as patients since we talked about there hasn't been a new drug in this disease in quite some time. It really is okay though if you have lower risk disease and your blood counts are not too low and what too low is can be defined between you and your doctor but to just observe and that's part of that setting up a very careful monitoring plan and if patient has symptoms from their low blood counts and doesn't have deletion 5Q, we'll talk about that a little bit separately, but they either have a predominant anemia, a predominant low platelet count or all the cell lines are low we really talk about what the right therapy path is, but I hope what you'll take home if not the details is that there's a lot of options and there's a lot of different ways to do this and you provider will help you get to the right path for you as a patient.

Most of the focus though is on patients who are anemic because red blood cells is a lot time in the clinic, it's a lot of frequent interactions with doctors and nurses which I think decreases quality of life in many ways and so a lot of focus is there.

Q17: What (inaudible 38:23)

Amy DeZern, MD: An erythropoietin stimulating agent.

So, the way… she asked what an ESA was which is a very good question. So, it's an erythropoietin stimulating agent. You guys know them as Procrit, Darbepoetin, Aranesp, Erythropoietin. There's a few different names. There's a little bit different regulatory approval in Europe and so some other types of drugs. They all usually end in 'poietin' of some variety and these growth factors are really important and what they are is synthetic version, so made in the

lab of proteins that are normally made in the body to stimulate the growth of red cells trying to alleviate that anemia we keep talking about. There are growth factor shots for white cells and they're actually are also growth factor pills or shots for platelets. We'll talk about this a little bit more, but it's the red cell growth factors, the Aranesp, the Darbepoetin, the Procrit that we use most readily up front in lower risk MDS and the way they work is they promote growth in differentiation of these cells and another way that they're thought to be helpful and this has been shown in the lab is they may inhibit apoptosis or cell death and so both of these you can see are good things for people who are trying to have fewer transfusions in their lifetime.

So, we talked about the red cell growth factors. The white cell growth factors maybe you've heard of Neupogen or Neulasta. These are often used fairly frequently in the clinic. There's some others that we use less often for some other reasons called Leucine and that's just another way of stimulating the white cells and then the platelet growth factors, I think, get a fair amount of press these days. You may have heard of Promacta or Eltrombopag or Nplate which is Romiplostim. The thing that you should realize though is these are not FDA approved for MDS. The red cell growth factors are very regularly used in patients who are on dialysis for kidney troubles and that's because the kidney is what in our own bodies makes the erythropoietin to stimulate the bone marrow to grow the new red cells and we use them all the time and I think they're good drugs. The platelet growth factors have some specific problems in MDS, which we'll get to later in the talk.

So, what's nice is we've really looked at who's going to benefit from these because even though we're saying, "Oh, you don't get transfusions," you're still getting a shot which may not be as bad as bone marrow biopsy, but it's still a poke and so it's helpful to know who's going to respond to these erythropoietin stimulating agents and most of this work comes from the Nordic MDS group which is in Sweden and they have very large registries and they're able to study very large groups of patients and what they showed quite a long time ago now scientifically in 2003 was that if you have a lower need for red cell transfusions so that would be less than two units a month at the time of your diagnosis or a baseline erythropoietin level because we can measure these levels in the blood of less than 500, you're much more likely to respond. So, 74 percent of people who meet those criteria respond to these ESAs, or erythropoietin stimulating agents, to have an increase in their red blood cells and a decrease in their transfusion needs, but if you are getting more than two units a month and your erythropoietin level at the start is greater than 500 only about seven percent of those patients respond and so that erythropoietin level of 500 is not meant as a hard and fast cutoff, but it is something that as doctors it should be checked before you start your growth factor and it doesn't mean all the time that we don't try the growth factor, but we do have to start thinking about plan B, plan C and what the next series of steps are in patients who have the higher values at the baseline.

So then what does it mean and I don't know if anybody in here has come along this path, but to no longer be responding to erythropoietin stimulating agents and so lower risk patients tend to start with a little bit of observation like you've seen then some growth factor shots for a while,

but then at some point these aren't going to work forever and we have to, again, be always just thinking about the next step, not dwelling on it, but making sure that we have a path along the continuum of the treatment options. So, the majority of responses that are going to happen in terms of decreased red cell transfusion needs happen in the 8 to 12 week range. So about two – three months and what we for sure know is that just dosing in a fixed way so just the same dose every week or every two weeks depending on your drug is more beneficial than looking at your weight, weighing you, writing the order and all these things and so it's very okay to get the same dose every time and the duration of response for about 50 percent of the patients is about two years and we talked about the people who tend to have longer responses. It's when they don't have their own erythropoietin level that's higher. If they have true lower risk disease and when they don't have a lot of blasts. So, less than five percent and something that I often mention and I try and be good about checking as a hematologist is sometimes if you're stimulating a patient to make a lot of new red blood cells, you use up all their iron and so some people can be rescued at the point when the EPO level or when the erythropoietin shots aren't working with just a little bit of added iron to the diet and they get a little bit longer response.

