

Speakers

Steven L. Allen, MD

Jayshree Shah, APN-C, MSN, RN, BSN, BS

?: (inaudible 0:00) and he's going to share his (inaudible 0:04) and we're going to call it MDS Supportive Care to Active Treatment. Again, we are recording. If you have any questions, hold them till he's finished and (inaudible 0:13) capture everything you guys have to share. Thank you.

Steven Allen: Thank you for that nice introduction. Let me find a place to stand. I won't get blinded here. I'm flattered that you all came out on such a beautiful morning to hear me speak. I guess the recording because they want to put up staring Steve Allen, but I don't have a piano. So, the talk I'm giving today, I didn't know if the audience would be newly diagnosed patients, patients who are already very knowledgeable. So, I'd like to do is give you an overview of Myelodysplastic Syndrome, current treatments and then move on at the end to some new treatments that are coming along for Myelodysplastic Syndrome and after that I'll be happy to try to answer any questions that you might have.

So, MDS is a hemalogically diverse. It's a clinical situation. There can be pancytopenia, anemia, low red count, thrombocytopenia, low platelet count and neutropenia which is a low neutrophil count. Neutrophils are one of several different types of white cells that we all have and neutrophils are the cells that help fight bacterial infections. So, they're very important in protecting us and in MDS all 3 can be low or just 1 of the 3 can be low. There's ineffective hematopoiesis, the defect in MDS is in the bone marrow in the stem cell and the reason these blood counts are low is that your bone marrow is not effectively producing those cells. It tends to happen in older individuals. My definition of older goes up as I get older, but unfortunately it's over 60, but it does occur in younger people although the disease is... tends to be milder in younger individuals and ultimately about 20 to 30 percent of patients with Myelodysplastic Syndrome can evolve to acute myelogenous... acute myeloid leukemia.

What are the characteristics of MDS? Well when we look at the bone marrow under the microscope, the cells look dysplastic. They don't have a normal appearance. What actually happens is that term you may have heard megaloblastoid means that the nucleus has matured where the chromosomes are has matured much less than the cytoplasm. So that the cells have this characteristic and abnormal appearance that hematologists pick up on right away. There may be too many of the most immature cells, the blasts, in the bone marrow and the bone marrow is hypocellular. A normal bone marrow as about 50 percent fat and about 50 percent bone marrow cells, precursor cells to the blood cells out in the circulation. In Myelodysplastic Syndrome, the cellularity can be over 90 percent, almost all the fat is gone and that's your body responding to the low blood counts out in the blood and trying to rev things up and make more cells, but unfortunately those cells don't mature and don't get out into the blood. The cytopenia, the low blood counts, tend to be progressive over time and when you look at the chromosomes, there are certain chromosomal abnormalities that are characteristic from Myelodysplastic Syndrome and many of them give us prognostic information and sometimes even information about what treatments might be appropriate.

What causes Myelodysplastic Syndrome? Well in the vast majority of people, we have no idea. It tends, again, to occur in older people and there are the known causes of Myelodysplastic Syndrome include exposure to radiation, various chemotherapy drugs that you may have received because of a cancer that the individual had earlier and industrial chemicals, particular organic solvents and benzene being the prototypical example of this. So, here's a bar graph showing the incidents by age. This is incidents per 100,000 people per year. So you see under the age of 50, it's rare. Between 50 and 70, it starts becoming more common and then over 70, it's... the incidents is at its highest roughly about 20 new patients per 100,000.

?: (inaudible 6:00) kind of blocking this side of the room.

Steven Allen: I have to stand someplace. (Laughing)

Interestingly if you go through the medical literature, there are only 143 cases of Myelodysplastic Syndrome reported before 1973. The disease was certainly there. It just wasn't recognized and but now it's become much more recognized and today in the United States alone, there are about 15,000 new cases every year and the prevalence in the United States meaning the number of patients at any given time is 35,- to 55,000 cases.

So, what treatments are available? So, the problems of the disease are associated with which one of the cell lines are low. When you're anemic, it can be... you can be very tired. If you have heart disease, congestive heart failure can be a problem. Angina can be a major problem. You can get shortness of breath particularly with exertion and the red cells are what carry oxygen to your body and that's if you don't have red cells, the oxygen isn't getting out and your body senses that and that's why you get this shortness of breath. Low platelet counts can lead to bleeding and increased bruising and neutropenia, the low neutrophil count, can lead to infection.

