Speakers:
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Simon Yeung, PharmD, MBA, Lac
Jayshree Shah, APN-C, MSN, RN, BSN, BS

Jayshree Shah: … first and my name is Jayshree. I'm a nurse practitioner. I work in Hackensack University Medical Center at John Theurer Cancer Center. I have been a nurse practitioner for over 11 years and I started my career in GY and oncology taking care of women and gynecological type of cancers. Shifted gears to hematology and recently shifted gears to medical/hem/phase one. So, (inaudible 0:28). It's quite exciting. So, I'm here today to be just a moderator, a nurse lead discussion in conjunction with other people that are here and starting with Dr. Klimek. Her team, Debra, Colleen. We also have a couple other representatives. So, I just want to introduce them so that you know who they are. We have Steve. We talked about Vince. Steve from Celgene and we have a representative from Onconova, Scott, and we also have Dr. Yeung and we also have a transplant physician also presenting right after Dr. Klimek. So, I want to stay on cue because we have lots to discuss and it's getting quite exciting. Feel free to get up when you feel like you need to stretch your legs. We have some pastries and it looks like some water and drinks and stuff. If you have any questions, I'm going to pass around or go around with this mic to go to you to ask a question. Let the presenter please finish. If you can, write down your questions please so that we can go person by person and do so. Again, I want to stay on cue with the timing because we are on cue from 10:00 to 2:00 and I want to make sure that everybody gets to do what they or the questions get answered. Also, I think there is a survey for you guys to fill out in the back. So, if you get a chance if you can, please when you take a few minutes here and there to fill it out to hand it back to us. Debra and Audrey from MDS Foundation are outside. So feel free to ask them any questions or any information about how to join or get information, how to give your E-mail and contact information for updates. Anyway, let's start the day. We're going to begin with Dr. Klimek. You guys are welcome to (inaudible 2:25) with her. She is renowned physician specializing in MDS and she's going to start with her presentation. Thank you.

(Applause)

Virginia Klimek, MD: I also would really like to thank everybody for coming making the trip into the City. I know it's not easy to come in and I know some of you came from quite a distance. So, we really appreciate you coming and I hope you have a good day and learn something that will help you and your loved ones with this disease. Jayshree introduced you to some of my staff at Sloan Kettering. I just want to mention them again. Debra O'Shea if you can raise your hand and Colleen Branigan, a nurse and nurse practitioner who work with us and anybody who comes to see us at Sloan Kettering knows how integral they are to our team and that we can't… no physician can do it alone.

So, and also to emphasize, I know that there's going to be a lot of questions. We're going to try to build in time for questions, but we also have a couple talks we want to make sure we get in. So, we'll try to have time during each speaker's session for questions and then they'll be opportunities during lunch time for questions. I'll be here all day as well. So, I'm going to talk from this mic because the sound is better, but the angle is a little tough for me. So, I'll do my best to use the pointer. Just let me know if you have any questions about what I'm referring to on the screen.

So, what I wanted to go over was just a general discussion about what MDS is and some general treatment strategies and I just want to preface my talk by saying that I think I could probably talk to every person in this room who has MDS and if you were sitting in front of me in my clinic and I was talking to you about your disease, it would probably be a different discussion with almost every one of you. So, it's a very heterogenous disease. So, I'm going to try to approach this generally and I understand that there's questions and maybe not everything I tell you is applicable to every one of you, but I'm going to do my best to sort of get across some general principles.

So, what is MDS? So, MDS is a… stands for Myelodysplastic Syndrome. I think everybody in this room probably knows that, but they may not know where this comes from. So, myelo is just a scientific word for the bone marrow which is where your blood cells are made. Dysplastic just means that the cells in your bone marrow are abnormal. They look abnormal under the microscope. They don't work normally. So, it's a disease of the bone marrow that causes a decrease in blood cell production and as a result you have low blood counts and over time this can change into something that we call acute leukemia. So to better understand MDS, I just wanted to talk a little bit about what the bone marrow is and does and what blood cells are.

So, bone marrow is a material inside of your bones and for the most part as adults we make blood in the bone marrow in our spine and in our hip bones and in our legs and I always talk to my patients about how the bone marrow is essentially a blood cell factory and when you develop MDS that factory is not working so well. It's inefficient, it produces defective cells and it produces insufficient numbers of cells. This is just a picture of the bone and you can see the bone marrow inside the bone and all the different types of cells that are produced. So, the bone marrow produces the red blood cells. It produces a variety of different types of white blood cells and cells called platelets. Whenever I talk to patients and whenever your doctor talks to you about blood cells, these are the three main types of cells they focus on. We have the red blood cells. The red blood cells are cells that are filled with something called hemoglobin and the job of the hemoglobin is to carry oxygen to all your vital organs, to your brain, your lungs, you muscles, your joints and so that explains why when your hemoglobin levels are low when your red cell levels are low you don't feel well. You feel tired, you feel short of breath, you feel dizzy, weak, you can't think right. So, it's important that we be aware of and we monitor the red blood cell levels. The neutrophils are one of the white blood cells that we use to fight off infection. So, that's another important cell that we keep an eye on with this disease. The platelets are cells that

you produce that can stop bleeding or prevent bleed. So obviously, important for us to keep any eye on those as well.

So when is MDS suspected? Most of the time when people are diagnosed with MDS, it's because to the doctor for some other reason and they have a blood test done. Maybe they're having a surgical procedure, maybe they're going to the doctor because they feel fatigued or they had some bleeding or they had a bad bronchitis and pneumonia and the blood work is done and you can find a low blood count to that time. Sometimes people come to me with a diagnosis of MDS because they had a bone marrow procedure done for something completely unrelated maybe another cancer even and they find MDS at that time when it wasn't suspected. We sometimes pick up abnormal bone marrow by x-ray studies. So, sometimes people will have an MRI, for example, after they have a car accident and the radiologist can see that the bone marrow in the bone looks abnormal and that leads to a bone marrow test and a diagnosis of MDS. We also suspect MDS more commonly in people in their 60s, 70s and 80s and the average age of MDS is around 70.

So, the symptoms of MDS that bring people to their doctors are fatigue, shortness of breath and weakness and, again, that's primarily from the anemia, the low red blood cell counts, or if they're having frequent or prolonged infections or bleeding problems. The problem is that a lot of these symptoms can be caused by other things. You could talk to anybody who's had fatigue and you can know that that it could be from thyroid disease, heart disease, diabetes, a lot of other medical conditions can cause some of these symptoms. So, MDS can mimic a lot of other medical problems. So that's why when MDS is diagnosed it's so, so very important that your doctor obtains a good history, they do a physical exam and they do a lot of basic bloodwork to make sure you don't have some of these other disease that can cause these same symptoms which can also cause low blood counts. So, the low blood count brings you in. You have these symptoms, but it doesn't necessarily mean that you have MDS. You can have something else or you can have MDS and another medical condition. So, it can get a little complicated.

We diagnose MDS by looking at the blood work, by looking at your blood cells under the microscope and then, of course, by doing the bone marrow test. Most of the people in this room probably cringe when you see this picture. This is a cartoon of somebody undergoing a bone marrow biopsy and aspirate. We take the bone marrow samples from inside the bone because remember I told you that's the factory, where that's where the blood cells are made inside the bone and we look… we do a lot of different tests on both the liquid from the bone marrow and we also go back in and we take a little piece of the bone and I've listed some of the tests that we do on these samples. All of these tests are really done and needed to make and establish a diagnosis of MDS and to find out what type of MDS somebody has.

So, there's really no single test that shows somebody has MDS. Remember, I said you have to eliminate a lot of other problems that can cause symptoms and low blood counts. You need to do a bone marrow that shows typical findings that we see in MDS and even then even if somebody

has low counts they have some symptoms of MDS. If we really can't be sure about it based on how the bone marrow looks, sometimes we have to take a watch and wait approach and I'm going to bet there's at least a few people in this room have been down that road where the doctor says I'm not quite sure. We need to follow your blood work and maybe have to repeat another bone marrow even to confirm the diagnosis.

This is a just a list of some of the other causes of low blood counts I talked about. So, people can have low levels of vitamins. Sometimes medications can cause low blood counts and even some of the symptoms of MDS, other cancers and then there's a lot of other bone marrow disorders that we have to think about when somebody walks in the door and to be evaluated for these low blood counts. This cartoon looks complicated and it would probably take about an hour to explain this, but this is what goes through my head when I sit down with somebody and I'm trying to think of everything that can go along with the symptoms and the blood counts and the medical history of that patient. We have MDS in the middle in that yellow circle, but there are a lot of other diseases that sort of overlap with and can look like MDS including PNH, paroxysmal nocturnal hemoglobinuria. It's a mouthful. Other bone marrow diseases like myeloproliferative disorders, for example. Aplastic anemia which is a related disease that you may have heard of and, of course, leukemia. So, a lot of… So even once you have a bone marrow that looks like MDS, you have to still have to make sure that you're not dealing with one of these other conditions as well.

So just as a summary, in Myelodysplastic Syndromes you have an abnormal bone marrow. You have low blood counts because the bone marrow is not producing enough cells. Unfortunately, some patients… fortunately, actually, a minority of patients, but some patients can develop leukemia as part of their MDS disease course and just to emphasize a point I made earlier, it's a very heterogenous disease. A lot of different types of MDS, different approaches to managing it depending on the individual.

So, I think I wanted to build in a little bit of break for just a couple questions. If not, we can just continue to move on. Let's move on.