Q18: May I ask something? For the majority of responses, this happened to my mom that they tried for 12 weeks, three months at Sloan Kettering and then stopped. So when you say majority, does that mean…? How do you know like what if you're in the minority that over three months trying of it would have benefited or is it…?

Amy DeZern, MD: Run that by me one more time.

Q18: If she… Sorry, my mom got 12 weeks of, I think, Neulasta and Darbe and then she wasn't responding, so they stopped after 12 weeks. So when you say majority meaning…

Amy DeZern, MD: Oh, you're talking about the tail.

Q18: How do you know that person wouldn't have been in the tail to try a little longer?

Amy DeZern, MD: Well, you don't. Unfortunately, it's this proverbial crystal ball that we all wish we had but as physicians, rightly or wrongly we tend to say well if you've met most of the metrics and you still haven't responded then it's time for plan B because we really do want to make some impact on your disease and sometimes patients say to me, "You know what? I like getting my red cells and you can just take your shots and that's that," and that's okay but usually if falling into these curves you're not in the majority we tend to look for the next step.

So, the last true success story in MDS is really specific to Lenalidomide in a very specific subset of patients and this is the del 5Q lower risk MDS and this is a really specific set of patients and a specific therapy, but I think it highlights why we're so eager in the diagnostic part of the talk and for our patients to hone in on a very specific subtype and classification for patients because we do know that people who have the deletion of the long arm of chromosome five respond

extremely well to a pill chemotherapy and that's Lenalidomide, the trade name is Revlimid. Some of you may have heard of it and people either take it every day or three out of four weeks of every cycle which is a month and 70 to 80 percent of patients who have this specific karyotypic abnormality have either transfusion elimination or transfusion reduction and it usually takes about five weeks, sometimes seven weeks to respond in patients who are going to respond and the duration of response, again, can be two or three years and this would be standard of care. It is approved and it front line therapy.

Q19: I have a question. Having gotten the bad one, what is the relative occurrence rate of like deletion on 3Q and this one? Is there more of one or the other or are they about the same?

Amy DeZern, MD: It's a broad question and there's some categories that you have a sense. So, del 5Qs around 10 percent of MDS. Yours is much more rare. Like winning the lottery in reverse and there's some of these other karyotypes that are also more rare. This is the only one that truly has a targeted therapy.

Okay but then you might say, "Well, that sounds like a good drug. It's a pill and I'd like to know more about it," and so there's a very nice study that was presented at our national meeting, the American Society of Hematology last December, was actually predominately run in Europe where, again, I mentioned the regulatory approvals are a little bit different, but they gave Lenalidomide or Revlimid to patients who, again, were lower risk MDS, but did not have the 5Q deletion and they were either unresponsive or refractory to these erythropoietin stimulating agents. Same type of dosing. So, they get 10 milligrams every day and this was a placebo controlled study. So, it was a 2 to 1. It was randomized and 239 patients, 160 patients were treated with Lenalidomide and 79 patients were treated with the placebo. These patients totally fit our MDS model. They are the median age was 71 years and the majority of them nearly 84 percent had all had therapy before be it these growth factor shots or otherwise and what it showed us is that after 56 days or eight weeks, the number of patients that were red cell transfusion independent was 27 percent in the Lenalidomide group and only 2.5 percent in the placebo. So, that's a very clear difference and that's one reason why it is nice to have data like this. The duration of transfusion independence was about 33 weeks. So, that's not a tremendously long period of time, but it's still a benefit. It's less time in the office and then about 18 percent of people maintained that transfusion dependence after 168 days, but the way that I think that this trial is really helpful to us because we've always suspected and had some other data that the response rate to Lenalidomide in patients who did not have a deletion 5Q was somewhere between 20 and 30 percent. This absolutely confirmed it, but of those patients who are going to respond, 90 percent of them responded within 16 weeks, which was four cycles and so a way that I used this information for my patients is kind of to your earlier question that that's the majority and so if we're coming to the end of those 16 weeks and that's where the majority of people respond, we need to start planning and thinking about the next series of steps.