So anemia is probably the most common of the 3 cytopenias. Over 85 percent of patients with Myelodysplastic Syndrome have anemia. The cells tend to be big in Myelodysplastic Syndrome. One of the ways hematologists classify anemias is by looking at the size of the red cells. Are they small which is typical of iron deficiency or of a hereditary disease called thalassemia? Mediterranean anemia. Are they normal sized which is a whole slew of different anemias or are they big and when the red cells are big the 3 leading causes of big red cells are low B12 levels, low folic acid levels and Myelodysplastic Syndrome. The anemia with MDS tends to be chronic. It's oftentimes by the time we see the patient when you go through their record they've been anemic for quite awhile and it often becomes transfusion dependence in Myelodysplastic Syndrome and transfusion dependence is defined as needing 2 or more transfusions in a 2 month period.

How about the low white count? So with the neutrophils, the main management of infections is to give antibiotics as soon as the person develops a febrile illness. There are growth factors. Neupogen which is granulocyte stimulating factor being most commonly used one. These are the hormones that we all make and just like insulin can be now made to use as a medicine. We can make G-CSF and use it as a medicine and it can drive up the low white count in people in Myelodysplastic Syndrome. However, it's generally not used. There's some concern that using

Neupogen might drive the transformation to acute myeloid leukemia and another concern is that studies have shown that it really doesn't change much in people with Myelodysplastic Syndrome. It didn't improve survival. It didn't decrease hospitalizations and it's very expensive. So in general, it's not used as a way to manage neutropenia. We look for other mechanisms. Low platelet counts. Well if they're very low, platelet transfusions are an option. There are medicines like Aminocaproic acid that you can use to help stop bleeding although that drug has its own problems and doesn't address... it addresses blood clotting, but not the low platelet count itself. There are also growth factors for platelets that they call... The growth factor for platelets is called Thrombopoietin and is both an injectable form of Thrombopoietin available and an oral form, but and everybody was very excited when those came out thinking, "Oh, this is going to be great for MDS." Unfortunately in the clinical trials they clearly increased the incidence of transformation to acute myeloid leukemia and they were abandoned for the treatment of MDS.

So, what's the transfusion management of anemia? Well, there's transfusions, but transfusions have their own problems. If you give blood, red cells contain iron and if you get too many transfusions, you can become iron overloaded which has its own set of medical problems. There's the volume of the transfusions. A bag of blood is 250 mls. That's a quarter of a liter and if somebody has kidney failure, renal insufficiency or congestive heart failure, giving all that fluid can be a problem and can lead to shortness of breath, pulmonary edema, the lungs being overloaded with fluid and then there's the question of quality of life for the person if they're getting frequent transfusions. In some communities, you have to be admitted to the hospital for the transfusion. If you're able to get outpatient transfusions, it's still involves coming to the office 1 day to get a type and cross drawn and then coming back a day or 2 liter for the transfusion and spending a half to three-quarters of the day sitting there getting the blood. There are growth factors for red cells which we'll talk about more. The growth factor for red cells is Erythropoietin, the brand names are Procrit and Aranesp and they have...

Q1: (inaudible 12:38) which do you prefer?

Steven Allen: Between the two? It's a toss up. They both work fine. And again, the supportive care transfusions, unfortunately, remains the mainstay of anemia but we'll talk more about that in a moment.

So, what's the situation with Erythropoietin in Myelodysplastic Syndrome? The first thing is your body's anemic and senses it and the organ that makes erythropoietin interestingly is the kidneys. As blood goes through the kidneys to be filtered and for the waste products to be removed in the kidneys, there are sensors for whether you're anemic or not and that controls how much erythropoietin the kidney makes. So if you have somebody with MDS and they're anemic, the first thing you have to do is check their erythropoietin level. It could be they're already pouring out erythropoietin and giving more as a medication isn't going to help because they're already making huge amounts and studies have shown that if your erythropoietin level is over 500, it's very unlikely that treatment with one of the erythropoietins is going to help. What about if your erythropoietin level is under 500? Well again, there's a chance that it's going to help and make the individual have a higher hemoglobin, require less transfusions, but the success rate is only about 16 percent. So, the vast majority of people are not going to respond to these treatments. One thing you can do to try increase the response rate is to add Neupogen, the white

cell growth factor onto the erythropoietin levels and that raises the response rate up to about 20 – 25 percent. So, there's an improvement and both drugs are given a subcutaneous injections. The Neupogen, the white... this one, GCSF, is given every day and, again, the expense is tremendous. Neupogen is probably about \$2,000 a week.

