

Speakers:

Peter L. Greenberg, MD

Lenn Fechter, RN, BSN

Lenn Fechter, RN, BSN: Hi. Good morning. So, I'm Lenn Fechter. I'm here to sort of coach you today along with the MDS Foundation and if you can say back to me to say I know that you are told where the restrooms are across the foyer there and you're welcome to just walk in and out of the room where the food is, go to the restroom, whatever you need to do along the way and ask lots of questions because we're here today for you. We want you to be comfortable. We want you to learn. We want you to meet new people and we want you to walk away from this day happy and having it be something very positive for you. In your notebooks that were handed out today, there is a consent form and the consent form is because the MDS Foundation today is going to record our meeting and the reason they do is because they use all of this information to educate patients and healthcare professionals and they gather it and they go over it. So if we can use what you say would you please sign one of those two consent forms and hand them back to us at the break. The microphones are in front of you every few people. Make sure that you turn them on when you want to talk raise your hand, hit the button and it'll turn on and then when you're finished you can either turn it off or it will automatically turn off after a while. Do you have any questions about that?

So, I'm going to introduce our first speaker this morning then. I have the honor of introducing Dr. Peter Greenberg. He's a professor emeritus in hematology at the Stanford Cancer Center and Director of the Stanford MDS Center of Excellence. He's dedicated his career to furthering research in treating MDS and mentoring young doctors by passing on his wonderful and compassionate bedside manner and inspiring them to enter the field of MDS research and clinical work. He's coordinator of the International Working Group for Prognosis in MDS and he chairs the National Comprehensive Cancer Center Network for MDS Practice Guidelines Panels. I could go on and on about our esteemed speaker today, but out of respect and to allow him time enough to do his presentation, I'll stop and present to you Dr. Peter Greenberg.

(Applause)

Peter L. Greenberg, MD: Thanks. Good morning. It's my pleasure to be here today to talk to you. It's really your day to ask questions and I hope that I can clarify questions that you might have many of which are up here, but in before doing that I just want to say that it was my honor to also have Lenn Fechter present me because Lenn is the nurse coordinator in our clinic and plays a critical role in communication with our patients and with me and helps a great deal with what we need to do to help all of you and a number of patients. It's great to see a number of patients here that I know from our clinic. Obviously, I haven't answered enough of their questions back at the time, so we'll hope that we can do that this time.

What you see up here are the questions that most of you ask your physician when you come in in one way or another, but before we go on and I'm going to show you some slides about this are there other issues that you would like to have covered this morning that could be helpful? Any

other questions that I've missed here that are going to be critical for things that you'd like to hear? Yes?

Q1: I'd just like to know why they discontinue using Procrit about 12.0?

Peter L. Greenberg, MD: Use Procrit what?

Q1: Above 12.0.

Peter L. Greenberg, MD: Right. Okay. Well, that's a question we'll come to a certain extent in the talk, but basically when we look at Procrit, erythropoietin for treating patients with MDS, we do it for patients that are anemic and not just anemic, but anemic and symptomatic. That occurs usually in patients with a hemoglobin below 10, sometimes below 9 or 8 and at that time we give treatment and the FDA for a while was very wary about giving too much Procrit because there was some studies that said in other diseases, not in MDS, that it could cause problems, clots, thrombosis, things of that nature, number one. Number two, a hemoglobin of 12 usually will raise the hemoglobin to a level that where patients are no longer symptomatic from the anemia. Above that they'd worry about side effects. So, that's how the FDA permitted us to use the drug at all in MDS so long as we kept it at a reasonable limit. So, it has efficacy and is less likely to cause problems.

Q1: Right, but they're extrapolating from a patient group that has no relationship to MDS, the chronic kidney disease patient and the other patients that have problems. So, I know it's an off label use. That's what you're referring that the FDA allowed you to use it in the treatment of MDS. Right?

Peter L. Greenberg, MD: Yes.

Q1: So, they're applying what they seen out in a different population to an MDS patient. The reason I ask is you have the same opinion many do that 12.0 is okay, but it may not be. I mean, I have a hard time understanding why the National Institute of Health defines the range of hemoglobin for women between 12.5 and 15.5 yet we can't administer the Procrit above 12.0. I mean, we can but the insurance won't pay for it. It sounds like a money issue more than anything, but maybe there are some medical issues. I don't know. I've tried to... I don't want to hide this, but we've gone over this with quality of life and the insurance company says it's not medically necessary, so I assume quality of life isn't figured into the equation of medically necessary.

Peter L. Greenberg, MD: Well, let me ask you are you discussing this because you're receiving EPO or your wife is and are you finding that you are still symptomatic with fatigue at a hemoglobin of 12?

Q2: Yes.

Peter L. Greenberg, MD: Okay. So, that's unusual. I mean, most patients don't and when that happens we worry about other things that it can contribute. It's very important to know that. In other words if you're still symptomatic at a hemoglobin of 12, we think about heart and lung and other kinds of problems that could be contributing. So rather than increasing the hemoglobin, we try to deal with other medical issues. So, those are things that really should be dealt with with your physician about that. So, that's an issue. We certainly are worried about quality of life and in most cases the hemoglobin level of 12 should be adequate. If not, we need to assess that medically.

Okay. Well, why don't we move on and just begin. What is MDS? What does it mean for my life? Is there treatment? How should it be treatment, when and why?

Okay. So as you know, this is a chronic disease. It's with us forever once we have it unless there's some dramatic cure that can occur and the only potential cure for the illness is bone marrow transplantation which is something that can be done and we'll talk about that for which there are pros and cons. It's heterogenous and that is when most of you I'm sure have been to the web and have looked up MDS. You may have what we often consider a worst case scenario. You think that this is a disease that in most cases will rapidly evolve into acute leukemia and something needs to be done quickly. However, as you know there's early, middle and late stages that we'll talk about which has us tailor the treatment to that specific subset of disease.

Symptomatic cytopenias. We've talked about anemia already. So, it's not just that your white count or platelet count or hemoglobin is low but how low is it and is it causing difficulty for you. A hemoglobin of 11 usually is not a problem but a hemoglobin of 8 or 7 can be and we should do something about it. A platelet count of 100,000 even though it's low, it usually doesn't cause problems, but one of 30,000 we need to worry about it. A white count that's a little bit low, not a problem, but below 1,000 we begin to worry about the potential for infection. Generally, elderly. What do we mean by elderly? There's several debates and several discussions. One is 10 years older than the speaker. I mean, that's certainly one. Okay. You know? Another is we can use the term CMM which is chronologically more mature. Certainly not emotionally or physiologically or psychologically more mature, but at least chronologically more mature. So, it's a tough diagnosis as to what we mean. So usually when we talk about elderly it's not just chronologic, but also biologic, how our patients, what are the comorbid conditions that patients have that could impact on what kind of treatment such patients could have. The progression to AML is the real issue that people worry about. It's Sword of Damocles hanging over one's head. Will that happen? If so, when? What can we do to abort that? There are therapies and we'll discuss that and the impact on quality of life is quite important for us.

Now, there are number of features in MDS that we pay attention to try to determine what stage of disease we're talking about. There's a so called prognostic classification that happens that helps us tailor treatment decisions and we then are able to place patients into lower risk or higher risk and that determines what kind of treatments we would enter. For example, lower risk patients, that is lower risk for acute leukemia evolution, lower risk for poor survival, we usually tailor that to try to help improve hematologic counts. Hematologic improvement is the main thing we try for lower risk. For higher risk patients because of the risk of developing leukemia,

we try to tailor treatment to alter the disease natural history. Can we decrease the ability of that disease to develop into leukemia? And then there's iron overload in patients that have a high number of transfusions should we or should we not do something to decrease the issue of iron overload and so we'll talk about these things.

So, the disease status. There's a clinical classification. There's also a molecular and biologic classifications, but we'll focus now on the clinical classification that occurs and the features include what the CBC is; what your blood counts are; the bone marrow blasts; the chromosomes that your bone marrow cells show; your age; whether you have transfusion, red cell transfusion need and what's your comorbidities are, what other diseases, heart, lung, kidney disease that you have that one needs to pay attention to to help decide on treatment and then people are then placed into prognostic risk categories. The IPSS, International Prognostic Scoring System, was developed in 1997 and they have four classifications. Over the last couple of years that's been changed so that we have a revised IPSS which now is a bit more precise for reasons I'll go into and there are five classifications rather than four, but basically there is lower risk and higher risk depending on what these other features are that I've described up above – CBC, bone marrow blasts and chromosomes.

So alphabet soup here, but you've been called... recognize the terms refractory anemia, refractory anemia with ring sideroblasts, refractory anemia with excess blasts, patients with 5Q-syndrome. **There's a whole variety of terms that have been used to describe the subsets of MDS. This is essentially based on what proportion of bone marrow blasts you have. The more progressed the disease is, the higher proportion of blasts there are.**

Chromosomes. Your bone marrow has chromosomal abnormalities in a substantial proportion of patients although about 50 percent would be normal, but in 50 percent of patients there are abnormalities that can occur and we have illnesses that are called primary and secondary MDS. Primary MDS are those that occur just out of the blue in individuals. Secondary are therapy related MDS are those that have prior treatment often for other hematologic disorders, other cancers, for example, and may have received chemotherapy or chemo radiotherapy and subsequently develop MDS. The chromosome abnormalities are quite distinct and patients that develop that have a somewhat poorer prognosis as far as the potential for developing acute leukemia and so one needs to be aware of that as to whether or not that may have played a role in patients developing their MDS.

Now, this is the International Prognostic Scoring System parameters, marrow blasts, the chromosome abnormality or karyotype, number of cytopenias and as you can see and depending on what the marrow blast count is whether they're good, intermediate or poor. Cytogenetics are how many low blood counts you have. You add them up and depending on what number there is put you in a classification. So, for example, if you have 5 to 10 percent blasts and an intermediate type of chromosome abnormality and only 1 abnormality of blood counts, .5 plus .5 and 0 would give you 1 which puts in an intermediate-1 category and that's a lower risk category and when one looks at overall survival of patients in these different groups you can see that those are low and

intermediate-1 have a relatively better prognosis as far as overall survival compared to those with higher risk status right here and the same thing with potential for evolution to acute leukemia. Lower risk is quite distinct from patients with higher risk disease and so that certainly has a major impact on what kind of treatment we would recommend. Now as I mentioned in '97, that was IPSS and then in 2012 a new publication came out that I've described which is the revised IPSS and there were countries from around the world in which 7,000 patients were evaluated with the features that were previously there as well as newer features to see if we could learn something better about what would be more precise and so what came out here was the bone marrow blasts that were important were whether it was greater or less than 10 percent. That made a big difference. The cytogenetics, that is the chromosome abnormalities, were much more precisely evaluated because now we had a larger number of patients and the smaller groups of patients that might have had some abnormalities in chromosomes now could be looked at more refined way and so there are now 5 groups rather than the previous 3 groups and not just whether patients had low blood counts but how low they were. Was the platelet count 90,000 or 30,000? That made a difference and so looking at that age and there are other predictors as well – performance status, serum ferritin, LDH. Those were features that also had some impact on what grouping the patient would be in and so we then had chromosome abnormalities and as opposed to the prior 6 or 7 groups, we now had 16 groups of chromosome abnormalities that put patients into 1 of 5 groups for chromosomes and then a little bit more complex way of adding up the different features. We now had 5 features rather than 3 to add up and whether or not the chromosomes were very good or very poor risk, blasts very low or reasonably high, the depth of hemoglobin, over 10 or quite low, platelets higher or lower and the same thing with the low white count. Now, because this is a little more complex, there are now web based programs as well as apps, iPhone apps, that docs can use, patients can use to see what their category is as to which of the subgroups there are and as you can see there are now 5 subgroups: very low, low, intermediate, high and very high as far as potential for overall survival as well as freedom from evolution to acute leukemia and the importance of this is that patients that are very low or low would be considered lower risk, these would be higher risk and intermediate would be somewhat group that we now consider to for treatment we would treat initially the intermediate groups in the lower risk group and then subsequently if they don't respond move into the higher risk group. So, it's a more precise way of looking at what a patient with MDS outcome might be and what we ought to do treat them. The additive features I've just mentioned to you which would be age, performance status, serum ferritin or the marrow fibrosis, LDH, beta-2 microglobulin which is important to a certain extent for survival not so much for AML evolution. So, these are features that are taken into consideration in addition to the major ones that I've already described.