So then I mentioned that there were in fact platelet growth factors. So, these are… Romiplostim is an injection and Eltrombopag which is Promacta is a pill. So, just to give you a flavor. Platelet problems in lower risk MDS are really tricky. As doctors they make us nervous because we don't want our patients to bleed. As patients it's very much annoying to come in, have your platelet count checked, once, twice a week, have to get platelet transfusions. About a third of patients with lower risk MDS have platelets that fall into the we have to think about doing something range which I would say is less than about 50,000, but these drugs have only been approved for patients who have immune thrombocytopenia and that is different than patients who have low platelets from MDs. There's actually an abstract being presented in 15 minutes across the way of looking specifically at Eltrombopag and MDS to see if we can boost these, but try… we try in the medical community to avoid using it outside clinical trials and that specifically because there was a study of 250 patients who got this Romiplostim for over a year and even though the drug did a good job and increased platelet counts and did a better job that it decreased the number of bleeding events, the study had to be stopped early because there was a concern that these were stimulating more blasts, those early leukemia cells and making people have more trouble with leukemia and the hazard ratio is just a way that we say it was 2.5 times more likely if you are getting the drug that that was going to happen to you. I will tell you though this just was published at the end of 2014. When everything settled out and they followed those patients for a longer time, there was no impact on overall survival and that ultimately once you stopped the drug those blast numbers went down and there wasn't a significant difference between survival and leukemia rates whether or not you are getting the drug. So, I think this is an area of active research and one where we'll have more data going forward, but if platelets tare the main problem that a patient has with MDS, I have a very open discussion about the limitations of our knowledge and using those in MDS.

So, this is sort of a hot topic and this is a lot of confusing big words, but there's seven drugs that are an active investigation in Europe and then in the United States. It's both by the same company. The European drug is called Luspatercept. The American drug is called Sotatercept and they're just different molecularly a little bit, but this, again, was presented at ASH. Both of them were actually and this is a set of compounds that actually was used to treat osteopetrosis and just by happenstance someone realized that all the patients had higher red blood cell counts when they were getting them and so they started to be investigated in lower risk Myelodysplastic Syndrome and I'm very excited because I think that these compounds have some real biologic rationale and I also think that there's some promise at least in the very early data that we're looking at from the clinic and these are designed for people who have come through that erythropoietin stimulating agent treatment are now getting transfusions and having more anemia and need to be treated and so the sort of take home point here is that the (inaudible 53:25) response or the red cells getting higher was in 41 percent of the patients treated at a fairly low dose and so that's is really pretty good in this particular subset of patients, but getting back to this idea of really characterizing a patient's disease well. The subset of patients that did especially well were people who had a specific type of mutation called an FF3B1 and when we looked under the microscope, they had something called ring sideroblasts.

Q20: Does the drug to which you refer is it related chemically at all to Prolia and do you have any problem with a person who has a bone marrow transplant taking Prolia?

Amy DeZern, MD: A patient of Dr. Jones' should ask Dr. Jones. I'm teasing. Dr. Jones is my boss just so…

Q20: It's not…

Amy DeZern, MD: It's not. Not even chemically related, but it's a fair question, but I think the point of the question is really what someone has come through a bone marrow transplant should they be treated like a regular patient and adhere to all their other medical issues? Absolutely.

Q21: Doctor? What stage is that trial in?

Amy DeZern, MD: Phase two.

Q21: Phase two and how long did the response last for those patients?

Amy DeZern, MD: It's a very fair question and I present because many of the questions were related to newer exciting treatments, but this is in very early studies. So far, we need a lot more follow-up. The Sotatercept study is open with us though.

So then hypomethylating agents and I was just speaking to some people about this set of classes and hypomethylating agents is just the term in the field for Azacitidine or Vidaza or Decitabine or Dacogen and so you may… Usually when you Google MDS, these are the first few things that come up because these are the two FDA approved medications other than the Revlimid in Myelodysplastic Syndrome. In the United States, they really are approved for lower risk disease. This is actually not true in Europe, but we usually save them in patients who are having anemia until they've been through all those other treatments be it erythropoietin stimulating agents, be it Lenalidomide because they may be less effective and they also come with some reasons to give us pause and that they can take a patient that's predominately anemic which is certainly an issue but may be predisposed to infections which could be an example of us as a provider doing harm, but we really do think about it because it's certainly an active class of drugs and the response rates are all over the place, 30 to 60 percent.

So, there's been a lot of studies. This is meant for you to write home about, but I just wanted to give you a flavor. You can see there's all different combination… sorry… dosings that have been studied in various groups of patients. The in is how many patients this has been looked at and as I mentioned the response rate has anywhere from 61 percent to about 30 percent and it depends on the dose, it depends on the type of patient that was studied, but there's a lot of interest in these drugs just because they are FDA approved and because we know how to use them.

The other thing that I mentioned that is a little bit more of a supportive care, something else to think about but some of you guys may have had it on your mind is in lower risk patients or higher risk they're getting a lot of transfusions. Each bag of blood has about 300 milligrams of elemental iron that comes to the patient with the bag of blood and so people worry that is all that iron not good for a patient's liver, pancreas, heart, their body in some way and so do we need to use chelation or removal of that iron by medicines to keep a patient safe.