So the red cell transfusions themselves, we give people packed red blood cells. Nobody uses whole blood anymore. We give whichever one of the components you're low on as an individual product. So, packed red cells have nothing else in them. The platelets have been removed. The liquid part, the plasma, has been removed and it's just concentrated red cells. That also allows us to spread the blood supply better because that way one donor can help multiple people and generally you'll see that you get leukocyte depleted packed red blood cells which means they filtered out the white cells. The reason for that is that most transfusion reactions which are usually allergic type reactions, rashes, itching, most of those are due to the white cells, not to the red cells. So by removing the white cells by filtering, you decrease the incidents of transfusion reactions tremendously. Another thing in most institutions is that when a Myelodysplastic Syndrome patient gets a transfusion, they get irradiated blood products and by irradiating the blood which doesn't affect the person getting the blood at all, but by doing that any white cells that are still in there can no longer divide and by doing that you decrease the chance of the transfused cells and grafting in your bone marrow and then causing graft versus host disease which is usually something you only see after transplant, but there are rare cases where it occurs in MDS and other hematologic malignancies like leukemia and lymphoma. So, we just routinely irradiate all the blood.

So, what does a transfusion do? It increases your oxygen carrying capacity and the risk we've already discussed, volume overload, too much fluid, iron overload. Theoretically, we'll talk about it more. Infections, I mentioned the graft versus host disease and alloimmunization is when your immune system recognizes the donor's blood as foreign because the blood types weren't perfectly matched and then you make antibodies against that whatever that blood type was and that can complicate the future transfusions.

Q2: (inaudible 17:36).

Steven Allen: Graft versus host disease. That's where the donor's white cells start growing in your body and attack your cells. So, we already discussed this. Move ahead.

How about infections? Anybody who gets a transfusion, you always have to sign that release form before we can give you an infection and that's because we need to tell you that there is a risk of infection. Fortunately, the blood supply in the United States is very, very secure now and very safe. This is an old slide and the incidents of infections, I think, is even less than what I'm showing here, but the chance of getting a bacterial infection is somewhere between 1:100- to 1:500,000 the chance of hepatitis B is in 1:220,000, hepatitis C 1:160,000 and HIV is 1:1,800,000. So the risk is really very, very low and if you look at risk of things like getting hit by lightning, it's much higher than these risks.

Iron overload. Each bag of blood adds 250 mgs of iron into the patient's body. You have no way of getting rid of iron naturally once it's in your body. The only way you can get rid iron is to

bleed, to lose blood, and then the organs that can be affected by iron overload include the heart, the liver, endocrine glands like the thyroid and the pancreas and the bone marrow.

So, when is iron overload likely? After somewhere between 20 and 40 red cell transfusions people tend to become iron overloaded. It's most likely in patients with the low risk types which we'll talk about the risk categories in Myelodysplastic Syndrome because they're the ones who may be on chronic transfusions for long periods of time and get many, many transfusions. The way we... The easiest way to monitor iron overload is to check your ferritin level in the blood and generally a ferritin level over between 1,000 and 2,000 is considered to indicate significant iron overload. There're other things you can do. You can do MRIs to measure iron in the liver or iron in the heart, but ferritin is easy and much, much less expensive.

There are drugs that can remove iron from your body. Desferal, Deferoxamine is the classic one that binds the iron and then that complex of iron plus the drug can be excreted by your kidneys and the iron is removed through your urine. The problem with it is the best way to give it is as a subcutaneous injection. You have to put a needle in your arm when you go to sleep at night. It's hooked up to a pump and the drug gets infused while you're sleeping. I know some hematologists give it intravenously. They say, "Oh, the patient's getting a transfusion. We'll give them Desferal while they're getting the transfusion and get the iron out that way." It sounds good, but it doesn't work and a big problem, unfortunately, is that Medicare doesn't pay for the drug and, again, it costs several thousand dollars a month. There are oral forms of iron chelating agents available. Deferasirox, Exjade is one. It works just as well as the Desferal. Many people have... you have to drink a lot of fluid to take it and people have reactions to it and, again, it's incredibly expensive. The costs about \$7,500 a month.