Now, this generation is the beginning of where molecular abnormalities are going to occur. Out of all the things that I've talked about so far are clinical features you can get on a blood test on a physical exam whereas nowadays there are now changes within your cells that can show distinct abnormalities and there are mutations that can occur in a number of these. At the moment, there are probably about 100 mutations that can occur in patients with MDS of which perhaps 25 have implications as far as outcome, prognostic implications, of which at least 5 of them have major implications. So at least in the beginning we think that we now have a newer way of trying to

understand what features are present within your cells that drive the disease in a way that may be poor. Now, the hope is that once we get to this, we'll know what's going on as to which are drivers and which are passengers and if we can understand what the drivers are and attack them therapeutically and use them as targets for treatment, that's the next generation. So at the moment, the plan is to coalesce a large number of patients to be able to begin to understand which of these features, although in the beginning we believe we have something, can really breed true as to what outcomes will be and what we ought to do about that. So now, there are working groups that are beginning to look at that and put that together.

Now in addition when one looks at these molecular abnormalities and there are new techniques that called next generation sequencing. These are next generation with new technology that's available. It's not just whether there is an abnormality that's there, but how many abnormalities. Do you have one mutation or more than one and the more mutations there are the poorer the prognosis. So, this is something that will be important going forward to try to understand.

So I've just talked to you about both the clinical features earlier and just now the molecular features. Now, the reason that I have these in quotations is that it's early days that even though we have initial publications suggesting that these mutations are important, we still are not set on how reproducible they are and that's why we need more patients and more evaluation of that and those studies are now ongoing.

Now as far as treatment, the National Comprehensive Cancer Network is a group of 20 – 25 centers around the country that is involved with providing practice guidelines for all cancers and there is a program for MDS as well and that program has come up with guidelines for what kind of treatment should occur. It's a consensus system using with 20 or 30 faculty members that are involved from the different centers and as I mentioned to you the relevance are what type of what blood counts, how bad the blood counts are, what the age is, performance status, the prognostic risk category that is present, whether there's lower risk or higher risk. I mentioned to you you go either for hematologic improvement or alter disease natural history and whether a patient is a bone marrow stem cell transplant candidate. Now, the issue about a bone marrow transplant stem cell candidate is dependent on what the risk category is, age of the patient, performance status and whether a donor can be found for that. So most patients with higher risk disease, we try to evaluate this right up front to try to get a sense of whether or not a transplantation is something to consider down the road being aware that bone marrow transplantation, although can be curable, is a potentially harsh treatment with a fair amount of morbidity and sometimes mortality that one needs to consider as to put a risk for that treatment to the patient.

Now, the drugs that are approved. So, there are a number of drugs that are approved for MDS. We've talked about Procrit, EPO and a longer acting EPO called Darbepoetin and these have been around for a long time. In fact, as we talked about, they're really approved only for chemotherapy induced anemias, but we've been able through the use of the NCCN, American Cytohematology and a number of groups to have it available for MDS patients as well to help with the anemia and then G-CSFS or Neupogen is around to help with patients that may have low white counts and recurring infections and then Azacitidine became available in 2004.

Lenalidomide or Revlimid became available for patients that had a specific chromosomal abnormality, 5Q-. Those individuals with that specific abnormality a very high proportion respond. Seventy percent of patient with 5Q- subtype of MDS can respond with an improvement of their hemoglobin for a quite durable period of time. So, it's a very important drug for that subset of patients. It only works, however, for maybe 20 – 25 percent of patients that lack that chromosome abnormality and that's much less durable and is not approved for that, but sometimes doctors will offer it as well. Decitabine is another drug that's available that probably works exactly the same as Azacitidine and is available as a different type of regimen that's used and different types of patients could use it depending on whether they have kidney troubles or liver troubles and that will determine whether or not we use Decitabine or Azacitidine and we'll talk about the data for that. Deferasirox is a drug, another name for it is Exjade. You may be aware of that for iron overload. For patients that get multiple transfusions, there can be an excess amount of iron that accumulates that may cause problems and in the past we had to give what's called Desferal subcutaneously to remove the iron, but now there are oral iron pills that... pills that can remove the iron and chelate that. There's another drug called Deferiprone that is also available that could be used.

Okay. So, I've given you the names of the drugs and now the question is well, which type of MDS patients would be eligible or one could use for treating them? So, the lower risk patients, that is patients with intermediate-1 or low risk by the IPSS or the IPSSR classification and so anemia, we've talked about Erythropoietin or Darbepoetin. Sometimes the addition of G-CSFS can be used in patients that have what's called ring sideroblasts, a different type of abnormality in the red cell. I've told you about 5Q-, a subtype of MDS in which Lenalidomide can be useful. There's also and I'll show you some data about the fact that individuals that are relatively young and who have a lower risk disease can respond immunosuppressive therapy. One type of therapy is antithymocyte globulin, ATG, with one 4 day course can have a major positive effect on patients' diseases and so we need to be aware of that for some subsets of patients - maybe 10 percent of MDS patients.

Red cell transfusions. For individuals that have more than a total of 20 or 30 units of red cells may accumulate a reasonably large amount of iron and so if that's the case we consider the use of iron chelation. Now even though one accumulates a large amount of iron that doesn't mean it's going to cause clinical problems. It may accumulate, we see it, but whether it causes problems and whether or not treatment makes a big difference is not totally clear and it's a controversial issue. In fact, we will often consider using it in subsets of patients that have preexisting heart disease where excess iron may accumulate, but often that isn't done routinely.

Q3: Question?

Peter L. Greenberg, MD: Yes.

Q3: So with the iron overload if you don't have those other problems, do you need to go on Exjade?

Peter L. Greenberg, MD: That's a very good question. What I hope to do is go over some of the data in more detail in a moment.

Q3: Oh, okay.

Peter L. Greenberg, MD: But why don't we deal with it right now? Okay. So when one has excess iron that comes onboard, it just means that 20 or 30 units if patients have the potential for longer term use of transfusions and you're going to accumulate more and have lower risk disease, we do consider the use of iron chelation. Now as I mentioned, just because you have that doesn't mean it's going to cause problems. What are the problems? The problems could be it accumulates in the liver, heart, pancreas generally and those organs could have some abnormalities. We rarely if ever see any problems with the liver, but it's with the heart that we worry about and so it's cardiac iron overload that may be a problem that we concern ourselves with. There are specific ways of measuring this. Serum ferritin is one, but more precise there are MRIs, specific kinds of MRIs, that can look at the liver and the heart for iron overload and we do that to see if there's a problem. I'll show you some pictures in a moment, but what we found is it's rare to see that kind of accumulation in the heart unless you get very high levels of iron.

Q3: What do you consider higher excess? What level?

Peter L. Greenberg, MD: Okay. So that it usually takes not just 20 or 30 units of red cells, but maybe 40 to 60 units before that happens and that's when one can often see something like that.

Q3: What level of ferritin?

Peter L. Greenberg, MD: The ferritin level...

Q3: Does it really...?

Peter L. Greenberg, MD: ... we use in MDS the NCCN guidelines are 2,500 is something where one can consider it, but more relevant than the ferritin level is the total number of transfusions you have, so that the ferritin level is a very imprecise level. It helps you, but it's not that precise in part because the ferritin level cannot be modified by many things.

Q3: It varies.

Peter L. Greenberg, MD: Inflammation infection can cause it to be elevated. That being said, it's not just the overall amount of iron that's present, but when iron is excessive it can act in a negative way. Iron in itself, free iron, can cause problems. So theoretically, it's something that one should try to diminish if possible. What we lack is any study prospectively that says if you do it and you get rid of iron excessively it changes outcome. Does it change survival? acute leukemia evolution? There's very little... there's retrospective data suggesting that it could be, but prospective data we don't have. There is a large international trial that is ongoing now that we hope will provide some of that information. Until then I think we still are going to have a controversy.

Q3: Do you do the MRI before you start on Exjade?

Peter L. Greenberg, MD: In many study... in many places you do. Certainly, for any research study you do, but it's not something that's routinely available at all hospitals. At many universities, at our hospital we do and those where there the trials are done, it's done and that can be useful. Right.

Q3: Okay. Thank you.

Peter L. Greenberg, MD: Yeah. Yes?

Q4: In addition to that, there are certain other things that get in the way of the MRI. I have a pacemaker, which you're not supposed to do MRIs...

Peter L. Greenberg, MD: That's right.

Q4: ... and so is there another way to measure the load in your heart?

Peter L. Greenberg, MD: Okay. So, I think that that point is that an MRI can be helpful, but as I mentioned when iron is at excess we have in our blood something that buffers the abnormal iron that's present. That's a protein that's present and it's called transferrin. That can be overloaded and when that happens we have another test called non-transferrin bound iron. That's a somewhat toxic compound, which when you treat with Exjade or Desferal can go down. That's not done routinely, but done in research studies, but that is something that appears to be a good target for the therapy and is something that we do measure. That being said, we certainly need to recall that all treatments have potential side effects and one of the problems with Exjade and other drugs are the side effects and the side effects with Exjade include GI where the diarrhea can be a problem and some other GI side effects can be a problem or renal and so we need to be very aware of that. Some patients can get along well with it. Others, we have to monitor very carefully and may not be able to provide an adequate dose of the Exjade if need be. For example, if you have only 2 units a month of red cells, you can handle that reasonably with a standard dose of Exjade. Four units a month, that's more iron, double the amount of iron, you need a higher dose of Exjade to get rid of it and then the ability to tolerate the dose is a problem. The main thing I'm trying to emphasize is that yes, we have drugs that could do it. We aim not so much to normalize the ferritin level or normalize the iron overload, but to keep it from getting too high if it looks like it would be important to do. We do lack, however, the data that says even if we do that does it make much difference in a large population as opposed to in a general... in a specific individual that may have preexisting heart disease where we want to keep that from becoming more of a problem. Yes?

Q5: So with this number, it's 20 blood transfusions where you start having questions of the iron overload. Does it matter the size of the patient? So for example if you're 4' 10" and you weigh 105 pounds, 1 pint of blood is going to be much more than if it was someone like me. So, is that 20 a hard and fast number or is... or you have to do blood test to determine level?

Peter L. Greenberg, MD: Right. No, you're correct about that and so there's nothing hard and fast about 20. In fact as I mentioned, you need to go much higher. You begin thinking about iron overload at 20 or 30 units, but it does depend in part on the size of the individual. I have no question about that. Yeah. Good.

Okay. So, we've talked about the iron overload and, of course, Desferal was the prior use of chelater which was required to give you subcutaneous infusion of a medicine overnight for eight hours daily or at least five days a week which is very logistically difficult. Many patients cannot deal with that very well and so that's where the oral agents have become available and need to be considered.

Low platelet count. Now in patients with severely low platelet counts, we would like to be able to use something that would be useful. There are now agents such as that. There are two agents that are now commercially available for treating patients with severe low platelet counts, thrombocytopenia, but not for MDS. In other words, they've been approved for another illness called ITP, idiopathic thrombocytopenia purpura, for patients with liver disease and low platelet counts. We have within the next few years, maybe this year, they will become available for MDS because studies have become available that show that they are relatively effective and could be capable of being used. So, these two agents, one is called Nplate or Romiplostim. Another is Eltrombopag or Promacta. Both of them can be effective in improving platelet counts in MDS patients by themselves or frequently when we use them in combination with Azacitidine, Vidaza or Decitabine in patients where that may drop your platelet count in which you have problems with bleeding. If the platelets are too low these agents could be useful. So, the studies have been sent to the FDA and hopefully will be enough to provide some utility showing that these agents could be approved soon for that purpose. The first one is subcutaneous and this one is a pill that can be done.

Neutropenia in patients with low neutrophils, low white count that fight infection. Individuals we don't use the drug prophylactically. That is to prevent infections unless we have patients with low white counts in MDS with recurrent and resistant infections. If they're recurrent with a low white count we think about that, but often in patients that are getting agents such as Azacitidine or Decitabine, their white count gets lower and they have fevers or infections. After we give that we often will give G-CSFS or Neupogen to try to help the white count and diminish the problems with infections. So, these agents are available for that use.

So, what I've described for you then are for lower risk patients the subset of drugs that could be used and when they would be considered. Okay. And this comes back to the issue of immunosuppressive therapy. I've told you that in some younger patients with lower risk disease, a drug called ATG, Antithymocyte Globulin can be used in which a substantial proportion of patients that are less than 60, younger patients, half of them can be treated with a 4 day infusion of this drug and the patient's illness can be markedly improved and it changes as far as their long term outcome patient's can have a much better outcome and a lower incidence of developing leukemia. So for all younger patients and those with lower risk disease we look at several parameters to see could they be considered for this type of treatment and these are individuals

who usually have chromosomes that are okay, their blast count is relatively low and that's something that we do strongly consider.