There is absolutely no data looking going forward and there certainly is a suggestion in looking at patients going backwards who got them that they may do better. There is a perspective study that's been going on forever and is not accruing very well and so I don't know if this is an answer that we're going to have very near, but from the lab there really is thought to be a positive effect of removing this iron hematopoiesis or new blood making and the guidelines that we have and they're just guidelines. These are in no way mandates, but something you'll hear your doctors talk about is if the ferritin which is the laboratory that's the measure of the body's iron content is greater than 2,500 that might be a reason to start talking about these medicines. If you've had more than 50 units of red cells in your life, again, a reason to start thinking about it or if for whatever reason you had an abnormal specific type of heart MRI which is called a cardiac T2*. There are certain things that we can look at that make us pause. I personally not having taken them but watching patients struggle with them, the trade name is Exjade is the most commonly used one that you've heard about. They're very, very hard on the stomach and they're hard on the platelets and at some point you have to decide if the toxicity and the nausea and the awfulness of the diarrhea is worth what is in part at least at present a theoretical risk of the iron troubles, but it is a good discussion to have and it may be a reason to try the medicines, but I tend to tell people if they just cannot tolerate them then I think we have to think about if we're decreasing quality of life on something that we're not sure is 100 percent beneficial.

So, moving forward to higher risk MDS. The goals here are a little bit different. So, we need to stabilize the bone marrow and the concept of trilineage improvement is that improvement of the red cells, the white cells and the platelets and we really need to lower the risk of AML transformation and that's what, I think, a lot of the focus is, a lot of the discussions are and something that is a very real issue for patients that fall into the higher risk categories and we either need to use our next treatments in high risk MDS as definitive therapy or maximizing the benefit to get to whatever the next step is and that may be transplant. So again, it's similar picture that I made for you guys and, again, it's just to show you that there's a lot of different ways to do it but the discussions are a little bit more intense and that's because when a patient falls into the higher risk category, we have some other goals to discuss and a lot of it depends on the decision about are we going to transplant or are we not and if we think a patient is a candidate for transplant then we need to talk about HLA typing which is just the way of getting the patient… getting the family members that are related to you to have a sample for HLA typing and then this concept of HMAs which is the hypomethylating agents, the Azacitidine and the Decitabine that I've mentioned. Is it time to start those or do we need to do it on a clinical trial or

not and then depending on the discussions, in younger patients or those who have more blasts. So, a little bit closer to the continuum of being acute myeloid leukemia sometimes just chemotherapy is the way we go at that time and there's a lot of different ways to have this discussion with your doctor.

So, I use this as, again, a picture and we're looking at time across the X axis and the number of people that are alive on the Y axis and this is the study, it's called the AZA001 trial, that showed there was truly a benefit with Azacitidine compared to conventional care, transfusions or otherwise to getting this treatment when you had higher risk disease and so this is also the study that really we use as a lot of our guidance in terms of how much drug to give and how long to give it before we say it's not working or it is working and so you can see there's a clear separation of these curves pretty much from the very beginning that the purple line, those who got the Azacitidine really do better and that's why this is such an active part of our discussions with patients as to when to start the therapy.

Q22: Is there any consideration to giving Vidaza as a preventative treatment for relapse after BMT for instance?

Amy DeZern, MD: There's a lot of consideration and it's in clinical trials at our place and others and some people do it routinely depending on the clinical situation, but I think it makes a fair amount of biologic sense in situations where there's very either the concept of a mixed chimerism where you're still part of yourself versus all your donor and things like that.

Something that's important and I mention this. It is very easy for me to do some of this optimization because I'm at a large center. I only treat MDS patients and I have access to fabulous nurses and nurse practitioners and resources, but it can be easier for doctors in the community who are accustomed to treating more common diseases like breast cancer or colon cancer to hold drugs, to take delays for whatever reason because that's more of the paradigm for how you treat solid tumors, but something that is probably very much a certainty is the way to get that benefit of these drugs is to give it the way it was intended in a trial, rigorous fashion so that we make sure that enough of the drug is going in so that the patient sees the maximal benefit and the way that is probably best described is a certain dose of Azacitidine which is 75 milligrams per metered square for seven days in a row for six cycles and I think we're all very reasonable about the fact that sometimes hospitals don't work on Saturdays and Sundays or clinics and so there's also the concept of the five/two/two and so that's five days of drug, you take Saturday and Sunday off and then you get Monday and Tuesday drug, but getting those seven doses is probably the best way to optimize therapy. For Decitabine, we focus a little bit less on it because there's not quite as much data, but it's abbreviated DAC and that's, again, a drug in five days. Some people are investigating now if there's ways to give that differently and still get the same benefit and I think that information will be forthcoming, but minimizing delays if we can is important. You know, there's always an important graduation or an important milestone in somebody's life that we need to get to and within reason that's very fair, but quite

often I see patients after they've gotten their six cycles everybody thought things were good and so it just stopped and then by the time they get to me we're in a little bit of a pickle because we probably can't go back to that drug and have the same benefit and so that's a complicated paradigm that you should talk through even if your doctor and you are really happy that you're doing well from it.