So, what are the problems with transfusion as a treatment? It's temporary. When you first start transfusion, a transfusion will usually keep your blood count at a reasonable level for about a month, but over time that period gets shorter and shorter because you make antibodies against the blood, that alloimmunization that I referred to earlier and blood lasts for less and less time and ultimately many people need to be transfused once a week, once every 2 weeks and it becomes a huge, huge problem. The iron chelation becomes an issue, getting rid of that extra iron. The blood supply you hear on the radio all the time that there's an emergent blood shortage because, unfortunately in the United States, people don't donate blood that often as opposed to in Europe where they don't run into this problem as much and, of course, the impact on quality of life how anemia affects you, all the time you have to put into getting the transfusions. It's inconvenient and as with everything else, unfortunately, it's expensive.

So if you are red cell transfusion dependent, how does that affect survival? For this graph it just basically it just... if you're transfusion dependent it means your disease is more serious than if you're not transfusion dependent which is what this shows and it's, unfortunately that in transfusion dependent patients, the average survival is shorter compared to transfusion independent patients.

What about classification? You may hear your doctors talking about all these different classification systems. The original classification was the French-American-British system which was based in 1976. It's a quick interesting story the way they did this was that we knew we had

to have a way to characterize the disease, so they took the leading blood pathologists in the United States, France and England, locked them in a hotel room in London one weekend and told them don't come out until you figure this out. So, they worked very quickly and came up with a very useful system. That was ultimately supplanted by the WHO, the World Health Organization System, which is the one that we're using currently and simultaneously this thing called the International Prognostic Scoring System was formulated which also gives prognostic information. These 2 systems are based on what the cells look like under the microscope and what percent blasts you have in the bone marrow and the IPSS is based on the number of cytopenias you have, the number of blasts you have and on the cytogenetic abnormalities and the 2 together work very well.

So, how does the IPSS work? You get points based on how many blasts you have, what kind of cytogenetic changes you have and there are good changes which are these, intermediate ones which are well, there are good ones which are these 3, there's poor ones which are these classifications particularly chromosome 7 abnormalities and then intermediate is everything else and so you get points on that and then based on the number of cytopenias 01 versus 2 to 3 and then you add your points up and you get your score and that puts you into a risk category, low, intermediate 1, intermediate 2 and high. These 2 are considered the low risk and these 2 are the higher risk and this is the distribution. Most people are in the low to intermediate 1 risk category. Intermediate 2 risk is less common and the high risk is the smallest category of patients. And the score correlates with survival. This is true for patients over 60. Under 60, the prognoses are better and flow risk, the median survival is about 6 years, intermediate 1 about 3 ½ years, intermediate 2 1.2 years and high risk is about 3 months and then this is the incidence. Twenty-five percent risk of developing acute myeloid leukemia within 1 year. So for low to intermediate, it's 9.4 years until a quarter of the people get AML, intermediate 1, it's about 3.3 years, intermediate 2 it's 1 year and the reason survival is poor in high risk is the transformation to leukemia usually occurs in .2 years, so about 2 months. And this is survival by age and the IPSS score. So you can see under 60, the median... the median is the time that half the people survive is much better, about double. It's still not great, but double what it is in the lower... in the older people.

So what guides treatment? Well, this your IPSS category, your WHO classification, age because... what other medical problems does the person have, performance staff which is a way of measuring how active you are, HLADR status. That's your tissue type and that influences one type of treatment and, again, your chromosomes, what the chromosomal abnormalities are and the NCCN is a group of major cancer centers around the country who have gotten together and made up practice guidelines for various conditions including Myelodysplastic Syndrome and people use this as guidance as to what treatments are appropriate for their patients. So for the low – intermediate risk patients over the age of 60, the treatments suggested is either supportive care or low intensity therapy. So, that's transfusions, Erythropoietin since the major problem here is generally anemia. If their performance status is very poor then it's supportive care, usually transfusional support. If they're less than 60 and they're in good shape, people are recommended to either go into a clinical trial with new treatments or, again, just supportive care and in the intermediate 1 category, that's when you would start thinking about doing transplant because transplant remains the only way to cure this condition.

Intermediate 2 and high risk, less than 60 with a good performance status, high intensity therapy which is the hypomethylating agents like Azacitidine or supportive care and growth factors depending on the individual and their own preferences. Over 60 and with good performance status, low intensity therapy or high intensity therapy or supportive care. Again, that should be a conversation between the physician and the patient and try to reach an agreement on what the patient is most comfortable with. If they're in poor shape, again, supportive care and then depending on what other medical problems the individual has either choosing supportive care or possibly a clinical trial.