Now for higher risk patients that is with patients with intermediate-2 and high by IPSS there have two type of treatment. One is lower intensity therapy which is outpatient and another is high intensity therapy which is inpatient. Okay. Now, most of you, I think, are familiar with the two drugs Azacitidine and Decitabine as to what can be used for treating this and Azacitidine is generally given as a seven day subcutaneous treatment monthly for four to six months. It can now be given IV as well. Decitabine is given five days for five days monthly for at least four cycles to get a sense of whether or not a response would occur and the responses we look for here are improvement in blood counts and in bone marrow blasts to see that that will show degree of improvement and that's been shown to have an impact, a positive impact, on outcome. In individuals that get high intensity therapy. These are individuals that are relatively younger that are in very good clinical condition with good performance status and no bad comorbidities consider high intensity therapy and that is kinds of intensive chemotherapy that is given similar for acute leukemia that requires usually a month of hospitalization and which one needs heavy supportive care in which one would consider that kind of treatment, but usually it's in individuals in which there is also a bone marrow transplant option because although it can improve counts and bone marrows for a short period of time, it may not do so as long as we would like and therefore other types of treatment is required in addition and then there is stem cell transplant - standard or reduced intensity. Again, the standard means that there's when you get a bone marrow transplant you get chemotherapy up front to eradicate the abnormal cells in the bone marrow and then there's a rescue procedure in which stem cells from a donor that matches you is infused to set up shop within your bone marrow and permit it to grow and in addition have the ability to have what's called graft versus leukemia effect. Graft, the donor cells fight against whatever the MDS cells were to begin with. However, the side effect that's also graft versus host disease. That is that graft recognizes not just the cells as abnormal, but they recognize you as abnormal and that is a side effect, graft versus host disease, which can be substantial and for which now a lot of treatment is aimed at trying to (inaudible 45:55). So, that is the difficulty with the bone marrow transplant is the graft versus host disease that needs monitoring, but which has a substantial kind of morbidity or difficulty with outcome that one needs to deal with.

Okay. This just shows you the Azacitidine, Vidaza treatment. There's a clinical trial, a large international trial that was done that looked at conventional care versus Azacitidine. Patients had a median number of cycles of 9 cycles and the overall survival was 2 years versus 15 months. So, there was a substantial improvement in higher risk patients. So, patients with higher risk disease in which 15 months would be considered a median could be substantially altered and remember when we're talking about a median survival that means half the people do better, half do worse and what determines which is which is not totally clear other than what your comorbid conditions were as well. So just because you have it doesn't mean that this is exactly the number you're going to get. It depends on many other features. Decitabine, similar long term outcome although there wasn't a controlled trial, but again for higher risk disease it looked like there was similar outcomes.

Now bone marrow transplant. So, I've told you about the methodology and outcomes. What I'm showing you here is that in patients with bone marrow transplants for all patients relapse free survival can be over 50 percent and small number of relapses and mortality can be, however, 30 percent or so in those individuals because of graft versus host disease, but when you then look at it based on what the subtype of disease is if you're dealing with lower risk or higher risk disease, you can see that patients who need it the most, intermediate-2 and high, there is still a fair amount of relapse, 30 to 40 percent of patients could relapse with that treatment. The disease could come back, but the most important component is this right here. The non-transplant, the nonrelated mortality that can occur. Twenty to 30 percent of patients could die as a result of the procedure within a relatively short time because of the complications. Now because of this, the age of patients getting standard transplant has been altered, so that usually standard transplant with conditioning with intensive chemotherapy is given only for individuals less than 60. For individuals above that it's what's called reduced intensity conditioning, reduced intensity treatment, so that the kind of chemotherapy that's given upfront is diminished and altered so that the toxicity is less and this number here is markedly altered and so the aim of that is to increase the age of patients that could be eligible and at some centers the age has gone up to 75 by using reduced intensity conditioning and some of those programs are pretty well tolerated and morbidity and mortality is much less and some degree of efficacy appears to be quite good. So, it's a bit early, but certainly there are procedures and approaches that recommend that transplant could be useful up to the age of 75 in a certain proportion of patients. Now, again, best are patients even if they have... it's usually for lower risk patients, lower risk disease. In higher risk patients that need this they often are given medicine to bridge to transplant to decrease the blast count. That is if they have 10 – 15 percent blasts, give a form of therapy such as Azacitidine or Decitabine, get the blast countdown to permit the transplant to work better. Yes?

Q5: Can the reduced intensity stem cell transplant be done on an outpatient basis?

Peter L. Greenberg, MD: There's the transplant itself can be done pretty much as an outpatient, but one needs supportive care as well and that's often done in proximity to the center so that low blood counts can occur and one needs to monitor patients for that so that if transfusions or antibiotics need to be done that could be done more effectively. Right.

Now the other issue is the fact that a substantial number of patients may not have a donor. If you have a sibling, you have a 1 in 4 chance of a sibling being a match. If you don't have a sibling that matches, it's 1 in 20,000 and there's a national blood bank that one looks for to try to find a match for you. However, there are ethnic subgroups in this country and around the world that are much less well evaluated and represented in these national blood banks and so as a result another approach is the use of umbilical cord blood. Umbilical cord blood has stem cells that can be used for transplantation and can be effective particularly if you use double cord blood units because the number of stem cells are less than in the transplant... in the bone marrow transplant and in studies that were done at Memorial Sloan Kettering and now at other places there are a substantial number of patients with acute leukemia and others and the important thing is those individuals of non-European descent can be transplanted. If they don't have a full match, that is the tissue typing match, they could be and whether or not it's standard or reduced intensity. That can also be used and the long term mortality is not distinct from what happens with standard

bone marrow transplant. However, there's still graft versus host disease, but overall the responses appear to be similar to those with standard bone marrow or blood transplants. The main point is we can now extend transplant to ethnic minorities that might otherwise not have been able to be transplanted.

This just gives you a review of what I've talked about so far as far as treatment. In blue are those individuals with relatively lower risk disease and these in red are higher risk disease and we've talked about the fact that that Lenalidomide is useful for patients with 5Q- abnormalities that younger individuals here we have hatched area less than 60 years of age. These individuals can respond to immunosuppressive therapy such as Antithymocyte Globulin. In individual with ring sideroblasts, they may need both a combination of Procrit and G-CSFS and if they don't respond... if individuals do not respond to these there are clinical trials that one goes to for the next step. Higher risk disease, we usually use Azacitidine or Decitabine and if that doesn't respond then a clinical trial and these in hatched areas, the younger patients, may be candidates for transplant. As you can see at the moment, the number of patients eligible for a transplant are relatively small and hopefully that will be expanded as the toxicity and tolerance of that procedure is improved over the next few years.

Now, this gets us back to iron overload and the MRI. Just to show you what the MRI can do and there are now ways a picture whether or not patients have iron overload so that yellow indicates where there's excess iron and you can see that it can be quite distinctive in patients with different forms of iron overload conditions and these are ways that the MRI can be useful. As I mentioned more relevant than this is with the heart MRI rather than the liver right here is what the liver picture shows, but you can do the same thing with the heart.

Q6: Does it really hurt the liver that much to have the iron overload? I mean, you can function with just a little bit of your liver, so is that a big concern even?

Peter L. Greenberg, MD: That's right. So it's rare that we've ever seen that patients with MDS have liver failure as a result of this, so that even though you see a lot of iron in the liver that's not usually the issue that we worry about as opposed to a heart problem.

Q6: What about in the... You said in the pancreas.

Peter L. Greenberg, MD: That's right. So, diabetes can occur. Yes. So, that can occur and we see that not infrequently and one needs to be concerned about that although the diabetes can be treated either with pills or with insulin. Right.

So, to reiterate 20 to 40 units, further transfusion need, mainly lower risk disease or in patients that may have the opportunity to have a transplant. Those individuals, there's some evidence to suggest that giving chelation therapy and diminishing iron overload can be useful pre-transplant for such individuals, but it's really a prehistory of cardiac abnormalities that are a problem. The serum ferritin, we aim to try to decrease the ferritin levels, but it's really the iron overload by MRI.

Okay. So, I've told you about the standard treatments and that at nearly all medical centers there are clinical trials that are going on for patients that don't respond to standard therapy and at Stanford we have trials for lower risk and higher risk individuals and we had a trial that has just been completed with regard to the iron overload and as I mentioned, we still need a larger prospective trial to be sure that it will work. Right now, the use of Azacitidine or Decitabine and the platelet stimulating agent has been completed. As I mentioned it appears that that platelet agent appears to be useful and we're waiting for the FDA to see whether they will approve it. There's a drug called Rigosertib which is a kinase inhibitor which appears to be potentially useful in patients who have anemia, lower risk disease and may not have been able to respond to standard therapy and that would have been, as I mentioned, Procrit or the Azacitidine and so clinical trial is ongoing now using this pill to see whether or not it will be useful. For higher risk patients, those that have failed standard therapy, have failed to respond to hypomethylating agents such as Azacitidine or Decitabine. Again, this Rigosertib given in higher dose IV is something that has recently been evaluated. In fact, there was a large what we call phase 3 randomized trial, about 300 patients in which patients were evaluated either with this drug versus best supportive care and although all patients did not get benefit, it appeared that those patients that had failed to respond to the Rigosertib did have an improvement in overall survival. That drug is now being looked at in a more extended phase to see whether or not the toxicity and tolerance will be useful and has gone to the FDA to see if it will be approved. So, that's a trial that's ongoing now at Stanford and other places. There are trials looking at other agents in addition to Azacitidine to see whether they'll be useful and in some situations they are, in others not clear and trials are ongoing. There's further trials looking at the platelet stimulating agent and there's a new agent that's an anti-ephrin antibody. Ephrin is... Ephrin receptor is present in fetal tissue and usually not in normal tissue, but it's present also on tumor cells and so the question is if we can attack the tumor cells since normal tissues in adults are not there will that be useful and so that trial is ongoing at Stanford and we're beginning to look at that to see if that will help the bone marrow of these higher risk patients and then the combination of Azacitidine and Lenalidomide in a portion of patients could be useful as well and these trials are ongoing in addition.

So just in near summary here, let me just say where we are, where we might be going and that is directions are can we have what we call bio specific treatment and that is depending on what the marker is, is there a specific chromosome or molecular marker that is present? Can we use that as a target for therapy, be more specific and perhaps less toxic. Randomized trials. Looking at standard versus reduced intensity transplantation and certainly quality of life assessment should be part of any clinical trial to know that we're doing reasonably alright. The laboratory focus really now as I mentioned the next generation looking at these molecular abnormalities that are present, looking at the stem cell and the environment where the stem cells sit and cost effectiveness as well. These drugs, as you more than I know, are extremely expensive and are problematic and the medical community has tried for a long time to try to modify dose and drugs costs and there needs to be some forum, series of forums, where all the involved individuals all (inaudible 1:01:01) individuals are involved to try to come up with ways of financing these drugs in a more equitable way.

Information resources. You're here today. That's part of what the MDS Foundation does and so there's lots of paperwork for that, but the Aplastic Anemia and MDS Foundation is another source. Leukemia and Lymphoma Society, the National Comprehensive Network is also availability to look at what your physicians and others have access to. At Stanford Medical Center you see at Stanford Medical Center, others are available as well.

So, I hope I've given you a reasonable overview of where things are, where they may be going and I open it up now for questions so that we can spend some time getting at what further issues you'd like to talk about. Thanks very much.

(Applause)

Q7: Okay. Dr. Greenberg, what happened when you have increase of blasts in your blood? What is happening with the bad blasts? Would it go in other part of body, create tumor or how would that handle the body?

Peter L. Greenberg, MD: Right. When you see blasts in the blood, they usually are a reflection of the activity in your bone marrow. So, those blasts in the blood even though they're there, they're not going to go anywhere and cause problems. It's really the bone marrow blasts that are the problems because they can interfere with the function of your bone marrow. That is cause anemia, low platelet count, low white count and so... and that's a marker for the disease maybe progressing a bit and the idea is to try to decrease that. So, I wouldn't worry as much about the blasts in the blood as opposed to it being a reflection of what is going on in the bone marrow. Yes?

Q8: Just a couple of things. One is in answer to you, it was Medicare that prohibited our doctor from upping it to 80... 80... I don't know, units, whatever they're called... We worked up to 60. It was working fine. He thought maybe a boost to 80 might help and Medicare said no. Is that a doctor's decision or is that a financial decision?

Peter L. Greenberg, MD: Well, what Medicare often does is base it on what the literature has said and so the literature had shown that 40,000 to 60,000 units once or twice a week could be useful. There's no evidence that 80,000 by itself would be as opposed to 40,000 units twice a week and that's in the NCCN guidelines. So, the NCCN guidelines are often a source for what Medicare uses and so they should have been able to approve it based on that.