Q23: Ma'am? What do you call working?

Amy DeZern, MD: That's a great question and I probably left it vague on purpose, but it means different things for different people. Classically, so to doctors, there is something called the International Working Group Criteria for Hematologic Improvement and Response and we can define it very rigorously, but you can say yeah, yeah that doesn't mean a lot to me as a patient, but the working is usually decreased blasts, less transfusions, better blood counts and feeling well.

Q24: Do you ever hear of the oral Azacitidine or is that… Well, anyway, as a…

Amy DeZern, MD: Yeah. No, Azacitidine, Aza, we can call it whatever but yes. So, it's in clinical trials. So, there was a phase two. It was done at Hopkins at some other places. I'm proud to say I have the patient who's been on it the longest in the world who's been doing fine and so it's a pill, but there's a lot of interest in bringing forward to the clinic. The current registration trial is a phase three that's been open for a long time all over the world that is randomized to placebo and it has very… No, I understand. It's a complicated paradigm because in the United States people are less amenable to the concept of a placebo which I understand then you can't have had the IV form previously. So, it's going to be a little while.

Q25: What's IV form?

Amy DeZern, MD: Through the veins.

Q25: Oh, no.

Q26: As opposed to the shot in the skin.

Amy DeZern, MD: Yes. That way, too. You can't have had any of those before you get the pill.

Q25: Oh, but couldn't you use it after? You're saying that you should never stop it once it's working. Okay. It's working. Can you change to the… Can it change to the oral?

Amy DeZern, MD: You're asking all the questions that we would love. It's not FDA approved and you can't get it off clinical trial anywhere in the world and because the trial criteria are written with specific eligibility, it's an impossibility right now, but there's a lot of interest in the

scientific community and frankly in the big pharma community in bringing an oral only regimen to patients. I just think it's going to be a while.

Q25: Okay.

Q27: Dr. Stern, you brought up the topic of big pharma. Has there been so little progress on MDS because there aren't enough of us and therefore not enough money in it?

Amy DeZern, MD: No. I don't think that's it. I think it gets back to the points that I tried to make in the diagnostic section. It's a very heterogeneous group of diseases. We have this big umbrella term for MDS, but it's really a lot of different diseases. Yeah. I don't know that it's many cancers, but I used the example of the del 5Q and the Lenalidomide. That's great, but is some higher risk MDS is really leukemia and then some lower risk is just low blood counts that don't matter and so when you lump all of those patients into a clinical trial that either works or doesn't work usually in our situation it works less. It's hard to get a drug to approval.

Q28: Do you know of anyone who's out there looking for an Ibrutinib?

Amy DeZern, MD: They're all in the hall across… No, really, I think… I'm very hopeful and very excited. I'm very realistic too, though. A targeted agent is the holy grail of medicine. It's the true concept of personalized medicine that we all want, but biology is biology and so there's going to be a lot of time because it's not… There's very, very few diseases that it's just one mutation and one drug and then you're fixed.

So in terms of therapeutic options at the time of these Azacitidines or Decitabines not working, there's still a lot of options. So, you shouldn't lose hope at that point, but in higher risk MDS when you do reach that point with your doctor, there's a lot of discussions that have to take place and I think they're very important and as patients I would encourage you to advocate for yourself and really listen to them to decide what is really right for you at this point because this is a challenging place both for the patient and the providers at this point. So one thing that's commonly done is whichever drug you are getting be it Decitabine or Azacitidine, people tend to switch to the other one. There's really very little data to suggest that that's of any benefit to anyone. So, I personally tend not to do that, but it's a discussion to be had. It can be considered if somebody is not truly not tolerating one of them, but how we define not tolerating I think is patient specific.

The next way that the community is really eager to go is combination therapy and often this is the addition of the other approved medicine in the disease which is Lenalidomide or Revlimid. This has been studied up front and actually not shown to be of any benefit to Azacitidine alone, but I think it's something we do not infrequently and the HDACs is a class of medicines. We don't have to get into the science of it, but it's this whole class of medicines that people had a lot of enthusiasm to combine with Azacitidine and so one after the next after the next has been

combined in clinical trials and so far there's a signal that they may be helpful, a signal, but there's a clear path that they cause more toxicity and so that's been one of the limitations of the combinations of the drugs.