So, this is a really common question I get from patients and their families. Never heard of MDS before I was told I had it. Does that sound familiar to people here in this room? Yeah. I see a lot of heads nodding. It's not a common disease. So, it's not surprising that people have never heard of this. This is not something you hear about on the news. Although with some… people coming forward more recently… recent time about their disease now there's some more public awareness about this disease. Instance increases with age and what I was trying to show with this graph if you can see the pointer. Although we see MDS diagnosed in people in their 40s and 50s, you can see that as your age goes up to the 60s, 70s, 80s and beyond the incidence of MDS goes up and the median age is right around 70 and although this graph looks like it's a lot of patients, it is and I'm trying to show the relative increase in people as we get older. So, it's still a rare disease and I put a little comparison on the bottom where in the United States alone over 200,000

people are diagnosed with breast cancer each year. For MDS, we're talking about between 10,000 and 20,000. So compared to other cancers that you hear a lot about, MDS is a rare disease.

Another common question people have is how did I get this? Is it something I did? Is it something I ate? What do you do? And what we think is that the cause of MDS is probably a combination of changes in our bone marrow as we get older because we see it mostly in people in their 60s, 70s and 80s. There may be some exposures that people have to certain chemicals. Benzene is one that's famous for causing this type of bone marrow problem. It's possible, although this is still something we're studying, it's possible that people are maybe born with an increased tendency to develop this disease. We also know that people who've had chemotherapy or radiation therapy for another cancer are more likely to develop MDS as a result to the exposure and the damage to the bone marrow from that chemotherapy or radiation. So, you're trying to cure one disease and you end up maybe causing or contributing to another and this type of MDS and leukemia that's caused by prior chemotherapy for another cancer, we call it therapy related MDS and leukemia and we have a strong interest in studying this here and what we found is that on average, it takes about five years for people from like when they get their first chemotherapy to develop MDS. So, 62 months in this study and 60 months in our study here and the diseases that we see it most commonly in are people who are previously treated for lymphoma, breast cancer and gynecologic malignancies and prostate cancer.

We can describe MDS by using these classification systems and these systems are beautifully described in the books that you receive today. So, I'm not going to really go into detail about this, but you've probably heard about the FAB and the WHO classification system. Again, the books that you receive today describe them and go into a lot more detail and I'll let you take a look at that later because it's not something we have time to go into today, but even outside of those classification schemes, there are other types of MDS or at least MDS that presents with other sort of profiles that don't quite fit into those categories. One of them is MDS with myelofibrosis. There may be people in the room who have been told they have something called overlap syndrome which means they have MDS, but they also have some features of another condition called myeloproliferative disorders. The therapy related MDS I referred to and sometimes people develop MDS that looks a lot like something called aplastic anemia which is another type of bone marrow failure syndrome.

The International Prognostic Scoring System is a way for us to look at the bone marrow and the blood counts of people who have MDS and it gives us an idea of how they're going to do with their disease and the likelihood that they might develop this complication called leukemia. This is also described very nicely in the books that you got today and you can sit down with your doctor and talk with them about what your IPSS score is and what that means to you.

We're developing even better scoring systems to try to predict how people will do with their disease based on cytogenetics. This is a very busy complicated slide, but just to get across the

point that we're finding that chromosome changes, genetic changes, are extremely important in this disease. They tell us a lot about how this disease will respond to chemotherapy. It tells us a lot about the likelihood of somebody developing leukemia and so just be on the lookout for increased use for this revised IPSS which will really take into account much more so these chromosomes and genetic changes.

Okay. So, you've gone to your doctor, you've had these tests and MDS is confirmed. So, what's next? So again, I'm going to talk generally because everybody is different. So, whether or not… what you need to do after you're diagnosed with MDS really depends on what's going on with your disease, what are your blood counts? What does your bone marrow look like? Sometimes there's no treatment needed. We just need to monitor you and there's people that I've diagnosed with MDS and I haven't given them any treatment for years. I'm just monitoring them. Other people we make a diagnosis of MDS and I have them in treatment within a week or two depending on, again, their blood and their bone marrow counts at the time.

Whether somebody is receiving therapy or not, once you're diagnosed with MDS, you're going to always have to be on a sort of a monitoring plan. The doctor is going to have to monitor you blood counts because even if things seem to be stable, your counts stay the same, they don't go down lower at least initially they have to be monitored because eventually they will change and so you need to be monitored regularly to pick up on those changes.

Some general things to consider about treatment. Just like any medication that you might take for heart disease, kidney disease, lung problems, anything, you and the doctor have to have a discussion about what is treatment going to do for me and what are the side effects going to be? Are the side effects going to be worse than the treatment? That's not what we want. We want there to be more benefit than risk to the treatment. So, the types of things that we think about and we talk about when we're thinking about starting treatment for this disease is is it possible that maybe I can be cured and if so I would be willing as a patient to accept a lot of side effects if I could be cured. Some people want to feel like well, I'm going to try treatment because I want to know that I tried everything I could do. Of course, everybody wants to feel better because people with this disease especially because of the anemia, you don't feel well and even if you can't be cured, well, maybe if I can at least keep the disease where it is without getting worse maybe I can feel better and with better disease control. The flip side, the downside, of course, is side effects. Side effect, side effects, side effects, Travel, the time you have to spend in the hospital going to the doctor's office. Anybody who's been down the road knows what I'm talking about especially when I tell my patients they have to come into the City from New Jersey like three times a week. Nobody wants to do that.

I'm going to go through some of these treatment options that we have, but not in a lot of detail, but I want to kind of touch on all of them.

So, supportive care for MDS means that we support you. We try to treat symptoms and the way we provide support in MDS is by giving transfusions to treat anemia. If the white blood cell count is low and you're running into trouble with infections, we use antibiotics to treat infections and sometimes we use antibiotics to prevent infections as well and in addition, we use injections of medicines I call growth factors. These are medicines that can make the bone marrow just work harder to make white blood cells or red blood cells and some of you may recognize some of these names – GCSF, Epogen alpha or Darbepoetin. Those are these medicines that we use to increase the white count and the red blood cell count. We also have two drugs that are FDA approved for MDS that are called hypomethylating agents. The names for them are 5-Azacytidine which you probably know… most of you know as Vidaza and Decitabine which you may know as Dacogen. Those are two hypomethylating agents. That's the type of drug that these are. Lenalidomide which is called Revlimid is a medicine that's FDA approved for MDS primarily for treating anemia. Every once in a while when people have the MDS that looks like aplastic anemia, we recommend immunosuppression, but we don't use that very often. In my practice and maybe there are doctors that you work with we talk a lot about receiving treatment in clinical trials if there's a clinical trial that's appropriate for you. The reason for that is because we're always trying to find new treatments recognizing that we don't have a lot of treatments for this disease and some of these newer treatments may be a good choice for you and so in clinical trials, we're studying new drugs, we're looking at drugs like Vidaza and Decitabine in combination with other drugs. So, there's a lot of different types of clinical trials that are out there. Sometimes when the MDS gets worse and it develops into more of a leukemia-like picture, we actually will go on and use leukemia therapy for this disease. The MDS is still there, but now you also have leukemia on top of that. So, sometimes people actually need to receive leukemia therapy. Last but not least is something called allogeneic stem cell transplant also known as bone marrow transplant or just stem cell transplant. Stem cell transplant is not for everybody because it is very risky and a lot of people just are not strong enough to receive that type of intense treatment. It is one treatment out of all of these treatments that if you can undergo this procedure safely and with some luck, it has the potential to cure people with this disease, but the bottom line is that most people with MDS either don't have a stem cell donor or they have other medical problems or because of their age, they're just not going to be strong enough to do that type of intense treatment. However, we're going to have a speaker following me that will go into different types of transplants and I think she may tell us a little bit about how we're trying to change that situation that I just described so that we can now maybe transplant more people than we used to be able to.

So just to go back and cover a couple important principles about treatment. Supportive care is the transfusions, the antibiotics and some of those injections, those growth factors I talked about. Those are the cornerstone of treatment for MDS whether you're on chemotherapy, having a transplant, no matter what other treatment you're receiving, supportive care, monitoring, transfusions, antibiotics, that's a… you're always going to be receiving those or being monitored to see if you need to receive those. A common question I have is once somebody has to start

chemotherapy, they say, "Well, will I still get supportive care?" Of course. So, that's going to always be there and sometimes that may be the only treatment that people need.

These are the growth factors I talked a little bit about. The (inaudible 30:00) the white blood cell count and the red blood cell counts and then this is a summary slide I put together just sort of give you an idea of how we choose treatments for a particular person and this is really how we think about it. So if somebody has a low neutrophil count or a low white blood cell count, you can see this column on the left? If somebody has neutropenia or low white blood cell count, the treatment for that person could include antibiotics, some of those growth factors I talked about, those drugs that I mentioned, those hypomethylating drugs, the Vidaza, the Decitabine and then also consideration can be given to going into a clinical trial if there's one that's appropriate. For anemia, transfusions are always an option. The Epoietin and the Darbepoetin, those are those injections I mentioned that can help make the bone marrow work harder. The Lenalidomide or Revlimid is another drug that can be used for anemia as I mentioned a few moments ago. Again, these hypomethylating agents can be used as well as clinical trials. For thrombocytopenia that means low platelet count. Remember those are the cells that you need that you to make blood clots and to prevent bleeding. We're kind of limited with how we can treat that and this problem and so the mainstay for this is transfusions and if somebody is starting to need transfusions, we don't like to have to continue transfusions. After people start receiving platelet transfusions, we start thinking about starting them on chemotherapy, these hypomethylating agents, because over time you can be resistant to transfusions for platelets. So, we have a shorter list of treatments to treat low platelet count and then stem cell transplant which is the bone marrow transplant can be used in some cases and I know this sounds like kind of a complicated situation, a complicated algorithm to go through and it really is. Again, everybody's different, but I just wanted to just give you an idea of how we use some of the information from your bone marrow and your blood counts to decide on a treatment for somebody. So if somebody has anemia and they have this chromosome 5 abnormality, I may be more likely to suggest that they go on Lenalidomide. If they have something called a low EPO level, I may be more likely to give them injections to stimulate their bone marrow to make more red blood cells. If somebody has a bone marrow that looks a little bit more like aplastic anemia, this hypocellular marrow, I may be more likely to prescribe therapy that's usually given for aplastic anemia and if somebody has a lot of chromosome abnormalities, those genetic abnormalities I was talking about, that's somebody that even if they don't need treatment right away, I'm going to be watching them more closely because we worry that those genetic changes are going to make the disease change more quickly.