Q8: Or go around it. Going twice a week and...

Peter L. Greenberg, MD: Right.

Q8: Yeah.

Peter L. Greenberg, MD: That's right.

Q8: The other question I have is I'm on my sixth month of Revlimid and it just suddenly took a turn for the good we think. We have to do another blood test tomorrow or I mean on Tuesday, but is there a rest period after you stop the Revlimid before you start a clinical study?

Peter L. Greenberg, MD: Okay. So, that is... the answer to that isn't well known. In most cases, people have continued and it's the same thing with Azacitidine. If you respond, the question is can we stop. Anecdotally people have found that if you stop it becomes more difficult to restart and have efficacy. So generally if people respond, we stay on there. Now with Revlimid, there are two different regimens. One is daily and the other is 21 out of 28 days.

Q8: Yeah. That's what we're on.

Peter L. Greenberg, MD: And so that is what is often done and a certain dose minimum is probably important to maintain the efficacy.

Q8: Right. Okay. Thank you.

Peter L. Greenberg, MD: Yeah.

Q9: Kind of on that same subject back to the Procrit. If you're on 40,000 and you're (inaudible 1:05:14) your blood transfusions, does it do any really do any good to go to 60,000 or go to twice a week?

Peter L. Greenberg, MD: It may.

Q9: It may?

Peter L. Greenberg, MD: So, in individuals that had a response to 40 and are losing that response and you're now not getting it, we often do go to 60 to see whether or not that will be useful, number one. The other alternative is the addition of G-CSFS. G-CSFS or Neupogen appears to be synergistic. That is it can work together and in about 20 percent of patients it may be useful particularly if they have ring sideroblasts...

Q9: Which I do.

Peter L. Greenberg, MD: ... as part of there so that in fact people with ring sideroblasts that's the first thing you do is you often use the combination because G-CSFS appears to permit the red cell stem cell to survive better to be able to receive the EPO signal. So, that combination is often what can be useful.

Q9: Does it matter though that I've already been on it for like 3 years of 40,000 units.

Peter L. Greenberg, MD: Well, if you've responded and now you're not responding as well, the use... the addition of G-CSFS could be useful.

Q9: Still.

Peter L. Greenberg, MD: Yes.

Q9: Oh, okay.

Peter L. Greenberg, MD: And important is the dose. That is there are different doses of G-CSFS that are used. In patients that are getting chemotherapy is a relatively high dose that's given afterwards to help the bone marrow, but in individuals that are not getting chemotherapy it's a relatively low dose of G-CSFS that's used in which the NCCN guidelines essentially indicate how it should be given.

Q9: Okay and just one other quick thing just on the Revlimid. If you have the 5Q and you're on... I take transfusions every 6 weeks. I've not started my Revlimid but my ANC is .5. What are the risks there of going onto it now with such a low ANC?

Peter L. Greenberg, MD: Right. As you know, the side effect of Revlimid the first degree side effect that you have is a low white count and platelet count. Both of those can be substantial. So, one needs to be wary of that. Now, you then have to weigh in the case of what is your chromosomal abnormality? In other words is it 5Q-?

Q9: Yes.

Peter L. Greenberg, MD: By itself or with...

Q9: By itself.

Peter L. Greenberg, MD: By itself. So using it by itself, yes, it can be used and one would often move in with it at a somewhat lower dose to begin with, let's say 5 as opposed to 10 milligrams a day, and then monitor carefully and if need be to add in G-CSFS to get your white count up to a good level.

Q9: But there is a big risk of starting it and it could affect my quality of life of being able to go and do things.

Peter L. Greenberg, MD: The only quality of life difference that would occur is if you get an infection. That's right. So, that's where one needs to consider that and then use G-CSFS if need be. So, you have weigh in how much the transfusions are causing problems compared to what would happen if you were to alleviate the need for transfusions.

Q9: That's true. There's no cutoff then on the ANC of starting... If I even go lower, I would still have the option of starting Revlimid.

Peter L. Greenberg, MD: With the low count there is and so you'd use a lower dose to begin with and then you would add in G-CSFS.

Q9: Okay. Thank you.

Peter L. Greenberg, MD: Sure. Yes?

Q10: So, I'm concerned about multiple transfusions and the iron overload, but prior to doing an MRI which I'm sure insurance would scrutinize the liver and the heart and the pancreas, wouldn't there be lab values like metabolic panels that would show that there's a problem happening with the pancreas or with the liver prior to doing an MRI?

Peter L. Greenberg, MD: Sure. Yeah. We routinely do that. In other words when you get a clinical screening battery, those... and that includes liver function tests and blood sugars. So, those are done routinely and would monitor to see if there are any problems going on. Cardiac evaluation is done clinically. When the doctor examines your heart, gets your symptoms, gets a sense of what's going on. So, those are things that need to be monitored in a routine way. No question about that.

Q10: So, once they're low or they're off the normal ranges then an MRI would be indicated?

Peter L. Greenberg, MD: It might be. As I've tried to say even though the abnormalities are there, whether one can impact that positively remains to be seen so that even though we do that even though we use Exjade and we can make a difference in some of the numbers, will it change your overall life expectancy? Will it change the development of acute leukemia? That isn't clear. You're going to find if you're to go to the literature a great debate about this and some people would be proactive. Others would require more data to say this is something that we need to be very practice on. If someone young enough that might be in need in the future of a transplant, that's a plus... that's a reason to really strongly consider iron chelation to diminish iron overload for someone that might need a transplant in the future decrease the toxicity of the transplant. So, that certainly needs to be considered. Yes?

Q11: If you're transfusion dependent and you use to every pint go up a point and then now suddenly it after the transfusion, it isn't up a point. It's maybe like two pints it would go up two points is now just a point and a half or even less. Is this a progression of a response because of your... of MDS or is this you're getting not great blood or something? I just wondered that and also when you do your CBC, sometimes the numbers are so off. Can they be off enough so that one week, it's up, it's down, it's up and down. I just wonder how consistent should all those numbers be.

Peter L. Greenberg, MD: Right. It's a good question. That's not an uncommon problem patients have. Be aware that blood in the blood bank is there red cells lasts for about five weeks. If you're getting blood that's four and a half week old rather than one week old the blood cells will live less than the younger ones. So often what we try to do is to alert the blood bank for patients who have bone marrow that is poorly functioning compared to a, let's say, a younger individual that come in with a big GI bleed. They can get red cells, their bone marrow reacts reasonably, but in individuals that aren't able to produce much red cells, we try to get relatively

young blood that would last longer. So, it may be that your doctor would need to look at what the age of the blood cells that you're receiving is to help you understand why you're not getting as big a bump as you might, number one. Number two, it's feasible that one can develop antibodies over time. A blood bank is usually well aware of that and do monitor that carefully, but occasionally an antibody pops up suddenly and then all of a sudden you break down things more readily. Another issue is your spleen. Sometimes in individuals with MDS, the spleen starts getting a little large. The spleen doesn't cause problems usually in MDS, but it can be a trap for red cells. So, transfused red cells can be trapped a little bit more. Usually, that's one of the things that's going on. Occasionally, it's also related to your bone marrow not working as well as it had been. If you initially required two units a month and now are requiring four units a month, it just means that your ability of the red cells to make useful red cells is diminishing and is a marker of its contribution related to disease progression. So, if that's going on and you used to rely on that that means your bone marrow could be showing some degree of progression as well.

Q12: Quick question on the fresh... I'm sorry. Were you done? The fresh versus old blood because I have always questioned that like I always write down the date and not too long I got when they were going to expire within 24 hours and I thought this is not going to last long and I'm from Bakersfield where I just go to a... you know, it's a local blood bank. What order can I ask for them to put on there that I would receive fresh blood? I mean, I have questioned this before and they look at me like I'm crazy.

Peter L. Greenberg, MD: Right. It's really your physician that needs to call up the blood bank and he needs to say to the head of the blood bank please for this patient can you use relatively young blood? One of the problems will depend on whether or not you have known antibodies. In other words if you do, it's more difficult to find a donor to come in at regular intervals but that can be scheduled. I mean, if you have a specific set of donors that come in then it can be scheduled at intervals. If you don't have antibodies then they should be able to do this a little bit more regularly.

Q12: At least look at it if like you said, I mean, it's so much... somebody that loses a certain volume, they're going to rebuild whereas I can't rebuild and I need that fresher and I like the blood bank if they... sometimes we have shortages, but if they have it so it's the physician that can just order it each time. He would have to need to probably call?

Peter L. Greenberg, MD: He should be able to say for each time you get it...

Q12: Give me the freshest.

Peter L. Greenberg, MD: ... compared to the other 80 to 90 percent of patients that don't have bone marrow failure problems should... you would be one that should get that.

Q12: Okay. Thank you.

Peter L. Greenberg, MD: Yes?

Q13: I don't understand foreign languages like medical terms, but we read about Dexamethasone added to Revlimid. Is that possible? D-E-X-A...

Peter L. Greenberg, MD: Oh. Okay. Dexamethasone. Okay. It's a form of steroid and you're raising an important point. This is new information. It's not as well understood in literature as should be, but it does turn out that Dexamethasone which is a variant of a steroid like Prednisone. You probably heard of Prednisone. That's more powerful, can be additive to Revlimid for patients that who had responded to Revlimid initially and don't respond as well and in part because it works... There's a mutation that can occur in patients with 5Q- and that mutation can be modified to a bit by the Dexamethasone. So yes, for patients with that subset that are responding Revlimid and then stop responding, the addition of Dexamethasone can be helpful.

Q13: Okay and that would be checked by the doctor. Right? I mean, is...?

Peter L. Greenberg, MD: Right.

Q13: Just for the history as it comes because Revlimid for me did nothing except improve the whites and the platelets, put them in the right spot, but didn't affect the reds. They kept doing their same fading act through the month until this last week when it jumped and so we're hopeful that's how long it took. This is the sixth 21 day period I'm in now.

Peter L. Greenberg, MD: So if it works for your red cells well enough by itself fine. If not then the addition of Dexamethasone for a finite period. You'll know within a month whether or not it's additive or not. It's something that could well be considered. Yes?

Q14: Does a diagnosis of unclassified MDS eventually evolve into one of the more defined subtypes?

Peter L. Greenberg, MD: Could you say that again? I couldn't hear.

Q14: Does a diagnosis of MDS unclassified eventually evolve into a more defined subtype?

Peter L. Greenberg, MD: Often. MDS unclassified means that you don't really have any cytogenetic abnormalities that are as clearly shown and the morphology is not as obvious, but often it does evolve into something that's a little better recognized and the responsiveness and its outcome in great part depends on the blast count. If you're dealing with someone with a low blast count, they usually do pretty well for a longer period of time than with a higher blast count and therefore the treatment depends more on that than for anything else. Yes?

Q15: I'm wondering if you could explain like Linda receives the Procrit 40,000 units once a week for 4 weeks then she's retested, her hemoglobin, to meet this, what I call an arbitrary criteria of 12.0, but the hemoglobin spikes on her. The doctor says that the Procrit bumps the hemoglobin a quarter of a point max. Is that your understanding?

Peter L. Greenberg, MD: Well, it can vary. It depends on where things begin.

Q15: Well, for instance, she starts off at 11.9, has 4 shots and then a test at 13 and change. So, there's no Procrit. Next week it peaks at 13.8, the next week it comes to 13.6, the next week it goes 13.2 then the next week it goes to 12.2 and then the next week we hydrate and it goes to 10.4. That's the other question. Dehydration does affect the hemoglobin test, does it not?

Peter L. Greenberg, MD: Yes, it does.

Q15: It would elevate her. Right?

Peter L. Greenberg, MD: That's right.

Q15: Artificially elevate, but well, certainly, the hemoglobin is what it is. So if you hydrate, she gets a unit of saline and then you retest, you get a more better idea of what's going on, but I can't understand why her system quits working and then it seems like it all of a sudden does work and it's not all due to dehydration because her... she's almost near normal. That's why we're trying to get him to get it above 12.0, but I can't figure out why it peaks and then all of a sudden the slope of that line when it takes off down is like this.

Peter L. Greenberg, MD: Okay. Most patients that are symptomatic from anemia with MDS, the hemoglobin is below 10. In fact we're getting down 9, 8, 7. So if we ever see a patient at 11 and 12, we're very happy. You know, we would love it. Okay. So, what you've raised though is an important point. Dehydration. You're absolutely right. Patients that are dehydrated, you concentrate the blood a little more and it goes higher and people that are dehydrated can be symptomatic. So, the real question is why does she get dehydrated? There are medical reasons for dehydration that need to be dealt with and giving saline at intervals is one way to deal with it, but the question is why. Why does she need it? And I think that that's something that should be focused on for her a great deal. The difference between 11.5 and 12.1 that's almost irrelevant from the point of view should it make any clinical difference, but so I think the main thing is why the dehydration is there and then if one can deal with that prospectively that might help some of the fatigue.