Induction chemotherapy. I am a leukemia doctor and a transplanter as I told you. So, the concept of induction chemotherapy as a paradigm doesn't make me uncomfortable, but a real conversation about why it's being done, I think, absolutely has to be had so that you as the patient understands and so the doctor understands what the goal is. Just to give high dose chemotherapy just to give it because we can I don't understand that. If it's a bridge to something usually to transplant then I think it's reasonable to discuss, but the ethicacy, the rates of working are a lot lower than in patients who just get chemotherapy from the get go and so that's why it has to be discussed, I think, pretty thoroughly. There's off label use of all kinds of agents because as I said this is a challenge for patients and doctors alike. People have tried in clinical trials or in anecdotal practice all kinds of other agents with pretty limited results. In terms of the stem cell transplant, this is a challenge and I will give the disclaimer. I come from a very large transplant institution, but it's a discussion that probably is better had earlier in a person's disease course than at this time and that's pretty important yet hard to do when you don't feel bad and you hear all these bad things about transplant or it sounds horrible. You just don't even want to consider it, but at some point it becomes too late for a variety of medical and patient specific reasons and so even if you think it's not your goal the discussion and time for referral is something you should probably bring up before you get to the point where the Azacitidine is not working to at least of had a discussion so that everybody goes in eyes wide open. I mentioned I have another bias and that's clinical trials and I think to the question that was just asked and the point is some people find the concept of clinical research offensive or bothersome or just unnerving and I understand all those things very much, but it's something to be discussed at least at a tertiary center where these are at least options so you know what else is out there because sometimes to your question if you've had another treatment and another treatment, you might not be eligible for what could be the next big thing and so that's just something to consider.

Q29: I'm sorry to keep speaking. I'm on 50 milligrams (inaudible 1:13:27), but really, really go into any clinical trial with your eyes fully open. I did when I did the one at… it wasn't Sloan Kettering. It was Weill Cornell. Got all excited. I thought this was the new big thing for my follicular lymphoma and the follicular lymphoma rebounded in four months and in another three months I had MDS from it. So, and my local doctor… the local doctor. I went back to see her. She says, "You know, (Attendee) I would not do that. We can handle this with (inaudible 1:14:06)," and if I had listened to her, I would be popping one Imbruting in a day and living happily ever after.

Amy DeZern, MD: Okay and then the other discussion and I mentioned this and we all have our own histories and backgrounds at the table, but supportive care should never be construed either by the doctor or hopefully by the patient as doing nothing and like I said this is a hard place to be and transfusions we want to reduce them and we talk about that as a measure of response and it's

important, but they're not the devil and so if you decide I've had it with your transplants and I've had it with your shots and your bone marrow biopsies deciding to get transfused is okay. It's just, again, it's an eyes wide open recognizing what we're trying… what are our goals. It's all about the discussion of goals.

So, I told you that there's a little bit of data with Azacitidine plus Lenalidomide as a combination. Because these are the two approved drugs in the United States this is again where we usually start and I think this is just a flavor for the feel that you're seeing that there's the concept of a complete remission in about 44 percent of this particular relatively small cohort and then another 10 patients who had this hematologic improvement. So by very strict international criteria the blood counts getting better and those people who got a response had it last for a very long time and, again, trying to figure out who these patients are that do better with different approaches is this idea of knowing your mutations and studying it first retrospectively for us and then moving forward so that we check in all patients so we can start to predict who's going to need this type of combination and treat the patient.

Q30: Would that inclusion criteria have (inaudible 1:16:02)

Amy DeZern, MD: No. This was… Well, it was done a little bit uniquely but the phase one and the phase two were the specific eligibility criteria were a little bit different, but the concept of adding it in or starting it from the beginning both have been studied.

Q31: Ma'am? Before we leave, Vidaza and transfusions, is there a connection? What is the connection between Vidaza and transfusions?

Amy DeZern, MD: When you ask what is the connection, are you asking the way that Vidaza makes them less or the way that it makes you get transfusions or both?

Q31: I'm sorry.

Amy DeZern, MD: I'll answer both. So, Azacitidine, I showed you the survival curves and that's really what I think most people want to focus on when they come and decide to take that paradigm of therapy, but very clearly after four to six cycles from that same AZA001 study, patients gained transfusion independence and that's one of the big goals of therapy for starting Azacitidine. However, some of you probably live this and know there's a very predictable pattern of the 28 day cycle and so initially you have to accept that there's going to be more transfusions before the medicine kicks in to start working. Unfortunately, MDS is not the type of disease where you start a therapy and you see a response. It takes a lot of time, which is onerous and tiring emotionally but you get your drug for a week and then your blood counts are low and maybe you get an extra transfusion over those next 10 days and by the time that you get to day 24, 25, 26, 27 you're starting to feel better and the counts are coming up and then we hit you again, but those dips get less in people who respond over the course of those four to six cycles

and so that's something that can be very frustrating for a patient is that when they decide to get that treatment and they are getting maybe four units a month and then all of sudden in the first three cycles they get eight units a month and they're just like, "Grr. It's worse," and it makes people not want to do it, but if you can ride through that hump with your doctor and with your spirits, it's worth it to look for that response at the end of four to six cycles. Does that answer your question?