So, another general principle for deciding on treatment for somebody who has MDS comes down to this question of transplant. So when somebody comes in the door to see me or an MDS doctor, one of the first things we have to think about is is that person… do we think that person might be a transplant candidate and if so how soon do we think we need to do that treatment because that changes how we sequence the treatments. It changes how aggressively we pursue testing to see if somebody has a donor, for example. So if somebody comes in the door and I think that they're healthy and they're young enough and that they need a transplant, we start that whole workup

very early and I'll let my colleague talk about that some more, but if I don't think that somebody is going to be a transplant candidate or if somebody has walked in the door and they said, "I've read about this. I've learned about this. It's not for me. It's not something I want to pursue," then we focus on nontransplant treatments like the supportive care, the injections I talked about, the chemotherapy when it's needed and, again, I'll just emphasize another general principle that for MDS therapy it is not one size fits all. Everybody is a little bit different and those differences including what treatment is used and the timing for that treatment when you start the treatment. Anybody that treats this disease knows the importance of encouraging people to at least consider enrolling in… receiving treatment in a clinical study or giving blood or bone marrow samples for research because we have so much to learn about this disease and we really want to develop and need to develop better treatments.

One of the last things I wanted to do was touch on this question of iron chelation. Do people know…? Does this term sound familiar to a lot of people in the room? Do you know what iron chelation is? So, when people are treated with supportive care with transfusions, you can develop something we call iron overload in your body. The iron can be deposited in your bone marrow, in your spleen, in your liver, in your heart and in some of your other organs like your thyroid, your glands and your pancreas. So, there's a lot of concern about what that means to your overall health that there's extra iron in your body and there's been more interest recently in giving drugs to try to get rid of this iron because of concerns… because of these health concerns from the iron and in part that interest is stimulated by the development of some new drugs that can be used to actually get rid of that iron in your body. So, people read about it, there's a lot of interest and a lot of… always a lot of questions about this.

This is a little bit of a busy slide, but I just want to draw your attention to what I put in red. These are two clinical trials for a drug called Deferasirox. It's also known as Exjade which is an oral chelating agent that's available for treating iron overload. What I wanted to draw your attention to is the fact that in these two clinical studies although the ferritin level, which is a measure of iron, although the ferritin level does go down, it's fairly modest by only about a quarter here and maybe about a third here, but importantly a lot of people have to stop taking this drug because of side effects. It's not an easy drug to take. Getting back to that slide I showed you with the scales where is there more risk than benefit. So, we're using these drugs very judiciously, very carefully in people with MDS because know it can cause more side effects than benefit in many people and also because there has not yet been a study that's done in MDS to show that using these iron chelation drugs changes your survival or your outcomes with your disease. It may bring down your ferritin level, but it has yet to be proven that it's going to change things for you in the long run. So, we have to be careful and one of the most concerning side effects that we have with this disease is problems with kidney function as well as problems with your intestines – diarrhea and so. So, it is not insignificant.

This is an ongoing clinical study. I don't know if anybody in this room is in this study or they heard about it, but this is an ongoing study comparing one of these iron chelation drugs to

placebo because that's the only way that we can tell if these drugs are affecting the disease and the survival of people who have MDS. So, this is a study that's ongoing and hopefully we'll be able to get enough people on this study so that five years from now we'll be able to say whether or not this drug is worth it to give to people on a regular basis.

And then so the last thing I wanted to go over quickly is about what's new in MDS. As I mentioned, clinical trials are always ongoing. We're looking at drug chemotherapy combinations. We're always looking for new drugs. Shortly, we'll hear more about new transplant… stem cell transplant techniques that might make transplant available to more people and also we may hear also about things that you can do even after transplant to help prevent the MDS from coming back.

Some of the drug combinations that we're using are the Vidaza and the Decitabine or the 5-Azacitidine and Decitabine in combination with other new drugs or some of these newer drugs by themselves to see if some of these drugs will work by themselves and some of them have kind of funny names like Hedgehog inhibitors, MAP Kinase inhibitors. So, there's strange names, but these are drugs that don't really have a company name assigned to them yet. So, they have all these funny names and numbers when they're first being tested, but suffice to say that clinical trials, I think, can and should be considered as part of the treatment option menu, if you will.

A very exciting and I think will be ultimately very fruitful line of research is to look at the genetics of people who have Myelodysplastic Syndromes to look at things like the chromosome changes and very specific changes called mutations, very tiny changes in your DNA that can have a big impact on how your bone marrow works and the last time I hosted this MDS forum, this paper was new. It had just come out and this was a paper that showed that most patients with MDS when we really drill down and we looked at these very, very subtle changes in the DNA, most people with MDS have these changes and we're now starting to learn about what those changes mean and even more exciting we're now in partnership with pharmaceutical companies are now starting to develop clinical studies to try to test new drugs that will target those abnormalities. So, it's not just that we're finding things. Now, we're finding things that we can actually drugs to target, so I find that very exciting. We have a number of studies here and there may be studies at the center where you go to where we can use these new drugs to target these genetic changes. Importantly what we're also learning is not just how to treat it, but we're learning more about why people… maybe why people actually develop it and, again, I have a specific interest in therapy related MDS and leukemia and we're taking a close look at the changes… in these genetic changes in therapy related leukemia and MDS and as you can see from the differences in the height of the red and the blue bars there are differences in people who develop MDS or leukemia after they've had breast cancer therapy, for example, or lymphoma therapy. There are differences between people who've had that type of MDS and have MDS without having another cancer beforehand and so they're starting to sort of dissect out to kind of separate out these people based on their genetics with the hope that we can develop targeted therapies and more personalized therapy, if you will, for people who have MDS.

This is a very busy slide that I use for my regular talks that I give to my colleagues but I just want you to look at the upper middle circle where you see mostly the pink. That pink portion of the pie, if you will, it shows that the majority of people who have a certain type of MDS called RARS. I don't know if anybody here has RARS, but if you have RARS you are very likely to have this SF3B1 mutation. I don't expect you to memorize this and there's not going to be a quiz, but just to get across a point that we're finding these mutations not only in MDS in general, but we're finding specific mutations in people with specific types of MDS and as we speak there are companies that are making drugs to target mutations like this. So, we're really looking forward to what's coming down the road in terms of new treatments for this disease based on this type of new research.

And with that, I'll say thank you and just on the subject of genetics and research, I brought some posters from my group and some of the laboratory colleagues. I put them back there just to sort of give you an idea of the type of research that we're doing here spanning from the laboratory to clinical studies, looking at treatments, looking at new ways to establish a diagnosis of MDS and I'll be here through lunch and we can… if you have questions, I can go and kind of explain to you what some of this new studies mean and what we're trying to do here at Sloan Kettering and with that I'll take some questions.

Q1: What if anything is the benefit of a genome sequence (inaudible 45:33)?

Virginia Klimek, MD: Oh, not fair. Not a fair question. It's a very good question. I'm not surprised that somebody asked that actually. We don't know. We don't know yet because the technology is getting a little bit ahead of what we can act on. So, we now know that we can look at the genetic sequence, the entire genetic sequence of a human being and we're starting to find things that we don't understand completely. We have… As an example, there are mutations, some of these genetic changes I was talking about, there are mutations that are commonly seen in people with MDS and leukemia. We think that based on laboratory studies, we think that those are important and are causing this disease, causing the MDS and leukemia. However when we start… We can actually look at normal people and find some of these abnormalities as well, people who are normal. They don't have MDS. They have normal blood counts. So, we have to be very careful about taking a laboratory finding and saying, "Okay, if you have that laboratory finding that means you have a disease," because we're finding that it doesn't necessarily mean that you have a disease and it's very difficult to counsel somebody about that. If they have this mutation, for example, we don't know if that means like five years from now or 10 years from now they're going to develop MDS. We don't know that. So, we have to be very cautious about how we interpret these findings. If you already have an established disease, that's a more defined setting and we feel a little more confident about how to interpret that because we ca look at a lot of people, hundreds of people who have that abnormality and make clinical correlations to how they do what that disease, but when we start finding things that are new and really not validated, it's kind of risky territory.

Q1: Thank you.

Q2: You mentioned hypomethylating agents, but you really didn't say much about what they were.