The only cure for Myelodysplastic Syndrome is high dose chemotherapy, wiping out the bone marrow followed by transplant from a donor. You can't use your own stem cells because they're myelodysplastic. It's not going to help. The cure rate for stem cell transplant is about 50 percent. The older you are, the more morbidity, the more side effects there are from the transplant and the higher the mortality, the percent of people who die from the transplant. Fortunately, mortality from transplant is fairly low on the order of about 5 to 10 percent and transplant is poorly tolerated in older patients because of other medical problems we develop as we get older. One of the things that they're working on now is nonmyelo ablative stem cell transplants using less chemotherapy to condition the bone marrow for the transplant and that may allow us to try transplant in older individuals. Unfortunately in the end, less than 5 percent of MDS patients end up being appropriate for a donor transplant. It's generally the younger patients with good cytogenetics who are in good shape and who are able to find a donor for. Sibling donors, your brother or sister, are always the best choice, but the chance for a sibling to be a match for you is 25 percent.

So, we sort of covered this already. Let me move ahead.

So again, a curative treatment based on chemotherapy with stem cell transplant is only appropriate for a small minority of MDS patients. Supportive care and clinical trials are a mainstay of treatment of MDS and we have great need for new better treatments for the management of MDS. So, what do we have currently? Well, the primary treatment for MDS is Azacitidine which its brand name is Vidaza and it's a hypomethylating agent. The methyl group, which is CH₃ when it's added on to the outside of DNA, promotes myelodysplastic development in the bone marrow and Azacitidine hypomethylates it. It helps get rid of the methyl groups and hopefully allow the cells to mature normally and then for blood production to improve. Azacitidine has been approved for the all the different subtypes of Myelodysplastic Syndrome and listed here are the French-American-British classifications and it's approved for all of those. This was the original trial by Lou Silverman at Mount Sinai, which he conducted the Cancer and Acute Leukemia Group B, which is a nationwide consortium of major of cernuous and cancer centers around the country. My institution, North Shore, is a main member institution of this group and we participated in this trial and it shows the response and the take home message is that the patients treated with Azacitidine compared to those who only got supportive care, transfusions and Erythropoietin, did have actual response rates, complete and partial remissions with bone marrow went back to looking more normal and/or complete remissions where the chromosomes went back to normal also, but most importantly the improvement that that refers the blood counts improving markedly occurred in almost 40 percent of the patients. So that although the bone marrow getting better was a minority of patients, overall about 60 percent of

the patients had benefit from treatment with the Azacitidine compared to supportive care alone where nobody had what was defined as their response to treatment. Azacitidine also delayed the time to transformation to leukemia from 12 months in the supportive care group to 21 months in the Azacitidine group and the number of patients who developed leukemia was much less in the Azacitidine group, 15 percent of the patients compared to almost 40 percent of the patients in the supportive care group. Quality of life studies also showed that the Azacitidine group did much better with much less fatigue, shortness of breath, ability to function physically, overall sense of wellbeing and in terms of psychological distress.

Another drug which is a first cousin of Azacitidine that's frequently used is Decitabine and the brand name of that drug is Dacogen. The FDA, the original trials were done with this very difficult regimen where the drug had to be given every 8 hours for 3 days and that required going into the hospital and the response rates really were not as good as what we saw with Azacitidine, about 40 percent. Subsequently, a different regimen giving the drug once a day for 5 days which could be done as an outpatient was developed and had a better response rate, but Azacitidine was the first drug out and they did their studies in a much better way than the Dacogen people did and the Dacogen people were never able to demonstrate a survival benefit which Azacitidine did demonstrate the reason being that they didn't design the trial well. So, it's Dacogen is sort of second line behind Azacitidine behind them. Here's the 3 different dosing regimens that are currently being used.