Q31: Yes and it leads to another question then. Basically, I think what you said is you continue then to take the Vidaza.

Amy DeZern, MD: Well and I think it probably gets back to your earlier question of response, but if we see transfusion decrease or transfusion independence and a patient is not having terrible toxicities from the medicine, that is probably a real reason to keep going. To stop it at that point is not what we do.

Q31: So, what's the prognosis for the future?

Amy DeZern, MD: It depends on a lot of things and it's little case by case basis, but if people are having a response and they are truly are responding to normalization of counts we know that those responses really have quite a tail, a couple years, but it just depends on the duration of the response and how durable the remission is. If people had a very complex set of chromosomes and those chromosomes normalize then they're probably going to do well for some period of months. It's not decades though certainly in this particular disease.

Q31: Well, I'm one of those cases and with the fifth iteration and it appears like I'm responding to that…

Amy DeZern, MD: Congratulations.

Q31: I'm looking like okay what's the future hold?

Amy DeZern, MD: Yeah. You're asking the right question and everybody's different and I'm sure you and your doctor have talked about it but continuing to take it on a 28 day cycle is what would be recommended both by the literature and just in clinical practice.

Q31: That's pretty heavy.

Amy DeZern, MD: I know. I do and that's the concept that's really hard to hear in the early discussions with patients is that these drugs are not curative. They're intended as maintenance therapy.

Q31: Thank you.

Amy DeZern, MD: I'm going over a little bit. My apologies. So, I really didn't put a lot of slides on transplant in particular even though I know that some of you probably have a lot more questions about this. I'm happy to take them, but something that is important to realize for MDS is that the only potential cure is a stem cell transplant and just so you know my little spiel stem cells come in various varieties. Donors come in various varieties and types of transplants are of different varieties. So, the rates of cure it sounds so appealing, right, it's a cure. Why would anybody not want to do it? And the reason is is because we know that transplant can be harmful. It can bring with it toxicity and a whole another set of problems, but also in MDS in particular it is not as effective of a therapy as it is in some other diseases and so it's a tool, very much a tool, and I send a lot of patients to transplant, but it's one that we have to think about and use very carefully and as a field we don't quite know exactly the best patients to choose and some things that are more coming out in the literature even very recently is specific mutations that should suggest that a transplant is a better or worse idea. Some of the somatic mutations and then, again, it's a very important discussion that's patient specific about what the goals are and people usually have a fairly gut reaction to it from the get go, but then in terms of where they are in their disease kind of to the earlier point that was made it can be very sobering the concept of taking a therapy lifelong but transplant… it's only a potential cure. It's not a guarantee and that's why we're thoughtful about it.

And this gives you a little bit of a flavor. This is from an older article. It's about 10 years old, but Cory Cutler who's at Dana-Farber has done some great research and actually gave a point/counterpoint that was great earlier in the week actually arguing against transplant for MDS. So, that should give you a flavor that when transplanters are at least thinking about what we should do it's an important thing that can't be taken lightly, but when patients get transplanted at diagnosis they do pretty well and then this is years of life expectancy and then when they get transplanted after a couple years they do okay and then at progression it just depends, but we're really talking about the concept of higher and lower risk patients taking them to transplant and we do know that we can certainly shorten a person's life with transplant and that's the reason that we have to talk about it so carefully.

So, in conclusion, I think most of these things I've hit we start with a point for risk stratification and we use this to guide our therapies, but it's not an absolute for everyone. It's very important to set the goals of therapy and it's really all about you. When you're sitting in that doctor's office, you have full permission to be selfish and just focus on you. We've talked about growth factors and support of transfusions. We've talked specifically about Lenalidomide and lower risk disease and we've talked about these HMAs. They're also called DNA methyltransferase inhibitors and I just put these so you hear all the words, but Azacitidine, Vidaza, Decitabine, Dacogen that they are associated with increased survival compared to conventional care regiments which are usually supportive care and then stem cell transplant is certainly a potential for cure, but it is toxic which is why we think about it and are thoughtful.

So, a lot of the questions were related to what's currently available and what's in development and just want to finish this talk on Thursday night. I just wanted to give you guys a real world snapshot. If you actually look specifically on open recruiting trials for MDS in the United States specifically, there's 292 trials that are open which is actually pretty good, but a lot of those encompass both Myelodysplastic Syndrome and acute leukemia at various stages of the disease and it includes quite a few transplant trials.

And something that you'll quite often look at and I just give you a flavor because it's my frame of reference is a paradigm for Myelodysplastic Syndrome and we usually clinical trials can be put into various boxes for patients who are treatment naïve never had a therapy to get various treatments when they fall into the low risk category or when they fall into the high risk category and this is just our Hopkins portfolio for reference and when patients have passed through those other therapies what we would call therapy refractory or treatment refractory. Again, a different set of treatments depending on what a person's disease is.