Virginia Klimek, MD: The hypomethylating agents, those are the Vidaza and the Decitabine chemotherapy drugs. They work… The name is that they're called hypomethylating. That means they remove a chemical group called methyl and methyl chemical group that's actually technically what it does. It removes it from your DNA. When people develop cancer, many cancers have this problem as well MDS and leukemia, there's too much of that methyl group on the DNA and it interferes with the way the DNA works. It's kind of like having like a locked file cabinet like your body needs to get that information to make your body work normally, but the methyl group and there's a lot of methyl groups on the DNA, your body can't access that information. So, the way we think these drugs work is that it moves those methyl groups and allows your body to use your genetic information, your genetic blueprint if you will, to help your bone marrow function more properly. When I'm in my office I use my telephone cord and I show how the DNA is all coiled up and you can't access it, but I don't have that, but that's the basic idea.

Q2: Thank you.

Virginia Klimek, MD: You're welcome.

Q3: Hi. Two questions. What sort of antibiotics do you use to fight or prevent infections and does that mean that there would be a larger percentage of MDS patients who actually have developed or develop C. difficile because of that connection with taking antibiotics and maybe getting C. difficile and the other question is could you mention if there's been any literature that has tied AG221 to MDS and good effects of that as opposed to just AML?

Virginia Klimek, MD: So, the AG221 is targeting an abnormality that's far more common in AML. The antibiotic question is… so we don't use antibiotics in everybody. Even if you have a low white blood cell count, you may find that you're not running into trouble with frequent infections. You'd be amazed at what your body can do. I mean, you can have a low white count, your neutrophil count can be low, but you won't necessarily… it doesn't necessarily guarantee that you're going to have problems with infections. So, the majority of my patients who are neutropenic who have low white counts, they're not on chronic antibiotics, but if somebody has a low white blood cell count or even if their white count isn't so low, but they're running into trouble with frequent infections. In that setting, the benefit… remember this is this whole benefit/risk balance. So, the benefit of preventing a bad pneumonia or the benefit of preventing skin infections, whatever you're prone to, the benefit outweighs… in that setting it outweighs the risk of the C. difficile which is, obviously, (inaudible 51:44).

Q3: When the MDS Foundation puts your verbal talk on their screen, will it also be accompanied by your slides that were great?

Virginia Klimek, MD: I don't know.

Jayshree Shah: (inaudible 51:58) asked the MDS Foundation to do so. I know that her slides will be available. If you choose to just let Debra or Audrey know outside and just tell them to mark it. Send it to your E-mail that (inaudible 52:14) provided and she will do so.

Q3: Thank you.

Virginia Klimek, MD: I think we'll move on. I've invited one of my colleagues here to give a talk about transplant. Now remember, I mentioned earlier that transplant may not be an option for everybody, but we are working our hardest to try to make transplant available and safe for as many people as possible and so I really wanted her to come and talk to us about allogeneic stem cell transplants for MDS and she's going to talk about for whom, when and how. This is Dr. Boglarka Gyurkocza.

(Applause)

Boglarka Gyurkocza, MD: Hi. So, my name is Boglarka Gyurkocza and thank you, Virginia, for inviting me and the MDS patient forum. So, I am an internist and a hematologist and oncologist who has been specializing into bone marrow transplantation. I just want to clarify a few things and then talk about the basic concept of bone marrow transplant today. I could talk about this for about two days, but I'm trying to limit to for 15 minutes. So, the old name, the old terminology, for this is bone marrow transplantation because that's how it all started that people transplanted bone marrows, but today it comes there's more inclusive of a term of any kind of hemopoietic cell transplantation and it just means that we are transplanting stem cells that are committed to make blood. So, these are blood forming stem cells. These are very different from the embryonic stem cells that can differentiate into anything. The stem cells we are transplanting are able to differentiate into blood components.

So, this… I would love to talk about the history of stem cell transplantation because we learned a lot from that history, but here I'm just going to mention that this procedure was pioneered by Dr. Don Thomas who recently passed away. I had the good fortune to know him and he got a Nobel Prize in 1990 for this work and basically we learned a lot from him and he was the one who was able to transfer this procedure from the animal models to humans in the late '70s and early '80s.

So, here is the basic principle of marrow grafting or bone marrow grafting but, again, these days we use this as synonym for any kind of stem cell transplantation. So, the basic idea, the very basic principle, is that there are these hematopoietic stem cells residing in the bone marrow. So, these stem cells, the one characteristic that differentiate these stem cells from other cells that they are able to renew themselves. So, they are able to undergo this asymmetric division when one cell will go down

on the road of maturation, mature into different type of cell components, but the other one will be able to renew itself and continue to be a stem cell and this is what differentiates it's from other cells that are more mature. These cells are differentiated into specific cell types and they are not able to renew themselves anymore. They are gaining function, but they are using different (inaudible 55:50) of renewing themselves. So, this stem cell here it tries to lymphoid progenitors or lymphoid stem cells and myeloid stem cells and as they undergo their maturation, eventually they will enter the blood stream as mature cell forms of different cells.

So, the idea of bone marrow transplantation is to replace this cell that may be diseased by MDS or other type of malignant diseases with a healthy stem cell from the donor. Again, there are different types of stem cell transplant. There're autologous and allogeneic. When we say allogeneic we mean that the stem cell is coming from someone else. Autologous stem cell transplants usually are not effective in leukemias or MDS or these type of diseases, but that's another story.

So, the whole principle of stem cell transplantation is that we give when it was started, stem cell transplantation, the idea was to give high dose chemo radiation therapy. That will eventually destroy the diseased marrow and also at the same time suppresses the patient's immune system. So, the marrow graft from the other person or the donor can be accepted and then the healthy marrow graft from the donor will replace the diseased marrow and repopulate the marrow and make healthy cells that eventually enter the blood stream. As they started doing bone marrow transplantation in the late '70s, early '80s, it has been increasingly recognized that this is not the only mechanism in how stem cell transplantation works. So again, the initial idea was by replacing the stem cell, we are able to give higher doses of chemotherapy and radiation. However eventually, it was recognized that when we do bone marrow transplantation or hemopoietic cell transplantation, we practically transplant a new immune system to the recipient and this new immune system, true immunologic ways and methods eliminates contributes to the elimination of the diseased marrow. So in addition to the chemotherapy, the high dose chemotherapy and radiation there is an immunologic component of the efficacy of this procedure and that's what we call alloimmune reactions and these reactions when they are directed to the diseased cell called graft versus tumor or graft versus leukemia effect meaning that the graft from the donor attacks the diseased cells and this has, again, this contributes to the success of the process. The problem is, however, and one of the biggest limitation of this procedure that this a double edged sword and this immune reaction does not occur exclusively against the diseased cells or the leukemia cells but also healthy tissues of the recipient. This is what we call graft versus host disease and very unfortunately many times they go hand in hand and this represents today one of the major limitations or barriers to the success of this procedure, but I will get back to that.

So, this is just some statistics from the TCIBMTR, The Center of International Bone Marrow Transplant Research, transplant performed in the United States. This is the most recent data we have in 2011. In orange you can see the allogeneic stem cell transplants and in purple the autologous. As you can see, autologous stem cell transplants work for different set of disease. For MDS, we exclusively use allogeneic stem cell transplantation and there was about 10,000 transplants performed in 2011 for MDS. We would like to change that obviously.

So, here are the components or how this procedure looks. Allogeneic hematopoietic cells transplantation. So, there are three main components for these procedure. The first is the conditioning regimen. The second is infusion of the cells or the graft from the donor and the third is immunosuppression that we give to try to modulate this reaction that I mentioned to prevent graft versus host disease.

So, let's start with the conditioning regimen. So again, when I talked about on my first slide I mentioned that initially stem cell transplantation we used high dose or what we call myeloablative doses of chemotherapy and radiation to eradicate the marrow. However when this role of graft versus tumor and graft versus lymphoma or leukemia effects were recognized, people started thinking we may not need those high doses of chemotherapy and radiation when most of the effect is coming from these immunological reactions and that's when people started performing reduced intensity conditioning regimens and this just means we don't have to give those very high doses of chemotherapy and radiation before infusing the graft, but just enough to suppress the recipient's immune system to enable engraftment and this concept itself resulted in a paradigm shift in our field because it enabled more mature or older people to undergo this procedure and people who had underlying medical conditions that would have excluded them from high dose conditioning, but because this is a myelo type of conditioning, now we are able to transplant more mature and not quite healthy people at the same time. So, this is a big breakthrough in the late '90s and early 2000s.

The next big component is the infusion of the graft. So, I will talk a little more about different donor options. As I said earlier, the early times people used marrow. These days we like to use mobilized peripheral blood stem cells. This just means that we give the donor growth factors and some of the stem cells in their bone marrow get detached from the bone marrow and start circulated in the bloodstream and we are able to sort of fish them out through a procedure that is very similar to hemodialysis. It's a one or two day procedure. We call it athyreosis. We just take some… We have two lines, IV lines, going in the donor, take some blood out, put it in the little centrifuge and take the current… the refraction out where we think the stem cells are and the rest of the blood is returned to the donor. The major difference between marrow and mobilized peripheral blood stem cells is the composition. When we do mobilized peripheral blood stem cells, there are lot more components, mature T cells and more mature progenitor cells in that graft and this will result in different characteristics in terms of graft versus host disease and graft versus leukemia effect. So, we still use marrow grafts for certain types of diseases and mobilized peripheral blood stem cells for other diseases and of course, this also depends on the donor. People are not able to receive growth factors. So for them, we would just take marrow and other people just don't want to go to the OR to get marrow harvested. So, there we do appreciate the donors' wishes or do. Of course, we have to work with the donors, so we do respect the donors' wishes.