Another potential approved treatment for Myelodysplastic Syndrome is immunosuppression. There's a type of Myelodysplastic Syndrome called hypocellular MDS where when you do the bone marrow instead of the bone marrow being packed with red cells as I mentioned earlier in my talk, the marrow is empty. It looks almost like aplastic anemia and in studies done at the National Cancer Institute, they found that by treating those patients the same as we treat aplastic anemia with antithymocyte globulin which is antibody that destroys many of your lymphocytes and the cells that make antibodies plus Cyclosporine, another immunosuppressive drug, that they could get responses in a significant percentage of people with about a third of the patients becoming transfusion free. The ones who had low platelet counts, about half had improvement in their platelet counts and the ones with severe neutropenia, low white counts, again, about half of those had a marked improvement in their neutrophil count. The side effects of this treatment are the first few days the antithymocyte globulin gives people an arthritis type syndrome. It's called serum sickness, fevers, rash, arthralgias. So by giving people high doses of steroids at the beginning, you can avoid that.

Q3: (inaudible 37:51)

Steven Allen: Antithymocyte globulin. What's in the title there.

Q3: Got it. (inaudible 37:58)?

Steven Allen: It's made in horses and rabbits, yes, and horses work better than rabbits and there's only one horse in the world that they make this from which is that horse leads a charmed existence. Again, the horse died unexpectedly about 15 years ago and we had a period of time where there was no horse antithymocyte globulin available because they had to immunize a new

horse and get its production up and I remember how shocked I was when I learned that there's only 1 horse in the world.

Which patients are most likely to respond to immunosuppressive patients? Well, you have to have the hypocellular MDS. It tends to be younger patients. I mentioned tissue type earlier. There is a suggestion that if you have HLADR15, that improves your response, but people are questioning that now and interestingly the patients who gotten less red cell transfusions seem to do better.

Another drug that's available to treat MDS is Lenalidomide. The brand name for that is Revlimid. It's a cousin of the drug Thalidomide which you may remember from the '60s when those babies were born without limbs. Revlimid, Lenalidomide, was originally approved to treat multiple myeloma. Subsequent studies done by Allen List had shown that it's in a subgroup of patients with Myelodysplastic Syndrome. It can be a very powerful treatment. So in List's original study which is, again, done with the Cancer and Acute Leukemia Group B group what they noticed was it was particularly effective in improving the red cells and in these various different subtypes of CML, it had different efficacies in refractory anemia which is usually low grade and the most common type of MDS. Three-quarters of the patients responded to the treatment in this type, refractory anemia with ring sideroblasts, half the patients and these other 2 higher grade subtypes which had more blasts, about a third of the patients responded. If you look at the patients by their IPSS risk category, the low risk patients, 70 percent responded and intermediate 1, 50 percent responded and then what they noticed when they broke down the patients further, the patients who had a particular chromosomal abnormality, deletion 5Q which is the loss of the long arm of chromosome 5, 83 percent of those patients had a red cell response and the patients who had a normal... who had normal chromosomes, men with 46 XY, women with 46 XX and nothing abnormal in their chromosomes, 60 percent of them responded to treatment and then in all the other patients very few responded, but normal carrier type is the most common cytogenetic finding, 50 percent of patients with MDS. So this was all, again, very exciting.

This is just a breakdown of the different chromosomal abnormalities. We reviewed that already. Another thing that was interesting was that almost everybody who's going to respond to Lenalidomide, within 1 month of starting treatment they were advance fusion free and the hemoglobin had gone up by 3 to 4 grams meaning if they started out with, let's say at 8, they went up to like 11 or 12 which was remarkable. The side effects though of Lenalidomide are they can make the white cells go down and the platelets go down, but usually we monitor that. You can adjust the dose. You can give drug holidays and the let the counts come up and usually that can be worked with. Fifty-five percent of the patients with cytogenetic abnormalities and 83 percent with deletion 5Q had a cytogenetic remission meaning when you check the bone marrow again, all those cells with the chromosomal abnormality were gone. So it's not a cure, Revlimid. The responses last usually for about a year and then you lose the response and the myelodysplasia acts up again, but it's an oral therapy although, again, it's incredibly expensive, about \$7,500 a month.

So, there's a great need to make things better in MDS and to come up with new treatments. What happens to patients who have already been treated with Azacitidine and it didn't work, well,

they've lost their response. Again, Azacitidine remissions last about 1 to 2 years when you get a remission and then you lose the response and the other thing with Azacitidine and with Revlimid is there's no end to the treatment. You have to keep going. So when people who have responded, the treatments have to continue. If you stop the treatment, the person is going to relapse within a few months.