Q15: Well, we're dealing with it by hydrating, but you're right. What's the underlying cause? It could potentially be failure just to drink enough fluids.

Peter L. Greenberg, MD: Well, that's part, but there are many other reasons to become dehydrated that relates to kidney function, cardiac function, electrolyte balance. I mean, those are medical issues that your doctor should be able to focus on for you and for her and to see what can be done about that.

Q15: The oncologist or someone else?

Peter L. Greenberg, MD: Say that again, please.

Q15: The oncologist or someone else?

Peter L. Greenberg, MD: Well, oncologists are internists. So, all internists deal with this problem routinely and so it also could relate to the medications whatever medication she might be on that could be playing a role in some of this. So, those are issues. Do you have a generalist as well as an oncologist?

Q15: Yeah. You mean the primary care physician?

Peter L. Greenberg, MD: Yes.

Q15: Yes. She has that. She has a cardiologist. I'm sure these people all have their extra doctors too and we've looked into that trying to define why she's becoming dehydrated, but she still symptomatic at up in the 13 range – tired, lethargic and some of the symptoms are due to dehydration, I think, slurred speech, blurred vision and stuff like that. That all define... the skin test. So, there's all these things that are showing that she's dehydrated and we hydrate her, but the peaking of the hemoglobin. You're saying even though those seem like large movements, they're small movements?

Peter L. Greenberg, MD: Yeah. Those numbers you've given are small for hemoglobin and, again, it's unlikely that her fatigue is related to the degree of anemia as opposed to the cause for the dehydration. So, I think that a lot of focus needs to be provided on that and either your internist or oncologist could certainly look into that in some detail.

Q15: Yeah I think because basically what our program is is she gets her series of shots and then the week that she's going to be tested she's hydrated, so we can get a base of more reasonable baseline of the hemoglobin as well as drive it down below 12.0, so she can get her shot. I mean, it's a crazy thing that we do. So, you think that there may be some other causes for her fatigue and all that?

Peter L. Greenberg, MD: Yes. Yes. Yes. That's what I'm saying.

Q15: God. We've been thinking that for a long time. I guess we should talk to the doctor a little more about that. Thank you.

Peter L. Greenberg, MD: Sure. Okay. Yes?

Q16: Eight months ago my neutrophil was .8 now it's .4. Actually, that's my only problem. Everything else is fine. I'm at risk. Can I have a bone marrow transplant or...? It isn't MDS. I don't know.

Peter L. Greenberg, MD: Well, as I indicated before, a lot depends on these other features. In other words what your bone marrow blasts are, your chromosomes. Say that again, please?

Q17: He doesn't have any blasts.

Q16: No blast.

Peter L. Greenberg, MD: Okay and your chromosomes.

Q16: Everything is fine.

Peter L. Greenberg, MD: Okay. You've had a very low white count by itself. Is that right?

Q16: Yes, it's 2.8.

Peter L. Greenberg, MD: Okay. One needs to be very strongly considering other possibilities of your low white count possibly being related to something else rather than just MDS and so reviewing your bone marrow slides, your blood counts and other things would be helpful to be sure that there are no other illnesses that could be causing that because that's an unusual thing you've just described. It would be worthwhile having that reviewed.

Q17: What test would that be then because on the CBS you won't be able to tell?

Peter L. Greenberg, MD: Well, no it would need someone else to look at the bone marrow to see if the quality of the smear, the bone marrow smear, to be sure that there is in fact adequate dysplasia to say that in fact you do have MDS compared to another illness. There are other ways of looking not just a matter of looking at the blood counts. It's having a hematologist review the case anew.

Q17: So if it is MDS, what's the option is other to take Vidaza or to go straight to a bone marrow transplant. I mean, we've been approved to... He's been approved to do that to do the bone marrow. He's got a donor. He's not too old for it and he's has no other illnesses. Otherwise he's healthy, he exercises every day. He doesn't feel weak. He feels normal. So, the question is do we take... does he have to take Vidaza or he's willing to do the bone marrow transplant, the reduced one anyway.

Peter L. Greenberg, MD: Right. So, a lot depends on being sure the diagnosis. If one is sure of the diagnosis then one has to weigh the issues that I've just raised up here, the pros and cons of it and how you're doing. For example, if you have a low blast count and all you have is a low white count, have you had many infections and you haven't had many infections. You go about your business. You're doing alright.

Q16: No, I'm fine.

Q17: But the platelets are...

Q16: I feel better given my...

Peter L. Greenberg, MD: What about your platelets?

Q17: It's 65.

Peter L. Greenberg, MD: Oh, so your platelets are low as well. It's not just a matter of your white count. So, it's a different story. So, I think that when you have a combination like that one needs to worry about the fact that your disease could be moving forward. How old are you?

Q16: Sixty-five.

Peter L. Greenberg, MD: Okay. So, you're young.

?: Thank you.

Peter L. Greenberg, MD: Right. So, it's something to be considered and I'm sure you and your doctor have talked about the pros and cons and you're debating about that right now. It's not an easy decision. It's not something we can make here, but it's certainly something that would be considered depending on how your disease progresses.

Q16: Do biopsy bone marrow.

Peter L. Greenberg, MD: When was your last bone marrow?

Q17: April last year. I think you have an appointment for next month.

Peter L. Greenberg, MD: April a year ago.

Q16: A year ago. Yeah.

Peter L. Greenberg, MD: So often one would do certainly before a bone marrow transplant would be done they'd repeat a bone marrow beforehand to see if things have progressed in any way and they'd want to know if your platelet count... you've just mentioned your platelet count is a bit lower. Your white count is a bit lower. Now would be a good time to repeat a bone marrow to see if things have changed which would give you an idea that things are moving. Now might be a time for the transplant. Yes?

Q18: I have a question regarding risk and with a low cellularity and low ANC less than 500. If one was looking at ATG or going onto hypomethylating agent, which is going to run the higher risk for infection with either one of those 2 treatments and the second part of the question is what about just using Cyclosporine by itself and not doing ATG.

Peter L. Greenberg, MD: Right. So as I mentioned, individuals less than 60 years of age that have this and there are other features, HLA subtypes and a few others that gives you an idea of a response rate of 50 percent or so if have this with ATG. ATG by itself shouldn't cause much in the way of infection. The problem with ATG is there's a side effect called serum sickness in which one can get flulike symptoms, aches and pains and as a result you get the treatment for 4

days in the hospital and you get steroids, Prednisone to try to diminish that. So, that's unlikely to cause infections during that period of time.

Q18: Don't those drive your white counts down though?

Peter L. Greenberg, MD: No.

Q18: No.

Peter L. Greenberg, MD: And steroids, in fact, will raise your white count, but the Azacitidine could. In fact, you'd have to modify the dose of Azacitidine for somebody that starts out with a very low neutrophil count.

Q19: Hey, doctor, on this...

Peter L. Greenberg, MD: He's not finished yet.

Q19: I'm sorry.

Q18: And the cyclosporine.

Peter L. Greenberg, MD: So, cyclosporine. Cyclosporine can work as well, but it's less effective than ATG. In fact, ATG plus Cyclosporine is what is generally used, but in a portion of patients the cyclosporine could be useful. It depends on how urgent the situation is, whether or not to treat with full doses or just the Cyclosporine. Yes.

Q19: Yes. This hydration problem they were talking about before. Is that affected by low serum sodium?

Peter L. Greenberg, MD: Well, that's the other way around. In other words, low serum sodium, there are two causes for low serum sodium. Either you're not taking in enough salt or it's being diluted by too much water. So, the sodium level is one important measure of level of hydration, but there are many other measures of degree of hydration that one needs to consider. Yes.

Q20: When do you consider, I guess, you have to apply to be in a trial, a clinical trial? Now, do you wait till all your options are exhausted or do you wait... do it intervene in between so that you still have options in case the trial doesn't do anything for you.

Peter L. Greenberg, MD: Right. Well generally, one would use standard therapy for an illness whatever the illness is and that's been something that's been proven by prior data trials that have been done. By definition a clinical trial means you're going to have an experimental agent for which we don't have enough data to know the answer. So usually, you start out with standard therapy and if that doesn't work then you move onto a clinical trial at that point.

Q21: Not simultaneously.

Peter L. Greenberg, MD: You can't really do it simultaneously. You need to give, for example, standard therapy a finite period of time, but that finite period of time needs to be defined. In other words if you're starting on Procrit, for example, and it works within a month or two fine, but you don't wait a year to find out if Procrit is going to work. Azacitidine, you get four to six months. If it works, stay on it. If not then you consider... So, the main point is standard therapy has a finite time to know if you're going to respond and if you don't then you consider a clinical trial.

Q22: (inaudible 1:33:22) in a trial with a (inaudible 1:33:26)

Peter L. Greenberg, MD: Well, you would, but you wouldn't want to get in a trial where it precludes standard therapy unless you know whatever you're going to has a clear cut track record and by definition we don't know the answer to that yet for experimental agents.

Q22: And you want to make sure, I'm guessing, that (inaudible 1:33:50).

Peter L. Greenberg, MD: So, what you're asking is a different thing. In other words, a three phase... three types of trials. There's phase one, two and three. Phase one trials are trials with initial dosing of drugs where you want to know what the dose is. What is the dose that is effective and tolerated? Okay? So, that's a relatively small trial where everybody gets a drug. Phase two trials say okay, we figured out the dose. Let's see if it's effective in a larger group of patients. That's a phase two. Everybody gets the drug. Generally in phase three trials, that's when you want to then compare this new drug against either the prior standard or against a placebo and there is a placebo related trial. Often they're two to one. That is two patients will get the drug, one will get the placebo, but that's a phase three trial in which, yes, some people would then be getting a placebo and you're told about this up front.

Q22: (inaudible 1:34:58)

Peter L. Greenberg, MD: Yeah. I mean basically what you do is you ask are there experimental agents and for your particular problem and then you would go to the institute that has agents that will tell you are these phase one, two or three trials and what your options are. Are you eligible and then you're given a choice of participating or not depending on what the eligibility criteria are. Yes?

Q23: To decide to start on an ATG when you're having no symptoms, is there a level of that CBC comes back that you would say now you would want to start because it's hard to choose something like that when you're feeling good and to (inaudible 1:35:44).

Peter L. Greenberg, MD: That's right. That's right. So, I think if you're feeling well and remember that one of the criterion for treatment is symptomatic cytopenias. If you're not symptomatic and blood counts are not changing, probably there's no reason to engage in that kind of treatment.

Q23: Well, blood counts are changing, but at what point do you decide even though you're still feeling well is there a...

Q24: We don't want to wait too long till your blasts get too high also.

Q23: Right.

Peter L. Greenberg, MD: Right. So usually, it depends on what your blood counts are showing. In other words, if you're having anemia, but it's only mild about 10 – 11 and your other counts are not a problem that's fine. We look at counts to see if things are moving. If they're stable and asymptomatic probably don't have to do anything. Things are moving and you repeat a bone marrow, see whether or not there's a change in there in which case you would consider some intervention.

Q23: Okay. Thank you.

Peter L. Greenberg, MD: Yes?

Q25: Dr. Greenberg, I understand that you are eligible for more clinical trials if you have not had any standard treatment before.

Peter L. Greenberg, MD: No, that's not true.

Q25: No? That's not true?

Peter L. Greenberg, MD: In fact most clinical trials require you to have had standard treatment before you're eligible for an experimental agent. There may be a few others that want no prior treatment, but in general not. Now, there might be some trials in which let's say Azacitidine you want to use that and individuals... Azacitidine plus something versus Azacitidine alone. That could be a trial where you can't have had Azacitidine beforehand. So to get into a trial with a combination. That's true, but at least part of that trial would be Azacitidine alone. Yeah. Yes?

Q26: I've heard of people going straight to stem cell transplant. Is that something that's becoming less or more popular? Who are these people that and why would they do that and then also the second part of that question is it seems like you're always trying to get people's blast counts down. It's almost like pulling them into a lower a lower intermediate class in order to do those procedures. How does all that correlate?