The third important part of transplantation is the immunosuppression. As I talked about these alloimmune reactions and graft versus host, host versus graft reactions, we find ourselves having to give prophylaxis or preventative therapy to prevent these reactions in the beginning and very gradually taper these off as time goes by. There again, many different ways to do this. Many ways to skin a cat. The traditional way has been a pharmacologic immunosuppression and here at the

Memorial Sloan Kettering this other approach has been developed, T cell depletion. This is sort of manipulating the graft to take out the cells that we think are responsible for this reaction.

Any questions? If anybody has any questions, please ask. I think it's better if it's interactive.

So, this would be a typical treatment scheme, but this is just an example. I will show you some other ones. So normally, we call the zero the day when the marrow graft is infused. This is very similar to a blood transfusion. I will show you pictures of a bone marrow graft how it looks. This is the hematopoietic cell transplant day. That is what we call day zero and right before we would infuse the stem cells, we gave some combination of chemotherapy. For MDS we mostly use chemotherapy based conditioning regimens. This, I'm just showing an example that is very commonly used in the nation for MDS, for example, which would consist of busulfan and fludarabine. In the previous, so from day negative five to day negative two, we usually give a day of rest between the chemotherapy and the transplant to let the chemotherapy to wash out, not to damage the graft and then on day zero infuse the graft. These two medications would serve to prevent graft versus host disease or the alloimmune reactions. This is the classic. Again, this is the standard or again I can't emphasize enough that here at the Sloan Kettering we use alternative strategies which would be T cell depletion. So, the classic way would be either to (inaudible 1:05:54) or cyclosporine which we usually continue until day 56 or 60 and very gradually over months and the months (inaudible 1:06:04) off and the other is the traditionally is Methotrexate, but again because graft versus host disease is one of the major barriers of transplant. It is one of the major focus of for research. So, this is a moving target these days and a lot of lot of research focusing on how to prevent and how to treat graft versus host disease.

So, this… here I wanted to show you that a spectrum of conditioning regimens. Again with the advent of reduced intensity conditioning, we have many, many different regiments. You don't need to memorize this. As Virginia said, there won't be a test in the end of the day, but I just wanted to show that if you have… we have to imagine this as a spectrum of intensity. So on this axis, I wanted to represent the intensity of the regimen. This would be the lowest intensity. TBI means total body irradiation of two grade. This is a very small dose. We are not able to go below this dose because people would reject their grafts. So, this would be as low as it gets, the intensity. On the other end of the spectrum is this very high intensity regimen containing Cytoxan and total body irradiation more than 12 grades. In between, it's a continuous spectrum of intensity, but what is important here that as the intensity goes up, the toxicity associated with that regimen also goes up and as the intensity goes down, the particular regimen is more and more relying on this graft versus leukemia or graft versus tumor effect. So, it's as Dr. Klimek said, this is… I think the beauty of this field that there are so many options that we are able to customize treatment and, again, one size does not fit all. We have many and many different options for many, many people depending on how we think they would be able to withstand the toxicity and we still think this works because of the GVR effect.

So, this curve just shows that since 1998 how the use of reduced intensity conditioning regimen evolved or increased in the United States for different diseases. This purple line represents MDS and as you can see since 1998, there was a dramatic increase in the use of reduced intensity regimens for

MDS and mainly because this is a disease of people in their 60s and 70s. So, we do need a therapy that fits people in their 60s and 70s and that is reduced intensity conditioning.

So, let's talk about the donor options. As it was mentioned before, previously a lot of people were not able to undergo hematopoietic cell transplantation because they did not have good donors. The best possible donor traditionally, again, would be an agely identical sibling. Agely means human leukocyte antigen. These are low proteins on the white cells that we test. These have to match between the donor and the patient and there is approximately one in four chance or 25 percent chance that a sibling will be matched. These are always… These numbers are always based on large numbers, these statistics. So, when it comes to a single person and they have one sibling, that sibling may or may not be a match. That's what I always say. So, it's impossible to predict whether a patient and his or her sibling will be matched. We just have to test that. If they don't have agely identical siblings, we start looking for an agely matched unrelated donors. There are good statistical chances that volunteer donors registered in the National Marrow Donor Program through the National Marrow Donor Program will be agely matched and acceptable matches. The good news is that large centers that perform many, many transplant, hundreds of transplants a year have equally good results with agely identical siblings or agely matched unrelated donors. So, we do not really differentiate between the two. So and then we can talk for a long time how likely it is to find agely matched unrelated donor in the registry. For people with different ethnic backgrounds, this is different because different ethnicities are represented in this registry differently. In general, we can say that for Caucasians there's approximately 70 person chance that we will find an agely matched unrelated donor. For the people with Asian or African American background this, unfortunately, drops to 30 to 40 percent for many reasons not just that these ethnicities are underrepresented in the registry, but also these ethnic groups are immunologically much more diverse and even if the same number of volunteer donors signed up, it would still be much harder to find donors, but the good news is that these days we do have alternative donor options and these are the two most common. You probably heard about both. One of them would be umbilical cord blood transplantation which means that we take stem cells circulating between the mother and the baby that is about to born and just save the umbilical cord and take the blood out of that cord and freeze it. Because this is a much more immature immune system, mismatches are more acceptable and more allowed and we don't have to match these umbilical cord units as closely as we would have to match an adult donor. The bad news, unfortunately, is that these are very small amounts of stem cells. From a cord blood, we get enough stem cells maybe to transplant a smaller child, but for adults sometimes we have to use two cord units and different strategies to provide enough stem cells and to provide enough cells before engraftment. It is, again, it's a very active field of research and it is becoming more and more common. Here at the Memorial Sloan Kettering, we have a very strong cord blood transplant program and different strategies to help people with small units.

Last but not least is the possibility of an agely haploidentical family member which means half matched donors. It just means that when we use… and there's more disparity between the donor and the patient. We just have to use stronger immunosupressents to prevent graft versus host disease. In this decade, the use of haploidentical transplantations started propagating and, again, this is a very active field of research. So technically, we would like to stay here at the Memorial Sloan Kettering that we do not want to turn anyone away because of lack of donors. We should be able to find some

donor to everyone because with the agely half matched, this basically means that either a parent or a child is going to be half matched by definition.

So, this just shows statistics from the CIVMTR of how unrelated donor transplants or past related donor transplants in the recent years. In orange, you see autologous transplants but, again, that's a little different animal. We use autologous transplants for different diseases for different diseases. So, that's a big element for us, but the use of unrelated donor grafts is increasing.

This is how it looks. Marrow harvest product. Again, this is done in the OR. It's very similar how a peripheral blood stem cell collection looks and then this is the graft that we infuse into the patient on day zero. Very, very similar to a blood transfusion and then the cells first just go to the lung and then eventually find their way to the bone marrow. They stick out in the bone marrow. We call that process homing and they start producing blood components then.

Just a few more words.

Supportive care… So, recent events in supportive care make this procedure safer and one of the… I'm listing a few of these here. We have better antibiotics to prevent certain infections (inaudible 1:15:05) for (inaudible 1:15:06). This was (inaudible 1:15:08) in the older time. Acyclovir for herpes and (inaudible 1:15:14) cell line infections. CMBs, a very important virus for us. It can cause severe morbidity and mortality. So, we are very aggressively treating CMB reactivation, better antifungal, prophylaxis and treatment medications. Still, I have to say very unfortunately this procedure is not without risks. There is substantial and significant morbidity and mortality that can develop during a bone marrow transplantation and there is an associated risk of dying from the transplant and this can be 20 to 30 percent in the four years after transplant and this is why we are not transplanting everyone. Right? So, this is, again, a major limitation to this procedure. We would like to transplant everyone, but we recognize that this is not for everyone. This is a high risk high regard approach. The aim of transplant is always cure, but it doesn't come cheap unfortunately and this is a little chart that shows you what factors may go into the decision of how to transplant someone. So, there will be patient associated and diseases associated characteristics pre-transplant. If people have comorbid conditions that may sway us to do a more reduced intensity conditioning. For people more mature in age, we tend to do reduced intensity conditioning. The disease characteristics may sway us. If it's an aggressive disease then we may want to do a more high dose conditioning regimen then, again, depending on what donor we have and, again, disease relapse risk can decide whether we want to do mobilized stem cells or marrow infusions and last but not least post-transplant interventions, maintenance or preemptive therapy post-transplant. That is a very important of field of research these days that after transplants for patients who either have mixed chimerism or high disease risk we may introduce intermit prevention after transplant. Mixed chimerism that both the donor and the patient contribute to blood formation.

So, the million dollar question arises when should MDS patients undergo transplant and this is important as Dr. Klimek said that MDS is a very heterogenous disease and some people do very well for many, many years with minimum therapy. Should we subject those people to this high risk approach? Absolutely no, but on the other hand the other end of the spectrum is aggressive disease

that within months would transform into leukemia and we definitely want to do transplant early as possible. So for us transplanters and for MDS doctors, the question is always how can we predict who has a more aggressive disease and who has a less aggressive disease and as Dr. Klimek already talked to you we use tools to predict the transformation to leukemia. There are many different tools. I'm just showing one. There are many others. The problem is that none of them is perfect. Right? We are not able to predict in every single case who is going to do what and who's MDS will transform sooner or later.