So one approach is let's add something onto the Azacitidine and see if that makes things better. So this slide, ORR, means overall response rate. What percent do patients improved if you add another drug on to the Azacitidine and includes the complete and partial remissions the bone marrow is getting better and patients whose transfusion requirements went down or their platelet or white counts came up? So some of these are commercially available drugs. Phenylbutyrate and Valproic acid are both commercially available. ATRA, all-trans retinoic acid is a drug that we used to treat acute promyelocytic leukemia and it's an oral agent. So, adding these drugs onto the Azacitidine, the Phenylbutyrate really didn't make much difference. It was the same response rate. Valproic acid, maybe had a little impact. Lenalidomide through the Revlimid did rate seemed to raise response rates somewhat to the 70 percent range. Erythropoietin not too much and Romiplostim which is that Thrombopoietin agonist I mentioned to you that's been subsequently abandoned actually decreased. That was the one that made the platelets go up. Actually made the response rates worse. So unfortunately so far combination therapies have not been a home run and we need to find new drugs to try to make life better.

What about investigational drugs? Well, there's Rigosertib Onconova which my institution was involved in that trial. It was an international trial. It just closed. These are drugs they would use after failure of either Azacitidine or Decitabine. The Rigosertib is a kinase inhibitor. It's given as a 72 hours infusion which means you put the IV in, a person has an IV line attached to a pump. It's a portable thing. You can walk around with the pump on your belt and the drug runs in continuously for around 72 hours. It sounds involved, but actually we use continuous infusion treatment like to this to treat colon cancer frequently. So, it's something that hematologist oncologists are used to doing. This study in high risk patients, so that would be intermediate 2 and high risk on the IPSS have already failed Azacitidine in the original report which was the phase 2 trial had an overall response rate of 46 percent. So, almost half the patients responded to it and the trial that just closed was the phase 3 trial comparing the new drug to best supportive care transfusions and growth factors and I don't know the results. They just closed it and I think they'll probably report these results at the American Society of Clinic Oncology meeting in June. So, everybody's looking forward to that. Sapacitabine is an oral drug. It's a nucleus side analog meaning it's getting incorporated into DNA and in the phase 2 trial, it had an overall response rate of 23 to 28 percent. So again, that will be in the process of moving forward to a phase 3 trial and trying to see how effective it truly is and then Clofarabine is a commercially available chemotherapy drug that's approved to treat pediatric, childhood, acute lymphoblastic leukemia that's relapsed. We use it in adults frequently to treat relapsed acute myeloid leukemia and now it's being looked at in Myelodysplastic Syndrome. It's available commercially in intravenous form on a trial basis there's a pill that's being developed and, again, in patients who have failed Azacitidine or Decitabine in the high risk patients an overall response rate of 30 to 36 percent was achieved which is, again, is very encourage. The problem with Clofarabine is you get severe myelosuppression. Myelosuppression meaning knocking the blood counts very, very low similar to what one sees when we treat leukemia patients.

So, I'll stop there and I'm happy to try and answer any questions.

Q4: Could you just (inaudible 48:44) a two part question. Could you just mention if your institution is using other drug, Ritalin for MDS patients because I was under the impression it's used for children to sort of calm them down, but I read that it's being used for MDS patients in order to sort of wake them up or have them be more energetic when they have a lot of fatigue and the second question is could you just comment on the connection between anemia and Alzheimer's disease and/or dementia and if you're over a certain age should you be taken Aranesp as a preventive or are there side effects to that?

Steven Allen: It's the first Ritalin is not approved for treating people who are fatigued. It's an amphetamine and that's why amphetamines are controlled substances, but there is a commercially FDA approved drug called Provigil that's used to increase people's awareness, but fatigue in MDS is generally due to the low blood counts and I would gear my treatment approach towards trying to improve the blood counts and I have not used Provigil. Usually, it's used like in people who are getting a lot of narcotics for pain control, solid tumor patients. No, I've not used those drugs and then your other question, Alzheimer's is many patients with MDS are older patients and may coincidentally have Alzheimer's, but they're not related and Aranesp I don't prescribe. I defer that to my neurologic and psychiatric colleagues. Nobody's using it prophylactically. I think it's in people with diagnosed dementia. Yes?

Q5: Quick question. My father is diagnosed with MDS RARS and also MPN. Do you see these two are related?

Steven Allen: So MPN is Myeloproliferative Neoplasms and that's disease is like polycythemia. They're or essential thrombocytopenia and myelofibrosis and there is an overlap syndrome. We have MDS in MPN at the same time and the choice of treatment depends on his individual situation and there is this particular disease called refractory anemia with ring sideroblasts and thrombocytosis very... with patients even though it's MDS, they have a very high platelet count.