Peter L. Greenberg, MD: Right. I think that as mentioned, the indications for transplant depend on risk to a certain extent. One has to balance the risk to the benefit and the risk is substantial. So for a low risk individual who has the longevity that's reasonably good, a little way of problems at the moment, you ask is it worth taking that risk as opposed to somebody that has higher blast count in the bone marrow with the potential for developing acute leukemia. Do we want to modify that? So, when you say some will go immediately to transplant, a lot depends on what their status is at the time. In other words, are they higher risk and good condition? Yes, those

individuals probably should go to higher intensity therapy soon... sooner rather than later. Lower risk patient you would wait. In fact they probably wouldn't take you as a transplant candidate if you're low risk. Intermediate-1 is the one group that is not clear and there it would depend on what are the other counts, how are they doing, are you red cell transfusion dependent, how symptomatic are you and then it comes down to personal choice of whether you want a long term or short term solutions that each individual has to make their own choice about.

Well, thank you for your patience and for persisting throughout this. I hope that this has been useful and it's good talking to you.

(Applause)

Lenn Fechter, RN, BSN: So, I want to thank Dr. Greenberg for staying extra. He stayed way after to answer your questions. Thank you.

Thank you very much.

So, I do want us to stop at 12 o'clock because lunch will be ready and also when we stop think about we want to get a group picture. So hopefully, we'll do that quickly and then we'll go on with lunch. My part today was to talk to you about the *Building Blocks of Hope*. That's part of your guide that you got today that the MDS Foundation has put together and a lot of thought and a lot of expertise went into it. So, we'll go over it quickly. You've got it all to take home with you today and it's also on the Internet. So, we don't have to spend a lot of time on each slide.

So again, the MDS Foundation has a large group of nurses in their leadership board from all over the world and they do a lot of work for patients all over the United States and all over the world. The *Building Blocks of Hope* is something... a tool that they put together for you to understand your diagnosis – how it's diagnosed, what the treatment options and also goes in a little more deeply about side effects of the treatment, what can be done to control them and what treatments are on the horizon to treat patients like the clinical trials that Dr. Greenberg told us about. They talk about the consequences of blood transfusions because most people with MDS if they're not getting them at the beginning may, in fact, someday need blood transfusions. They talk about iron chelating, how to select a bone marrow transplant center, how to select a physician and when to get a second opinion and also how to keep yourself healthy because that's very important. We all know that about 30 to 40 percent of patients with Myelodysplastic Syndrome can progress onto an acute leukemia. So, it's important to keep yourself as healthy as you can. Just like other people that are avoiding cancers. You're also a patient that's at a higher risk for cancer because you could progress.

So, Dr. Greenberg did a really great job about telling us about the IPSS and IPSSR risk categories. The *Building Blocks of Hope* will go more into talking to you about when you're choosing your treatment options how does it affect your life and your quality of life. How do you make decisions about where you're at when you want to treat and how you want to treat? You want to consider the schedule of the treatment option that you're considering. Is it an oral pill that you take at home or do you have to go to a center to get an infusion or an injection for a

week out of every month? For some people it's really difficult just to put together the transportation to get there and for some people the center isn't close. So, there are a lot of things to think about if you haven't already and a great way to get answers is to be in a group of people like you're in today to meet people and ask them how did they do it, what resources are available out there and that's something we'll talk more about this afternoon.

So, what is MDS? Again, Dr. Greenberg really went over that for us. Bone marrow cancer. It's clonal. It's not one disease. It's an umbrella of many different things. Every individual that has MDS in this room is a little bit different, if not a lot different, from the others. Cells are abnormal and Dr. Greenberg mentioned the word 'dysplastic.' It means that they look funny. They're not the right size or shape that they should be. They don't work well and it leads to ineffective hematopoiesis. So, there might be a lot of cells in that bone marrow. They might be young cells and they might be packed and they can't get out into the circulation. So, there's some reason that you don't have enough blood cells out there available for use. There is that risk that I said about developing leukemia in some cases. Not all patients have that same risk. Very low risk patients just by definition they are not as high a risk to get leukemia.

So this depicts normal, healthy bone marrow. You have a hematopoietic stem cell which is the pink one there on the left right here and it goes on and differentiates into all these other normal white cells that are in the bone marrow, but that's under ideal situation and for most normal healthy people, but in MDS there are factors that affect either the bone marrow or the stem cell and it can be the cells in the bone marrow that are nourishing the bone marrow cells that are going to be made in blood cells. Something goes wrong with that or it's the cell itself that starts having problem, but the outcome is that there tend to be a lot of immature precursor cells that, like I said, come and pack that bone marrow and they can't get out. They don't differentiate and become normal adult cells. So, then you get the peripheral cytopenias which means in your blood out in circulation not enough cells.

How do you diagnosis it? He went over that very nicely, too. Usually, you start with a blood count and people... It's picked up at different times for different people. Sometimes people will just go in for a regular checkup. They have a CBC and something doesn't look right or maybe they haven't had a CBC for a while and they get a horrible infection and they're in an emergency room in the middle of the night and they get told that your blood counts don't look right and we're going to recommend that you go see a doctor and get a bone marrow check. You might have MDS.

So, the bone marrow biopsy and aspiration is a lovely test that people go through in order to get diagnosed because you can't really diagnose MDS just from the peripheral blood. It's a diagnosis of inclusion meaning you have to have certain criteria, but it's also exclusion. You also have to rule out some very basic things before you go on to diagnose MDS. So, your doctor is going to test you not only with a bone marrow biopsy test, but before he even sends you do to that he's going to check your iron level and your nutritional status with your B12 and folate to see if there's something simple there that can be corrected that can help your bone marrow to make more blood cells. People who drink excessive alcohol can have... effect their bone marrow and they can have counts. So, part of examining a patient is to talk to them and ask them about what

their habits are and consider whether or not that can be affecting their bone marrow. Erythropoietin is made by the kidneys and sometimes when the kidneys are stressed and go into insufficiency over time the EPO level will go lower. So people with kidney failure have low EPO levels and don't necessarily have MDS. They can get those Procrit shots and their blood cells counts come up. So, you want to make sure that all of these things are tested for before you get a diagnosis of MDS not that you couldn't have these things together. Sometimes people with MDS you'll find that they do have a low EPO level, a low B12 level. So, correcting that at the same time adds extra benefit.

So, classification systems. Dr. Greenberg went over that as well. They help to decide what kind of treatment you get and also what your risk is over time of getting worse disease. IPSS and IPSSR, Dr. Greenberg is the expert on that and he talked to us about that.

So like he said, all of these things are available on the Internet. The revised IPSSR score can be looked up on the MDS Foundation website and also at other places. It's a bit complicated, but when you get it in front of you with your doctor and you sit down and plug in the numbers you can find out a little bit more about what's your prognosis and keep in mind when you look at that that the number of years that they have down as your prognosis is the number of years per people that are untreated that were included in this group. So that means if you decide to get no treatment, these are the years you're looking at. You can change that, hopefully, with treatments that might be available.

Q27: (inaudible 1:50:39)

Lenn Fechter, RN, BSN: What's that?

Q27: (inaudible 1:50:41) change it would be good.

Lenn Fechter, RN, BSN: Yeah. That's good news. You're not locked into those numbers at all. So, MDS like he said it's a little older population. The average at diagnosis is 73. It's an incurable malignancy for a majority of patients meaning those patients that aren't eligible for a transplant. The leading cause of death is the disease itself meaning either something that has to do with an infection and a low white count, a low platelet count and a bleed. Something to do with anemia and sometimes the anemia can stress the heart extra. So, that's one reason to keep the hemoglobin up or also the transformation to leukemia is the cause of death and the treatment strategies need to be stratified and, again, Dr. Greenberg went through a lot of that.

So individual treatments and the question came up what are the treatment triggers? When do you know when you're going to start looking at something to change what's happening? When you become transfusion dependent and usually doesn't happen unless your hemoglobin is less than 10, but if your hemoglobin is less than 10 you can start thinking about things like Procrit, transfusions, starting with the first steps. Progressive or symptomatic cytopenias are a time to start thinking. Increasing blasts. Definitely we all know that blasts are not a good thing and if we're seeing the number of them go up then it's time to consider talking to your doctor about treatment and it's very individualized. It's individualized because every person is different. We

don't necessarily anymore talk so much about age that older people are going to have worse problems are we're going to treat them more gently. It's more about performance status. How are you? How do you perform? What other kinds of diseases do you have? What's going to get in the way of treatment? And, of course, the IPSS risk category and we'll also talk about primary versus secondary MDS and Dr. Greenberg did mention that secondary MDS has to do with a progression... or a new disease that pops up after you treat a previous cancer with chemotherapy or some radiation and it can be secondary to other things as well, but that's the biggest risk of developing MDS is if you've had a prior treatment with chemotherapy and, of course, your cytogenetic status because with the deletion 5Q that was the first time there was a great target and a great test to say we can do it... do the test. If you have deletion 5Q we know where we're going to start. Once your hemoglobin drops below 10 and it's time to treat then we know we're going to start with Revlimid if there's no other reason why you shouldn't take it and, of course, your lifestyle and we'll get into that more this afternoon when you talk more about quality of life, but again it has to do with traveling interfering with what you're doing. Sometimes patients will ask us how much they can change their cycle so that they can travel or so that they can go to an event that they want. Lifestyle really needs to be worked around as much as you can because quality of life is just as important as quantity.

So current treatment options. Of course, there's supportive care and supportive care is something that happens not only as a first step but all the way through your treatment. Transfusions, growth factors, antibiotics, whatever's needed to support you for your treatment before and after treatment. Lenalidomide for mostly... most all of our 5Q- patients when they're ready to be treated will start with Lenalidomide, but a lot of other patients too will at least try it because like he said a smaller percentage of patients will actually respond even if they're not 5Q-. Vidaza and Dacogen similar hypomethylating agents. The harsher chemotherapies are still done for those that aren't going to benefit from some of the other current FDA approved treatments. Bone marrow transplant and then, of course, the clinical trial agents.

Q28: Question. On the blood transfusion beside iron overload what are other disadvantage of having a transfusion?

Lenn Fechter, RN, BSN: The other disadvantages. Well, the first time especially that you get a transfusion someone will sit you down and talk to you about all of the risks and benefits and there are very small risks that you could get some kind of a virus or bacteria through the product, the blood product, itself. The risks have gotten much smaller over the years and it's something for you to weigh whether or not that might happen to you and how much do you need that blood because there's no other option if Procrit doesn't work for you. We don't have artificial blood yet. It's been in clinical trials for many years, but the fact is that's the option to keep you going sometimes if you're not making blood, but other risks would be a reaction to the blood product and those can be very severe. I mean, there are reported cases of death from blood transfusion reactions, but the fact is it's very, very small. So, you want to keep that in mind and make your decisions about whether or not you're going to get a blood transfusion.

So, lots of clinical trials out there and Dr. Greenberg went into those in more detail. You can always go online, too, to clinicaltrials.gov and find out what's available and where in different parts of the country.

So, key principals to therapy, again, transplant is the only potential cure, but it's not an option for the majority of patients with MDS simply because as we get older and we develop MDS we probably picked up a few other things along the way. So, but still the ones who can get the transplant this is their potential cure. Age shouldn't exclude anything. You need to talk to your doctor about how you feel, how you function and how healthy you are. All the active therapies for MDS require time to work meaning like he said once you start Vidaza, you don't want to give up unless you're having a reaction to it or it's really affecting you adversely. You don't want to give up until you've tried it for at least 4 months then have another bone marrow biopsy and see if it's affecting your bone marrow. You don't want to give up too early on any of these treatments.

Blood counts frequently get worse before they get better. The bone marrow of MDS has abnormal cells in it and they have a lot of abnormal cells that crowd out the normal ones. When you start getting treatment, you'll see your blood counts actually drop because it's affecting mostly the abnormal but some of the normal cells. So, you'll see everything drop off, but then as you keep with it over the months they come back up with the good cells. So, that's the object is to get rid of the bad cells and let the good cells grow up and replace them.

So, that's just what these slides go through. Here you've got your abnormal cells starting out in treatment. You dip down and you come back with normal cells. So, don't give up on any of these treatments just because your cells go low. You might have to be supported severely during this time, hospitalized if you get an infection, lots of transfusions and it may not be for you. I'm not saying everyone is going to survive something like this, but remember that it's expected. Yes.

Q29: Just this question is it normal to continue your treatment while getting your transfusions?

Lenn Fechter, RN, BSN: Yes.

Q29: Okay. Thank you.

Lenn Fechter, RN, BSN: Yes and you might become more... have more transfusion need during your treatment. That's not unusual at all. Okay. So again, during the time of the toxicity... Okay. That was my alarm telling me it's time for lunch. Some people find these toxicities really difficult and both emotionally and physically, but if you keep focused on the fact that we expect it to get bad and then it get better then it'll help you get through it. So, I know it seems like we're just going to stop in the middle. Like I said, I let Dr. Greenberg have an extra half hour because it seemed that you were all really getting a lot from his talk. So, I'm going to stop this one and we'll just continue it after lunch. Okay. Are there any questions right now? Okay. Let's break for lunch then and gather in the other room and do a big group photo. Anybody that doesn't want to, of course, you don't have to, but it would be great if we could get everybody in the photo. Thanks.