The International Prognostic Scoring System takes into consideration a few factors. The marrow blast percentage, the karotypes. This means the chromosome aberrations and cytopenias meaning how many cell lines have low blood cell counts and based on that we come up with a number and based on that number we stratify people into risk categories, low risk, Intermediate 1, Intermediate 2 and high and in large… again, in large number of patients this is how these risk categories behave in terms of progressing into AML. This again, unfortunately, is not perfect. I think the future may be to incorporate molecular genetic changes into this or further factors that we are not completely aware right now, but Cory Cutler and Dana Farber did a decision analysis for MDS patients using prebaked data basis. The IRA, the IVMTR and the Fred Hutchinson Cancer Center databases and came up with this decision analysis who should be transplanted and who should not be transplanted and based on a large number of people and statistics, they were able to conclude that patients who belonged to the low and intermediate 1 risk MDS would benefit mostly from delayed transplant. That's when they have the longest life expectancy and those with Intermediate 2 and high risk MDS would benefit from a more immediate transplant. Again, very unfortunately this is not perfect. These tools are not perfect, but this is what we have now and this what we use now to predict… I mean, to kind of try to select people. There are always exceptions, of course. If somebody has very high transfusion requirements and a very young age, we try to transplant them sooner. So and of course, we always have to take into consideration the patient's approach, the patient's philosophical approach to life. I always have a very long discussion with everyone because I can't tell someone this is about taking risks, this is about their own lives and I think they have to tell me what they want and I just help them to get there in general.

So, this just shows some statistics. This is an older one. How the different risk groups do on the long term. So, these are years here that the low risk group… Almost done. Does better. The high risk group does worse. I will get back to that. This is from the NMBP how early disease stages with unrelated or sibling donors do very similarly and more advanced diseases there is separation of (inaudible 1:21:44) between unrelated and related donors. Again, this is a registry based data. Everybody like all centers contribute their data. In larger centers these curves don't separate as much between unrelated and related donors.

This is what Dr. Klimek talked about that in an effort to even better stratify disease risk, recently from the three group cytogenetic risk stratification they developed a five group recognize five group risk stratification recognizing that within the poor prognose cytogenetic group there are cytogenetic changes that predict even worse biologic behavior for this disease and they separated those out and the same applied for the good prognostic group that within the good prognostic group there was a subgroup of patients who did much better than the rest of the group. So, this is very recent. Dr.

Rashaan's reported it in 2012 in the *Journal of Clinical Oncology*, but this translates into the transplant world as well. So this five risk… five group karotypes risk stratification does predict behavior after transplant. So, people with bad cytogenetics, obviously, do worse after transplant. They have higher blast rates and lower survival. This to us does not mean we should not transplant these patients, but this to us means that this group of patients would be the ones who could benefit from further interventions after transplant. These are the patients who it's not enough to do a transplant. We have to do post-transplant interventions to minimize blast risk because these are the patients we know are at high risk even after transplant. So, the message here, I think, is that the journey does not stop at the transplant. Some people will need post-transplant preemptive therapy to prevent relapse after transplants which still represents one of the major barriers to success.

So in summary, I just wanted to say that because we know that the median age to an MDS is diagnosed is 71. We have to make allogeneic transplant available and accessible to that population, the population that needs it and reduced intensity conditioning regimens make us able to achieve that goal that reduced intensity conditioning regimens make transplant available for older people and for those who have underlying medical condition and that post-transplant relapse remains a major barrier to success and this is where we have to work together with our MDS doctor clinics who develop interventions after transplant that will prevent this relapse and this is where I would like to stop and take questions if there are any questions. Yes?

Q4: If you were accepted for this trial, do they stop all your other medications or do you still take them?

Boglarka Gyurkocza, MD: It's a very good question. So, it depends on what medication you are talking about. We like to stop medications before transplant about three – four weeks just to minimize toxicity of the transplant, but if it's Azacitidine or any kind of milder form of therapy we think strongly about reintroducing it after transplant especially with high risk disease… in patients with high risk disease to minimize those transplant relapse. So, we would probably stop the MDS medications for the time of transplant, but for some people we would introduce that after transplant for some time.

Yes? I don't know who was first.

Q5: Things are always changing, so I was just wondering what your cutoff age is for transplantation and when you talk about reduced intensity do you mean the same drugs but at a lower level or totally different drugs?

Boglarka Gyurkocza, MD: So, excellent question. Right now, I would like to say we published papers saying that transplants, allogeneic transplants, can be safely performed until the age of 75, but I have to say that we have transplanted older people than that and they had good outcomes. We just don't have a large enough number of these people to say at this stage, but the oldest person I transplanted was 78 years old and he's doing great and in terms of reduced intensity medications, yes we do use the same players, the same building blocks. We just give them at lower dose, lower doses

of chemotherapy and lower doses of radiation and just different combinations of graft versus host disease prevention.

Yes?

Q6: Can you kind of amplify the number of donor cells if you take the cord blood and put it in like a tissue culture or use re-competent DNA to stand the numbers?

Boglarka Gyurkocza, MD: Very, very good question. There are many centers that are using different approaches to kind of expand these cord units and one of them, I don't know if you want to look it up, is a notch receptor stimulation. So, a notch like in they can expand these cells and more into the neutrophil development sort of to bridge that period. Here at the Sloan Kettering, we use a different strategy that we give cells from a sibling, haploidentical or half (inaudible 1:27:34) sibling, just T cells depleted cells from the sibling that will bridge that period before the cord units can engraft just provides some neutrophils and this will be rejected, but they will provide cells for that critical period of time when the cord units are still just trying to grow up in the bone marrow. Is that making any sense?

Q6: No.

Boglarka Gyurkocza, MD: There are many, many different strategies, many difference (inaudible 1:28:00) and that is a very active research to try to expand the cord cells. Yes. Anybody else?

Q7: Is the bone marrow harvest injected in the arm or is it…?

Boglarka Gyurkocza, MD: It's an intravenous infusion. Our patients who undergo transplant have a central line inserted before they start conditioning. This is a large bore catheter with many lumens and it goes into one of the big neck ways, but it's tunneled under the skin which protects it from infection and this can stay in for weeks and months and we use these large catheters and we infuse the stem cells through this catheter into the central line. So, not into the arm, but into a central line.

Q7: I see. Thank you.

Boglarka Gyurkocza, MD: Yes?

Q8: Sorry if I missed it, but the decision whether to use bone marrow cells or the peripherally mobilized cells. How often do you use either and what's the impact on graft versus host versus graft versus tumor?

Boglarka Gyurkocza, MD: Very, very good question. So, we see that with that with bone marrow we see less graft versus host disease because there are less T cells in that graft and in the peripheral blood stem cell product there are more mature T cells and this works both ways. So if there is an aggressive disease and we want more pronounced graft versus tumor effect then we use the peripheral blood stem cells with T cells. We bite the bullet and say we will deal with graft versus

host disease later or may use different preventions, but we really need to be aggressive here because the disease is bad. While if somebody has less aggressive disease and we know from these risk stratification that the risk of relapse is lower, we can try to spare them from graft versus host disease and that's when we elect to do bone marrow as opposed to stem cells. So, this would be the simple way on our side and then we go to the donor and the donor has a choice. So in the end of the day the donor will say the final word. If the donor is willing to give either one, we can ask for either one, but if the donor says I cannot take GCSF because I have a disease that will be worse by that. I'm not going to take the growth factor, again, we just take whatever we get from the donor and work with it.

Q8: And is it the case that you always see GVHD when you have GVT or like are they…?

Boglarka Gyurkocza, MD: Very good question and the field has been working on this to separate graft versus leukemia effects from graft versus host disease. They don't always come together. There can be some clinical graft versus host disease that it does not really manifest as severely and very strong graft versus leukemia or graft versus tumor effects. Sometimes we see graft versus host disease and relapse of the disease. So, some people do get the worse of both worlds that it's not working on the leukemia or the cell gives them this complication. So, we do see some dissociation of the two, but most of the time they go hand in hand. Not all people develop graft versus host disease, but I would say about 40 percent of the patients do develop some form of acute graft versus host disease and somewhere between 40 to 60 percent of people chronic versus host disease. The field evolved in recent years and we are able to treat graft versus host disease much better. So, it's, again, not the end of the world, but there is some work to be done there.

Q9: What's the timeframe that a patient needs that Dr. Klimek decides that you know what, I think this person may need transplant of a patient with you till the time that they actually go for a transplant. Give me a…

Boglarka Gyurkocza, MD: So usually, we can transplant. So if Dr. Klimek refers a patient to us, we can usually transplant that patient within the month if we think that it's important that the disease is aggressive and we are running out of time we usually are able to perform like get going in a month. So, it's… Yeah. I think this is a very dynamic field and we are able to do things faster and better these days. It's not perfect yet, but hopefully we…

Virginia Klimek, MD: I'll just comment that it is very impressive that they're able to identify and screen and get these donors in quickly, but one of the factors, one of the big factors that affects the length of time between when we say that somebody should be considered for transplant and when they actually have transplant is in addition to finding a donor sometimes people need to undergo some MDS chemotherapy to prepare them for transplant. So, they might need two to four months of chemotherapy to get their disease under control, under better control, before they go onto transplant. So, there's additional factors in addition to the donor situation, but especially now with these cord blood units, they're sitting in a freezer somewhere. We don't have to find somebody in Holland or wherever they are and get them in and screen them. So actually, the cord blood unit now mean that we can get people to transplant much faster.

Boglarka Gyurkocza, MD: Thank you.