And then I mentioned at the beginning that my week started out I'm one of the protocol writers for the National MDS Study and, again, just I hope this gives you all hope that this is a way that the government, the NHLBI is really interested in finding out the natural history of Myelodysplastic Syndrome and categorizing patients who have MDS. It will be for patients who are newly diagnosed, but I think that shows you that all your efforts and your treatments and you're going through this is going to help people who are newly getting diagnosed to getting their information and their tissue banking into a very large study. It's going to be about 2,000 participants and for MDS that would be a very large study.

Okay. So, these were the questions that were E-mailed to me in advance. I hope that I hit most of them. You guys have asked most of them. The question on hydria, I didn't quite know how to fit that in, but Hydroxyurea is a bone marrow suppressant. Because we give it. It's a pill chemotherapy. It's a very old chemotherapy that we give when the white count is high and the question was if it has any effect on the hemoglobin and the answer is absolutely yes because it's not specific for just white count. When you take it all the cell lines go low, the platelets, the red cells and the white cells. I hope I've given you a flavor for a genetic based treatment.

Q32: That was my question Hydroxyurea. So, it was for my mom. She lives in New York. She gets treated at Memorial Sloan Kettering and it's too hard for her to get here unfortunately. So, I'm trying to take notes for her, but she specifically wanted to know about that, but also if it has effect on her bone marrow because she's been taking that low dose because her white blood cells spiked, but she had low red all along initially and so she's concerned… she actually did a consult with Dr. Stivek at your place. She sees Dr. Fleming. So, the question is…

Amy DeZern, MD: So, she saw Jerry. We can talk off... but sometimes this medicine is given for other diseases that aren't the perfect MDS. There's other overlaps with MDS that hydria is (inaudible)

Q32: She's been getting from Dr. Klimek at Memorial Sloan Kettering and her… and I guess she wants to know if it's helping the white blood to lower it. Is it bad for other… and her bone marrow and hemoglobin and other things?

Amy DeZern, MD: That is a relative term. Does it hit everything? Is it a nonspecific drug? Yes.

Q32: Okay.

Amy DeZern, MD: I think I've given you a flavor for genetic based treatment as we gain information with these various sematic mutations. I think we really ought to just start incorporating and to how we categorize patients and then down the line how we treat them.

In terms of medical oxygen and high altitude travel, that's a complicated one and I'll actually say my husband has great expertise in high altitude pulmonary processes and he said that's a tough one, too, but probably it doesn't have any benefit in terms of MDS specifically. In terms of the stem cell transplant and caregiver issues, I didn't touch on that in slide form. I'm more than happy to talk about it. A transplant is a… one of these situations that it takes a village and so certainly it's not a burden… or it's a burden of love, but it really takes at least one other person and probably a lot of other people to get a patient with MDS or any disease through transplant and looking for support both for the patient and the caregivers is something that I think is really important and then I talked about the epidemiologic information as well. So, thank you so much for your time.

(Applause)

Q33: You haven't talked about T cells.

Amy DeZern, MD: Well, we actually did. We spoke about the concept of CAR T cells. Is that what you're asking? Car T cells.

Q33: Okay.

Amy DeZern, MD: And I was just mentioning that CAR T-cells and so this just in case people aren't reading. It's been in the lay press a little bit and actually it was in "The Emperor of All Maladies" as well but the concept of engineering a specific type of white cell, a T-cell to attack a disease is a really interesting set of academic and scientific endeavors specifically CAR T-cell therapy for myeloid diseases. So, not lymphoid diseases. It's pretty early in its infancy and right now there's not a directive therapy against using a T-cell to fight MDS.

Q33: So, you're not doing that at Hopkins.

Amy DeZern, MD: The true CAR T-cells, no, but nowhere is doing it. The place that's best in the lab, but it's still early and I know the trial is not written because I just saw him yesterday is at Penn.

Q33: Actually, I had another question. Early on there was something about B12 and EPO levels. I don't have a comprehension of what those levels are supposed to be.

Amy DeZern, MD: In terms of normal values or why we check them?

Q33: Well, somebody with MDS.

Amy DeZern, MD: So usually, these are tests that are checked as someone's on the path to diagnosis and B12 is just one of the vitamin building blocks that can help red blood cells grow and sometimes people can have funny looking under the microscope big red cells if they don't have enough B12 and just giving B12 shots can really help that. The erythropoietin or the EPO levels that we talked about, we use that to make decisions on giving the erythropoietin stimulating agents usually less than 500 or above 500. It's not something that we per se routinely follow once a patient has a very clear cut diagnosis of MDS.

Q33: Thank you.

Amy DeZern, MD: Okay.

Valerie Ironside: I think at this time the nurses, Lisa and I are going to talk but they've brought in some coffee break things. If you'd like to go while we set up our things and then Lisa and I will get started. Okay?