Lenn Fechter, RN, BSN: Okay. Is it getting warmer? Good. Yeah. They turned the heater up. They said it might take a while, but I think it's already a little better. We're probably missing a few people, but we should get started. We only have about 40 minutes left to be together today and we want to accomplish as much as we can. So with that in mind, the last part of our program today is going to be about you and whatever you want to talk about and about quality of life and important things to keep like I said before, it's not just about the quantity, it's about the quality. And there are lots of things you can do to help keep yourself healthy both mentally and physically and emotionally and spiritually. So a balanced diet is a very basic thing that everyone should focus on. Daily activity and exercise. I'm a strong believer in exercise. Exercise is medicine on whatever level you're able to do it. It can increase your mood. It can help you with depression and it can also decrease fatigue. So if you don't have an exercise program, talk to your doctor and see what kind of an exercise program you can do if you're willing to do it and it can be anything from walking a couple miles every day if that's what you can do and what you and your doctor agree on and you have to take into consideration your whole body and your whole person. If you have cardiac issues and everything that needs to be factored into that, but it can be walking, it can be going to the gym or it can be simply sitting on the edge of a bed and moving around, moving your arms, turn on some really nice music and enjoy it and honestly we'll see a difference if you don't exercise. You'll see a difference in your mood and your fatigue and how you feel and how you approach your day.

Avoid infections. MDS, most many patients are prone to infection. If you avoid it, stay away from sick people. If you do get sick, treat it right away. Those are very important things for your quality as well as your quantity of life.

Avoid bleeding. The obvious thing is to avoid cutting yourself. So if your platelets are low, you're going to bleed, but the less obvious things are be really careful not to do anything that's going to make you fall. If you fall and bump your head that could be catastrophic. So, if you ride a bike and your platelets are 20 and below, you need to consider staying off your bike until your platelets are up a little higher.

Don't climb up on ladders. If you do have something that changes like you suddenly have a really bad headache, your vision changes, you need to go to an emergency room because you could have a bleed just from your platelets being low. So be really careful about that.

But that being said, continue to enjoy the things you love and live your life. Make a balance. Sometimes you have to change the things you love. You have to do some of them a little less and find something else enjoyable that you can do, but it's really important to keep yourself happy.

Get enough rest. There are a lot of reasons why people don't sleep enough at night. Insomnia can be caused from depression. If you have a disease that's affecting you, you have every reason to be depressed, but it doesn't mean you have to stay that way. See your doctor. Deal with depression.

Get your exercise. Eat right and get drink lots of fluid and try to get enough sleep at night.

Take advantage of all the available resources. The MDS Foundation is a great resource. They concentrate just on MDS. They do great things for nurses and doctors and education, but they also support patients and you can call them with questions and they have a lot of resources for you, but there are other resources out there, too. The Leukemia Lymphoma Society supports MDS and they will help you out with counseling. They'll match you one to one with a patient with a similar disease to yours so you can ask questions. Maybe you're thinking about going to transplant and you want to talk to someone who's had transplant. Give them a call. It might be a phone match, but this is a rare disease. You might not find that person in California. They might be in another state, but at least talk to them on the phone. There's an organization called Cancer Care that has social workers. They're on the Internet or you can call them and you can call the social workers and talk about cost of your medication, what resources are in your area. They'll help you find that. So, there are a lot of resources out there for you and in this room there are a lot of resources of people that have been through some of the things that you're facing and can give you advice, too. We have a support group, an MDS support group, at Stanford. I don't know what other ones are around because I'm pretty focused on that one, but I know that the MDS Foundation has them all over the country. If there's not one in your area, you could talk to them about getting one started in your area because talking to other people with the same disease is really valuable as far as finding resources.

So, always ask for help when you need help. Sometimes you need to adjust how you live your life. You won't be able to clean the house this week because you're anemic, but you're not quite at the level where you're going to get your transfusion yet and you really don't feel like it, but that's the time to think about asking your family or friends to help you out and a lot of times they're standing there in the wings and they want to help. They just don't know how to ask and sometimes you want the help, but you don't know how to ask. So, try it. There's a lot of support out there in your family and friends that you don't access unless you ask.

And be a really active participant in your care. Learn about your disease and that's why you're here today and be a partner with your physician. Don't be afraid to ask him, "I heard this. Dr. Greenberg said that," or, "I read it in a book. What do you think?" and if you need a second opinion, then find someone to go and get a second opinion. They're the MDS Center for Hope. There are several of them around the country, a couple of them right here in the Bay area and you can call up there if your insurance pays for it, you can go and get a second opinion, but if your insurance doesn't pay for it, call the MDS Foundation and ask them how you can get a second opinion and ask some questions.

So with that being said, what do you want to talk about today? Who still has questions and needs resources or has something that they've learned along the way in dealing with their disease that they'd like to share?

Q30: A question I have is with cytopenias. If there are 6 month intervals between blood tests, is it possible for blood counts to suddenly nose dive unbeknownst to the patient where, say, platelets can go from 100,000 to 50,000 in 3 months and the usual routine would be riding the

bicycle and that sort of thing, but not knowing that there's an increased risk of bleeding if there's a fall.

Lenn Fechter, RN, BSN: Yeah. Of course, your counts could change in six months and you and your doctor together should decide what's the reasonable duration of time to wait for a blood test. If you're really low risk and everything is looking good, your doctor might say every six months, but if you suspect that something may have changed then ask him if you can get a test early because even though we'd like to know when this is going to happen, if it's going to happen, we don't. So, you might notice some bleeding when you floss your teeth or you might have more bruising than you're used to having in the past. In that case, your platelets could be lower and you can give them a check. You don't want to check them every week, but checking them every three months or every month is reasonable if you have some reason to suspect that things have changed. Yes?

Q31: I think my comments were what they call the caregivers, but most of you people in here are like me. You're spouses and caregiving doesn't really cover it as far as I can see because you got a lot more at stake and you feel a lot... So, we need to take care of ourselves, too. Okay? Because we're suffering right along with the patient. I know it's not near like what the patient is, but because they're our loved ones it's a whole different show. So, don't forget to take care of yourself, okay, because you got... you're the one at least wise in my case that my wife relies on for primary care for the most part. So, take care of yourself and don't get sick either if you can help it.

Lenn Fechter, RN, BSN: Not just...

Q32: I'd like to add...

Lenn Fechter, RN, BSN: Can you turn her mic on for her?

Q32: ... to continue to enjoy things you love and live. That's really hard. It's really, really hard. You know?

Lenn Fechter, RN, BSN: I understand that is hard because it can be a whole new ballgame when you get this diagnosis and it affects everything.

Q32: I tend to go and cycle and so some days I'm good, some days I'm not. You know? And that's...

Q31: It's probably pretty common among all you. Right? You have good and bad days. Right?

Lenn Fechter, RN, BSN: Does anybody have a recommendation of how you live your life when you have good and bad days?

Q33: When the days are good, you take advantage of it. Go for it. Drop whatever you had planned and go do something else when those good days come and like I have to have

transfusions every 6 weeks, so I plan vacations and everything around this. I know I can do better and enjoy my vacations more if my hemoglobin is at least 9.8 is usually about as high as I go, but hey, that's good. I can do much better at that than in the 7s. Do you know when you're on Procrit how often is required for you to have, and I get weekly Procrit. They want me to have labs every week, which I don't. How often is required?

Lenn Fechter, RN, BSN: The CBC is required once a month, once every four weeks.

Q33: I could stay... I only... I mean, I had to fight to reduce it to every two weeks because they said that Medicare wouldn't cover it as a standard of care is something was...

Lenn Fechter, RN, BSN: The Medicare guideline. If you're not requiring frequent CBCs which I can tell if you're only getting transfused once every six weeks, you don't need it every week.

Q33: No, I don't.

Lenn Fechter, RN, BSN: The Medicare guideline is that every 4 weeks you have a CBC and you can prove that your hemoglobin is still below 12.

Q33: Go above 10. So, Medicare, I could get Procrit every week and only have a lab once a month.

Lenn Fechter, RN, BSN: Once every four weeks. That's right.

Q33: Every four weeks. So, they're just giving me... Okay. Because it was a big deal to just go to every two weeks when I said I won't do it every week.

Lenn Fechter, RN, BSN: Okay. Well, they need to look at the FDA guidelines.

Q33: That's what I need my defense to know.

Q31: The normal regime is four shots and then on the fifth week do a hemoglobin and they're asking you to do it every week?

Q33: Well, most of the... Yes, every week, but I do it every two weeks, but I'd like to at least to go to every three or four weeks.

Q31: You say it's not required.

Q33: No. See and they were acting like it was.

Q31: No, not according to what we treat when we get it.

Q33: Yeah because you just build up your scar tissue and everything else when you have...

Lenn Fechter, RN, BSN: And besides, you're taking that blood out.

Q33: Yeah, that you need.

Lenn Fechter, RN, BSN: Right. It's a small amount, but it adds up if they're taking it out every week.

Q33: Okay. Thank you.

Lenn Fechter, RN, BSN: Does anybody else have any recommendations on quality of life issues? How do you enjoy your life?

Q34: Well, we get enough rest.

Lenn Fechter, RN, BSN: Rest is key, isn't it? It may not even be how you cycle the month based on your transfusion but how you cycle your day based on when do you know that you have your best time of day as opposed to the time you're going to sleep no matter where you're at.

Q35: It's getting pretty close.

Lenn Fechter, RN, BSN: You're at that point? After lunch is your time where you lay down?

Q35: Well, after dinner.

Q36: The hardest thing for us has been getting her to when it is a bad day to realize that she's got to slow down. When she's having a good day she goes 90. Always has, always will. That's just here. She's a caregiver and is constantly taking care of everybody else, but it took us a lot to get her convinced that when she's having those bad days, you've got to step down and let us take care of you and there's 7 children. So, there's plenty of us to take care of her.

Lenn Fechter, RN, BSN: But she's taken care of you all of her life.

Q36: Exactly and she... It was... It's still really hard to get...

Q35: (inaudible 2:16:55).

Q36: Yeah. To get her to stop trying to be the caretaker.

Q35: I just don't want to miss nothing. I'm going...

Q37: We would like her to speak up and tell us how she does it.

Q35: I'm just not going to miss nothing. I'm going to go fast.

Q36: And she still continues to care for the grandkids and if we dare take them away from her she'd probably hurt us and if she's going to go out there in the garden if she has to crawl to it. That's just that kind of stuff, but it takes a lot for us just to hold her back. We threaten that we're going to tie her to a wheelchair or something because she doesn't know how to slow down.

Lenn Fechter, RN, BSN: But that's her quality of life. That's her enjoyment. I'm right there with you. I mean, don't take that away from her.

Q36: No, we don't want to take it away from her, but we want her to realize that... She knows when you're not... she knows if you got to slow it...

Lenn Fechter, RN, BSN: You know it, don't you? She knows it. She knows it. You sound just like my son. You have to tell me anyway. But, yeah, we're not. We're not.

Q36: She likes to wait till her levels are in the 6s and then she's... we have to force her to go and she... because she won't go to the hospital. If she can't go to the doctor's office and be admitted through him, she's not going in the emergency room.

Q38: Oh, no. You don't want to go to the emergency room. Too many bacteria infections in there and stuff, but don't let your hemoglobin go to six. I just found that it does zap your energy. You're not getting (inaudible 2:18:19) up to your brain. This is good. You can do it in the 7s. I have learned that that I don't let myself go as low because then you almost have to let them help you then when you get down low so you know... But we want our independence.

Q36: For the most part, she... I mean, she just keeps going. The biggest thing is that... the beginning of chemo week is fine. By about Thursday she can't taste anymore. By about Saturday she's got the weakness and she's been on chemo now for almost four years. So, it seems to take a little bit longer for her to bounce back. So, it's that five days right after chemo is the worst.

Q37: Get in there and do stuff without asking her.

Q36: Oh, we do.

Q40: Because we're going to refuse.

Q36: Most definitely.

Q37: So, just bring those meals over, clean that house when it's those days without and otherwise we're going to fight you.

Q39: What kind of chemo is she taking?

Q36: AZA.

Q39: Azacitidine. Okay. Do your blood counts drop afterwards?

Q35: Yup.

Q39: How low do they go?

Q35: I can go downhill three or four points in a couple days.

Q36: She's been staying around eight at her lowest.

Q39: The hemoglobin. What about the rest of the counts?

Q35: The white counts like in the toilet, but other than that the rest of them aren't too bad.