(Applause)

Virginia Klimek, MD: While they're getting lunch brought in and you're working up your appetite for lunch, I'd like introduce Dr. Simon Yeung. He's a member of our integrative medicine services here at Sloan Kettering. We value their input and consultation and expertise in the use of vitamins, botanicals, any kind of nonprescription supplement, how we work those drugs, if you will, into the regimen that we're giving people with MDS and I asked him to come and talk to us a little bit about his experience and maybe some recommendations for how these drugs in MDS.

Simon Yeung: Thank you for having me here today and thanks for the kind introduction. So, my name is Simon Yeung and today I'm going to talk about herbal supplements in terms of care with the focus on MDS.

First of all, I wanted to let you know about the (inaudible 1:35:09) cancer center integrated medicine department. Many of you have been (inaudible 1:35:15). We use rationale and (inaudible 1:35:18) without the… to treat both inpatient and outpatients.

The type of therapy we provide include massage therapy, mind/body therapy, music therapy, acupuncture, exercise centers, diet, nutritional counseling and also (inaudible 1:35:42) supplements. We do not actually use (inaudible 1:35:44) to treat patients though, but we do provide information and those products. So to that end, we have the (inaudible 1:35:51) website. This is the address and this is also a free app you can download if you have an Apple iPhone, iPad. We provide free information on supplements, vitamins and proven treatments that a cancer patient use. (inaudible 1:36:11) of this website.

So, I want to talk who'll use dietary supplements. The natural product that are most commonly used can be (inaudible 1:36:19) alternative medicine methodology and more than 70 percent of cancer survivor use dietary supplements. If you do use herb and things like that actually you're in the majority and the user tend to be female with high education level and physical activities. Many people think that people use herb because of ignorance. Actually, it's the smart people that use a product because of a personal choice and some study indicated that four out of five user use more than one supplements in a (inaudible 1:36:51) cancer patient survivors, many of you also using a lot of prescription drugs and this increase the risk of (inaudible 1:37:58) pharmacy (inaudible 1:37:00).

So why do cancer survivors use herbs? First off, it's a sense of control that their health after cancer diagnosis, MDS diagnosis if they didn't do enough for yourself and now you want to do something proactive. So, you resort to herbal supplement for your own health and they're perceived as natural and safe. I can show you that natural is not always equal to safe. Some of (inaudible 1:37:26) specify with the mainstream medicine. (Inaudible 1:37:30) poison then you think there must be a secret miracle herbal treatment that the mainstream medicine may have missed it or the pharmaceutical company may have suppressed its use. Actually, those are not true and also herbal medicine or (inaudible 1:37:45) holistic approach. They don't look at you as having disease in the blood and the

bone marrow. They look at you as a person and harmonize you. So, this is very appealing to many people and also most of you would use a product called prevention treatment as well as central relief.

So, I wanted to discuss some of the herbal product use of MDS. I think there are very few herbal supplement have been studied in cancer patients and they don't feel it has been studied in MDS patients, but I'm going to mention a few of them. The first one is this maitake mushroom. The maitake mushroom is just one of the medicinal mushroom used in Asia. It is very popular over there and the (inaudible 1:38:27) is its Japanese name means dancing. The reason is is that in (inaudible 1:38:31) people recognize the benefit of this mushroom. If they find it in the wilderness they will start dancing because it's happy there and they find a product like this. More (inaudible 1:38:42) find that it contained beta (inaudible) that has even a modulating activities and also there's some studies suggesting that it can reduce tumor toxicity by improving the white cell count and function and in Japan they also see where it's the case so they're suggesting that it can leap to tumor repression in cancer patients. Now, we did a study over here at Sloan on breast cancer patient trying to look for to see if there's (inaudible 1:39:10) activities and also to see what dose we can use in patients and related post-menopausal breast cancer patient and we defined that this product has (inaudible 1:39:20) activities. Now, we have to use this term very careful because (inaudible 1:39:25) activities not many people mechanism halfway, but we do find out that in some cases if you give too much of this product you would actually suppress the immuno-activities and they find out from this the study in breast cancer patient the dose, the optimal dose of use is 6 milligram (inaudible 1:39:34) per day and we use those information to get in our study in MDS patients which are (inaudible 1:39:50) investigate and we find out that (inaudible 1:39:55) patient that it can increase the neutrophil and monocyte function in MDS patients. Now this in (inaudible 1:40:04) we didn't find any good (inaudible 1:40:06) in the count but we found that the function itself sometimes is more important for example in better for reducing infection risk, but there are also some report suggesting that maitake mushroom may have some (inaudible 1:40:20) fact with high (inaudible 1:40:23) agent because it can actually lower blood sugar and also it can interfere with some anticoagulant drug and the result that we have is this, again, from a very small study and we plan to carry on to some even larger number of patients and maybe in Asia where there are more people have MDS and then include that we do not recommend people will use it as a treatment for MDS.

The second one is ginger and cacumen. This is also a small study on this one, but Gingerall is actually derived from ginger. Some of them we use as a spice in cooking and the other one is this cacumen. Cacumen is derived from turmeric that cacumen the turmeric has to been used in many clinical trial intensive patients. This is probably one of the more promising natural product than (inaudible 1:41:15) in cancer treatment. If you don't know what turmeric is and if you had (inaudible 1:41:21) the current common use in India in sort of major (inaudible 1:41:25) is actually turmeric and scientific study shown that they have (inaudible 1:41:31) and also anti-cancer activity and Gingerall somebody made a study also shown (inaudible 1:41:35) activities and in one of the small study reported one of the meeting they use eight gram per day of the cacumen just (inaudible) has this really low (inaudible 1:41:52) and also (inaudible) 12 gram of Gingerall and they give it to patients, a small number, like nine patients for four to 18 months and they find out that this product in combination is well tolerated and can have some potential benefit for patient who are not transfusion

dependent and we do not get a lot of information on this study because it's not actually published in the journal but rather say it's a big part in (inaudible) in 2008.

The next one I want to talk about is this wheat grass. It's also one of a very few natural product, herbal product, that's been studied in MDS patients. You may have (inaudible) wheat grass or wheat grass juice as (inaudible) to you and if prepared was (inaudible) wheat seed for five to ten days in water and they (inaudible) juice drink and many alternative medicine practitioner claim that it can neutralize toxin and carcinogens and also increase (inaudible) in the body. They thought that the (inaudible) and increase in hemoglobin production and this is not being supported by science. However, there is a study suggesting that it can reduce the need of transfusion in patients with (inaudible) by increasing the hemoglobin level and how does it work. We are not really sure and also there's some reports suggesting that it can decrease the myotoxicity in breast cancer patient undergoing chemotherapy. So, that's why many people have been looking into this product and suggesting that cancer patients should use them and in India some people also look into the benefit (inaudible) this morning about the iron overload problem. A group in India looking into whether (inaudible) have (inaudible) and they find that it can reduce the serum ferritin in patient with Myelodysplastic Syndromes. The reason they believe this is because wheat grass contain (inaudible) acid, malic acid. Those confined to the eye and intestine and act as chelating agent, but again this is in a very small group of patient. One thing I do want to caution use is that since this wheat grass juice, the wheat grass are prepared in water and they are consumed raw so this is a high risk of contamination and as mentioned about (inaudible) iron overload whether we should treat it or not we are not really sure, but the risk of infection is very more important. So in this case, the risk outweigh the benefit.

The next one I want to talk about is papaya leaf. This product has never been studied in MDS patient. It's marketed as a (inaudible 1:44:50) to enhance the immune system and also improve platelet function. In animal study, it does increase thrombocyte count and also this is one single… report on one single patient that it can increase platelet and neutrophil count for this patient (inaudible) is a secondary (inaudible) infection and people who have that tend to develop bleeding and low platelet count and things like that and perhaps papaya leaf may… as a antiviral effect to lower the virus count in fact on this patient, but this is no evident that it has any hematopoietic activities and again as I said it's never been studied in MDS patient, but nonetheless many patient have asked us whether they can use a papaya leaf if they have low platelet count and the answer is that currently this is (inaudible 1:45:41) they can do anything for MDS patients.

The next one I want to talk about is ginseng. Ginseng is a type of American ginseng and also Asian ginseng. The one I'm talking about is this American ginseng which is from the United State. Actually, this is made in the state of Wisconsin. It has been (inaudible 1:46:02) aside from being (inaudible) and also many people who have diabetes also use it because it seems to have high glycemic activities. In cancer patient, not so tend to use them because it has some CNS stimulation and calming activities.

This is one study. Actually this is quite current. Published only one or two years ago. This is one of very few herbal product that's been studied in cancer patient in large scale. This is a randomized

control trial. It showed that American ginseng extract can reduce cancer related (inaudible 1:46:46). This is (inaudible) patient and (inaudible) MDS patient. Nonetheless, this is a very good study and did suggest that besides that it can benefit patient (inaudible) it also does not interfere with some of the chemo drug. So, some physician actually aware of this study and they may recommend patients using it, but before you start going out to buy American ginseng (inaudible) it is a good thing to check with your doctor to find out it's cause effective. If it's due to anemia things like that then they be other better treatment for that but it's not uncomplicated if you want to try it. Speak to your doctor because American ginseng can interfere with some prescription drugs.

The last one I want to talk about is this (inaudible 1:47:31). This is used in traditional medicine with lung problem and there's a scientific study showing that it's a potent immunostimulation activities and (inaudible) toxic activities. Now in China so much as they tend to use extract (inaudible) and mix it with other herbs and it seems to help to reduce the side effect of chemotherapy. Now since there's some immunostimulant activities, again, this can be very complicated. It can mean a lot of thing, but there's this one in (inaudible) study suggesting that it can active counteract with the effect of some immunosuppressant drugs and this (inaudible) study also suggests that it can increase the risk of graft versus host disease. So before you buy this one and if you (inaudible) transplant patient and this is something you should be aware of.

So, I wanted to move on just to mention a few thing about the safety concern of (inaudible) in general. The first of all, most of the product on market are not standardized. That means if you buy something brand A they may (inaudible 1:48:34) amount than brand B even though a study used brand A, you may not have the same benefit when you buy a product from another company. Also many of these product attempt to be… they're prone to contamination and (inaudible). The contamination is a big thing. Contamination can be contaminated by heavy metal and can be contaminated by microbial. You know, virus, bacteria and things like that and in MDS patient who are neutropenic and this can be a big problem and that (inaudible) is sometimes connected the manufacture did purposely put something in there (inaudible) on label and they're very… they are faced recalled for example that people market things for sexual dysfunction. They actually have Viagra constitutes in there because (inaudible) imported from another country where they have less stringent law regulating this product.

Then there's (inaudible 1:49:28). As mentioned something like cacumen. Even though they can be effective in the lab and individual study, but when you take it it has to be absorbed in the body and carried by blood (inaudible) it could be effective and if they're not being absorbed then you have no benefit and sometimes we do not know what is a proper dose to use and, again, not that many product has been studied (inaudible) like we did in the maitake study. So, if you take another product (inaudible) a dose and you don't take enough you have no benefit, but if you take too much of them, you have toxicity and finally it is a concern of herb and drug interactions. Now herb and drug interacted (inaudible) like drug interact. They can go from many different mechanisms sometimes pharmacokinetic that means a drug can affect absorption, distribution, metabolism of a drug and also some of the (inaudible) dynamic. That means an herb can affect how a drug work, but in cancer patient setting these are four drug I tend to see the most common. The first one is when people use a blood thinning herb and they're using anticoagulant together. Now in this (inaudible) even though if

you're not using anticoagulant if you have a low platelet count or from cytopenic, you may want to avoid any (inaudible) activities because it can increase the risk of bleeding. Another one is this herbal part of the supplement has antioxidants and they can interfere with some of the chemo drug used even though in MDS patients the chemo drugs is by MDS patient they tend to not to go with a (inaudible), but other drug like Dr. (inaudible 1:51:09) was saying (inaudible) compound used in other anticancer treatment. Antioxidant may make those drug less effective. And the third one is this herb that has (inaudible) activities and for people who have (inaudible) of cancer again will (inaudible) maybe like breast cancer, prostate cancer, those type, some herbal product can interfere with (inaudible) treatment and finally there's this herb that has immunostimulating effect versus patient are using immunosuppressant drug and this is (inaudible) concern like (inaudible). So before you run to buy some of this product, make sure you're aware of this potential interactions.

If you decide okay I want to use a particular product and my doctor says it's okay. So, how can I find a good quality product? There are a few things that you can do. You can look for a product that has this either one of these logo on it and this independent institution or organization that evaluate the quality of herbal products and one of them is this United State (inaudible 1:52:20) supplement verification program. Another one is Consumer Labs program and the third one is NSF. They're very much like Underwriter's Lab when you buy an appliance. You know that they have actually go for some test, make sure they're safe. In this case, these three organization they make sure the product that has the logo, the label on it, are not contaminated and they have the stated amount and ingredient as they said on the label. One thing it does not guarantee is the efficacy whether this product is effective because that will be dependent on the clinical study itself.

So finally, there's just some take home points. Always speak with your doctor about dietary supplement and use. As some of you may be afraid to speak to a doctor because they're afraid your physician oncologist will disapprove diet supplement use because I said actually the majority and I'm sure the doctors are very eager to feel what (inaudible 1:53:16) you're using so that they can monitor your use and adverse effect and also select product from reliable sources. Now avoid missing products also. Some people, your neighbor, your friends, (inaudible 1:53:30) they come to you they know you're MDS or cancer. They offer all kind of product and people start buying a lot of these supplements together. The more supplements you take, the higher risk of interaction. Remember that and be skeptical about unproven treatment recommendations. The conspiracy theory with the big pharmaceutical (inaudible 1:53:53) is actually not true, but one of the sources that many of this dietary supplement has done is a big cause of the lack of funding. They cannot be patent so many feel company are willing to spend money to study, but nonetheless like NIH organization they do provide some type of funding. So in the future, we probably will know more about how these dietary supplement may work or may not work. And do not delay on deferring your regular checkup. If you have iron overload, don't start rushing to buy a supplement and think they will work. Just check the doctor because sometimes there are other better or more reliable treatment available. Report any signs and symptoms and also in considered noninvasive complimentive therapy. For example, you have anxiety. You don't need to buy a supplement to do that. Sometimes things like acupuncture or message therapy can be very effective and you can do yourself a lot of good without risking additional interaction of chemicals in your body.

Thank you.

(Applause)

Q10: Is the reason you're not recommending cacumen and Gingerall for patients who are transfusion dependent because you're afraid of bleeding?

Simon Yeung: That is one of the concern, but the major concern is that these studies are just a very small scale study. We probably would need to study this (inaudible 1:55:35) in combination. This a larger population before we can make the conclusion that this is effective and safe in this population.

Q10: And just one more question. You didn't mention anything about vitamins.

Simon Yeung: Right. Because my talk very focused on herbal product than (inaudible 1:55:55) another supplement deserve another hour of discussion. However, you do want more information. Again, I encourage you to look at our website. You can probably find some information on other vitamin that has been studied in MDS patient like someone like I know Coenzyme Q10, for example, is one of the product that has been studied in MDS patients.

Q10: What was…?

Simon Yeung: Coenzyme Q… Q10. Many of those studied, again, tend to be like (inaudible 1:56:23) study of phase one. Nothing that you can draw conclusion recommended as a treatment or recommended in general to all patient to use them. Not yet so far.

Q11: Would medical marijuana have any benefit for MDS patients and is there any particular reason why an MDS patient should not use medical marijuana?

Simon Yeung: I get this question all the time. The first thing I want to tell you that medical marijuana is just not a dietary supplement. Is not an herb they can buy over the counter. This should really be considered as a medicine. That's why they call it medical marijuana and better yet, I think medical marijuana should be called the political marijuana because people use it or the way they have described it in a patient is very political not medical. Medically marijuana or the active (inaudible 1:57:13) in marijuana has been shown to have beneficiary. THC can reduce nauseous and vomiting and things like that. Whether an MDS patient should use it or not, again, this is something that you need to discuss with your patient…. with your doctor because sometimes a doctor may feel that there are better prescription drug that can address your problem and another thing that you are perfect candidate for medical marijuana. Again, they would direct you to where to get them (inaudible 1:57:44) in New Jersey, you can actually get the smoke form like the part of marijuana, but New York we just passed the law that New York you're not allowed to get the sniffing form. You can get a brownie and things like that and currently I don't know… at least Sloan Kettering I understand is not one of the first five or ten hospital in New York that provide medical marijuana at this time.

Virginia Klimek, MD: I would just add we use marijuana sometimes for nausea in pill form and I guess we can't prescribe smoking marijuana, but one of the risks with that smoking is there may be a risk of fungal infection if you're neutropenic. So, (inaudible 1:58:31) to deal with that. I'm not sure we're… but that is a concern with smoking marijuana because marijuana has other things in it and it can be contaminated with mold.

Jayshree Shaw: I think the important point that they both are saying is that if anybody is interested or think that that would be something they should get or want to use, they need to talk with their doctors and I can only encourage is that have that open conversation like she just asked the question versus saying, "Oh, yeah. Let me go find somebody and give this to me." So, have this open conversation. I think that's really important. Go ahead. One more question.

Q12: To follow up on her question, have there been any studies done on the effect of Marinol on red blood cell count?

Simon Yeung: I think maybe Dr. Klimek may know the answer to this one.

Virginia Klimek, MD: Not that I'm aware of. No.

Jayshree Shaw: Marinol is the synthetic for in the pill… in the pill form, that has the marijuana component in it. It's a synthetic but pill form. That's what she's asking whether there's any direct relation. At this moment, I don't know of any like (inaudible 1:59:52)…

Simon Yeung: Thank you.

(Applause)

Virginia Klimek, MD: We have some pamphlets from Integrative Medicine Services Sloan Kettering that will have some of those resources that he had on the slides, the link to the About Herbs which is a really great resource and I think the information about the quality assurance organizations that he mentioned. So, there's some pamphlets.

Jayshree Shaw: So, we have actually a special treat today in addition to all the lovely speakers that we had this morning. For lunch entertainment we have a special person going to do an entertainment session of music and her song dedicated to her dad. Her name is Jenna Pell. I hope I'm pronouncing it correct. Is that right?

?: She just stepped for a moment.

Jayshree Shaw: Jenna Pell is actually famous. In your books that you have in the back end of it in the highlights part, page 23, her story is noted and her story of her dad who had MDS. There's Jenna. Jenna Pell is going to sing a song and it's called "Kick It In."

Jenna Pell: Okay. I'm going to do that one.

Jayshree Shaw: Go for it. No. Do you have another song? If you have another song, by all means…

Jenna Pell: (inaudible) and I thought we were going to do like (inaudible)

Jayshree Shaw: No problem.

Jenna Pell: (inaudible)

Jayshree Shaw: I thought she was going to do it while people were eating to (inaudible). It's lunch hour, so I think it's a good time to stretch and have some food, nourishment and feel free to chat and exchange phone numbers and contact information and we're going to have like a bit of a discussion session afterwards for…