Lenn Fechter, RN, BSN: So the important thing when you go out to the garden or you decide what you're going to do. If your neutropenic, if your white count is really, really low and you're in danger, keep that in mind that you are special for a while and you need to take care of yourself.

Q35: Mine never goes up. That never goes up.

Lenn Fechter, RN, BSN: It never goes up.

Q35: It always stays down.

Q36: Very, very low.

Q35: One 3 to 3.

Q40: What about (inaudible 2:20:10)

Q35: I don't pay any attention.

Q40: I always go by ANC. Why does nobody else (inaudible)

Lenn Fechter, RN, BSN: ANC is the important one because that tells you whether or not you're at risk for infection.

Q40: (inaudible 2:20:22) bacteria and fungal that can be in the soil.

Q36: She doesn't pay attention because she really doesn't get sick.

Q37: Yeah. She's never had a problem with infection.

Q36: Her counts go low and they stay low.

Q35: I'm very careful, make sure everything's washed or I have gloves or...

Q40: So, you are being careful.

Q35: Yes. That I watch.

Q36: Not really that (inaudible 2:20:37)

Q35: Yeah. Exactly. Don't take off your jacket because everywhere the dog touches you or something you... get scratched...

Lenn Fechter, RN, BSN: And if you do get a fever though and it may be the first time that you get a fever, but if you get a temperature and it's 100.4 or above, you need to call right then to your doctor. If they're not available go to an emergency room.

Q35: Never had one in the four years.

Lenn Fechter, RN, BSN: But if you do don't think that I'm that person that's not going to have a problem because you could.

Q40: Should she wait till 101... 104 did you say? Oh, 100.4.

Q35: If I feel anything and I've got a great doctor's office. I just walk in the door or I can call them on the phone. I have no trouble whatsoever. They take you instantly.

Lenn Fechter, RN, BSN: Definitely because if you get a temperature of 100.4 or you know that you're infected. Sometimes people won't even get a fever, but all of a sudden they feel really, really bad and different that's life threatening. You need to treat it immediately. If you're neutropenic meaning your ANC is low, less than 1,000 but especially less than 500.

Q35: They did tell me I was that so it must be.

Q36: Well, they treat her special when she goes to the hospital. She goes in the neutropenic room.

Q35: Yeah. They put me in the closet. That's exactly where...

Q31: Are these all your three daughters?

Q36: Yup.

Q31: Well, see, therein lies the problem. You got three loved ones that care for you. This is just part of your entourage.

Q35: I have the best seven year old nurse you've ever seen.

Q31: Well, yeah. The children are much better because they don't go crazy with a lot of this stuff, but you're experiencing the same thing all the rest of us do. Not the mother, the children because you're so focused like the rest of us on what's going on and then when your mother or my wife or somebody doesn't do what you think's right, it drives you crazy and they're like...

Q37: Crazy.

Q31: Yeah. Leave me alone.

Q37: I have learned though if I just kind of sit back and make her feel like she's making the decisions, it's a little easier.

Q36: We learned that a long time ago. We got to just make her think it's her idea.

Q41: You're not fooling her, let me tell you.

Lenn Fechter, RN, BSN: Well, being a caregiver is a lot of responsibility and there's a lot of stress involved in that in general and he was right about asking... saying that caregivers need to take care of themselves and make sure that you're getting away for a little bit every day. Do something fun. Your quality life is important too because if you let your immune system get down and you get sick... immune systems are great things. They protect us not only from bacteria but from cancers. So, don't let yourself get drug down thinking that you have to do this for the other person because you need to keep yourself healthy for that other person, too. Has anybody else come across any perils along the way of having this disease? Something that you'd like to share with the group? Something that somebody else could benefit from? Yeah?

Q42: So, my mom, who isn't here, she's in the Midwest, she was diagnosed with MDS in December... December 31st and I just want to stress to everyone she wasn't near one of these big centers and I think it's very important to have a second opinion because the first opinion for the course of care for my mother was not the standard course of care because the hematologist oncologist that saw her in a small hospital in Kansas City had only seen a dozen or less MDS patients. So I mean, it's great that we're all here. I think that just shows that people are being proactive and they want to learn, but also to question, to question what's being told to you and to search out other options and to be very thoughtful for those options because my mother would have quite easily just do what... She follows directions very well and she would have just done what she was told to do which would have been not as effective as the course of care that she's on now.

Lenn Fechter, RN, BSN: That's good advice because you could have the most brilliant hematologist oncologist but they see so many different diseases and they have to keep up to date on everything and they can't necessarily get into what's current for MDS because it's such a small population of what they see mostly unless you go to an academic center and an MDS center of excellence where they see a lot of it and they have the pathologists that see a lot of it on the bone marrows. It is important to get your second opinion. Yes?

Q43: I got second opinion at the UC hospital. It cost me \$49.

Lenn Fechter, RN, BSN: Forty-nine dollars.

Q43: I brought in all the papers and it costs \$49. They agreed with everybody else.

Lenn Fechter, RN, BSN: That's good to know. If that's the information you're getting, they agree with what you've been doing? That's really good information.

Q43 Yeah. That was a good (inaudible 2:26:22).

Lenn Fechter, RN, BSN: Okay.

Q44: What that a copay?

Q46: That you see the \$49 was the...

Q44: Was that the copay?

Q43: Yeah. That's all I had to pay for. I don't know. That's all I had to pay.

Q44: Dr. Greenberg charges a little bit more.

Q45: (inaudible 2:26:51) very valuable improvement our last... the last seminar was that if you... if somebody invites you to something you'll say if I can make it, I can make it, if I can't, I can't and people are really very understanding.

Lenn Fechter, RN, BSN: That is important. It takes the pressure off of you too because if it's the last minute you're really not feeling like going and you know that you've already got permission to not go and to go back to bed. So, give them a heads up especially your closest friends. Does anyone have...? We talked a lot about fatigue today and it's a big problem with MDS patients and their caretakers. Does anyone have a suggestion on how do you deal with fatigue?

Q31: Do you know about off label use of stimulants? I'm not kidding. Ritalin. No? They prescribe that for fatigue whether it works or not, it doesn't in Linda. Also, Provigil or Mode Alert whichever you know that drug by. Well, Ritalin's an amphetamine. So you got a problem there, but Provigil is a better drug. The only problem is it's \$30 a pill. So, and it hasn't had that much effect when we get some of it offshore, but then when you go offshore you have to worry about the, you know, how they make the drug whether it's being... the quality control and whatnot's there, but at \$30 a pill it's hard to get it here. In addition, these off label uses won't... our insurance won't pay for them because they're not prescribed for what they're supposed to be. So if you get one from your doctor, tell him to prescribe it for narcolepsy and then they'll pay for it. Really. Narcolepsy or sleep deprivation from shift work.

Lenn Fechter, RN, BSN: Shift work. That's what it's FDA approved for which is an odd indication, but if you have trouble sleeping because your shift changes. It's a very strong drug, too, and it's a little bit difficult to dose in people who are a little older because actually in the directions of how to dose it, it says to dose reduce for older people. So for aging for kidney insufficiency, for liver issues, the dosing is a little bit difficult, but for some people it does help.

Q48: You're talking Provigil?

Lenn Fechter, RN, BSN: Provigil. Yeah.

Q48: Where is it in the (inaudible 2:29:52)

Lenn Fechter, RN, BSN: I don't know that. I don't know that answer.

Q48: Maybe that's why they were worried (inaudible 2:29:59)

Lenn Fechter, RN, BSN: But that's a good point. There are stimulants and some people try caffeine, but a lot of times if your fatigue is from the fact that you didn't sleep all night because you were up worrying and you're depressed or your hemoglobin is low, caffeine really isn't going to help a whole lot, but to me I think it's really important to start with the basics that we all need which is some exercise every day and some enjoyment every day, hydrate well and eat well. Those seem like really basic things, but when we're concentrating on all of the getting to the doctor and what's my blast count, sometimes we forget and think those things are less important and they're actually not less important. They're more important. Make sure you get your water every day and that you're hydrated and exercise, again, decreases fatigue, increases your mood, helps you get past depression and depression is something that can go along with any disease and a lot of issues in life, of course, but if you have a disease like this don't overlook the fact that maybe you're Prozac deficient. Maybe you need a little Prozac and that can get you through the day and you can sleep at night and it can make such a difference. So, be open. Be open to all those things.

Q49: I have a couple things. Her second youngest granddaughter has ADD and she's now a senior in college and when she went from high school to college they... her doctor gave her varying medications like one is good for about eight hours. If she needed to be attentive for an entire day of school, she could take that, but then there's also ones that are good for about three hours which will spark you and allowed her to study and not be so hyper and still get stuff done and be able to associate with her classmates and everything. So, there are other ADD medicines like Ritalin but that are more time sensitive and then there's... I was injured years ago and ended up taking a restorative yoga class and got this book called *Yoga Anywhere* and it's you can basically sit and do yoga which doesn't involve getting down on the ground and just really working with your muscles and with that... along with breathing allows you to be a little more calm and allow yourself to rest and even... not that you're going to sleep there, but it'll give you a lot more energy just by sitting and breathing and moving a little bit. It's really... take three breaths before you do anything to calm yourself down, too.

Q31: One thing I do want to warn people about that I'm sure you're aware of is many of you like Linda are on some heavy duty drugs and you got to keep an eye on this stuff because often these young children, our grandchildren, are savvy of what you're taking and which ones get them loaded and they'll steal them from you. Not our grandchildren, right. We have four or five pretty heavy duty drugs in the house that she uses on and off. Painkillers and/or Ritalin is famous. The kids that are in college that take Ritalin are selling it to the kids that aren't to get them wired, so they can stay up for their finals. So, I mean, there's drug abuse going on and prescription drug abuse is definitely a problem especially amount young kids. So, I just warn you. Keep an eye on your drugs and know how many you got because...

Q50: (inaudible 2:34:03)

Q31: That would work.

Lenn Fechter, RN, BSN: It might, but keep them safe. That's a really good point.

Q51: But your grandkids could be somebody they bring over, too. It's best they don't even know.

Lenn Fechter, RN, BSN: No more perils for us today? I'd like to just do one quick exercise before we go because it's important. It's something that I discovered a few years ago and everyone whose used it if they like it and use it swear by it. It's really simple. I want you to get out a pen and a piece of paper and write down 3 good things that happened to you in the last 24 hours and I'm not going to judge what's good and what's not. You're not going to read it to anybody. Just 3 good things and I'm just going to give you 1 minute to do that. Not just patients. Remember caregivers are people, too. So like I said, I'm not going to ask you to read these things, but they're things for you to think about and if you do this every evening just before you go to sleep it's been proven scientifically that you'll remember things better and that they get into your... what you do the next day and so the next day you'll be looking for your 3 good things and it does help... It helps you to improve your quality of life. It helps you to find good things to have. It helps you to appreciate some of the things you didn't appreciate before. So try it just for 14 days. Every night before you go to sleep, write down 3 good things that happened to you that day and let me know if you find a difference and thank you.

Q52: (inaudible 2:36:34) everybody carry these that have the low white counts?

Lenn Fechter, RN, BSN: Yeah. Or the gel. Something...

Q52: These are great for (inaudible 2:36:42) if you go an airplane today I would (inaudible 2:36:45)

Lenn Fechter, RN, BSN: Antibacterial.

Q52: Antibacterial.

Q53: You need a bigger one to wipe down the whole...

Q52: I carry the hand when I get on the plane or something or opening doors with it. I'm touching things with it. They have the ones for the hand and they have the ones for just wipe... I'll wipe my hotel room with.

Lenn Fechter, RN, BSN: Yeah and you don't have to wipe down the whole plane. Like you said, as long as you're cleaning...

Q52: I wipe down the seat handles. I wipe down the tray. You'd be surprised.

Lenn Fechter, RN, BSN: And even after you did that make sure your hands, you're always because that's the part you need to keep clean.

Q54: Recirculated air...

Q52: I have masks.

Lenn Fechter, RN, BSN: Wear masks, too.

Q54: You do?

Q52: I don't care. There's air... There's little kids...

Lenn Fechter, RN, BSN: Did you have another comment, Cory.

Q31: I will add a pearl as we're at this type of foundation type meeting that they have found that people live 20 percent longer if they participate in these kinds of settings. We go to leukemia and lymphoma monthly meetings. All those types of things are very helpful and you'll live longer.

Lenn Fechter, RN, BSN: And you find out things that you didn't know you didn't know.

Q31: Exactly.

Lenn Fechter, RN, BSN: Thank you all for coming. I really appreciate that you took the time to learn today and it was a nice rainy day to be in out of the rain anyway.

(Applause)