Q5: That's what he has.

Steven Allen: That's what he has. Yeah. And he's JACK2-positive. JAK2 is a genetic abnormality people with... many people with myeloproliferative neoplasms. So, that disease interestingly they have looked Revlimid in that disease and they might... you might want to discuss that with his hematologist.

Q6: You said that Procrit along with Neupogen that Neupogen increases the effectiveness of Procrit. Now, I'm not sure if I heard you because I'm a little hearing impaired. Did you say before that Neupogen increases the conversion of MDS to AML or did I mishear?

Steven Allen: There is a concern particularly in people with the higher risk MDS. It's not the lower risk, but with the high risk MDS there's a conversion that it might push people over into leukemia.

Q6: So that...

Steven Allen: In general, though, the growth factors, Erythropoietins don't work in higher risk patients. That's why we go straight to Azacitidine and (inaudible 53:01) see in guidelines. They don't mention giving Erythropoietin. They went straight to intensive therapy. Azacitidine. It's the lower risk and intermediate 1 patients where the growth factors may be successful and in patients where Erythropoietin alone hasn't done the job, you can consider adding on Neupogen and that might increase the chance... that in about 10 percent additional patients it will give you a response. Instead of a 16 percent response rate, it goes up to about a 25 percent response rate.

Q6: Okay. I have two other questions, but they're so specific to me that I wondered if I might ask you those questions after the session is over if you don't mind?

Steven Allen: Sure.

Q6: Thank you. Thank you so very much.

Q7: I've been diagnosed with MDS for 12 years. The first (inaudible 54:04) 6 years, I was effectively controlled with Procrit. The last 6 years we tried almost everything that you mentioned up on the board. My question is is there any validity to revisit those items that didn't produce any good effect for me like Revlimid, Vidaza?

Steven Allen: It's highly unlikely that they would be effective. Over time with changes that occur, a treatment that fails even less likely to be effective and you still get all the side effects.

Q7: Thank you.

Q8: Do you have experience where you diagnosed with aplastic anemia and then it changes to MDS?

Steven Allen: Absolutely. There's a tremendous overlap between 3 conditions. Aplastic anemia, Myelodysplastic Syndrome and there's a very, very rare condition called Paroxysmal nocturnal hemoglobinuria, PNH, and people can evolve from 1... any of the 3 to the others and have either completely evolve from 1 to the other or have elements of each of them and that's because they're all stem cell defects and, again, the treatment of hypocellular MDS and aplastic anemia is the same. Paroxysmal nocturnal hemoglobinuria has a drug that specifically treats that disease. It's given as an infusion. That was commercially approved about 3 years ago. It's called Soliris or eculizumab and it's phenomenally effective for that disease, but as I said that disease is exceedingly rare.

Q8: You mentioned...

Steven Allen: I'm still answering his question.

Q8: You mentioned that in the bone marrow transplants, it's 50 percent of the people get cured, but what happens... what are the alternatives to the other 50 percent that do not get cured?

Steven Allen: Prognosis is usually very poor.

Q8: What's that mean? Do you (inaudible 56:38) mortality?

Steven Allen: Myelodysplasia comes back. They're back where they started. They're in worse shape perhaps and people die.

Q9: Are the symptoms the same for aplastic anemia, MDS and PNH?

Steven Allen: MDS and aplastic anemia, the symptoms are the same. PNH has some unusual symptom otology. It's called Paroxysmal nocturnal hemoglobinuria being night and hemoglobinuria meaning blood in the urine because there's a chemical defect in the cells that tends to literally make the cells explode in your circulation and release the hemoglobin inside the cells and that tends to happen at night when people would wake up, go to the bathroom and urinate blood. We don't hear that story much anymore because we make the diagnosis before the disease gets that severe, but then it has other unusual complications like blood clotting abnormally, people getting deep veins thrombophlebitis and they also get low blood counts like MDS and aplastic anemia.

Q9: Thank you.

Steven Allen: Yes.

Q10: Hi. Have you heard any instances of I had chemo 4 ½ years ago for a lymphoma and in December (inaudible 58:13) I found out my (inaudible 58:15) and my platelets were low. So, I've had 5 bone marrow biopsies. I just had the fifth one and my chromo... everything's tested negative including my chromosomes that... So they've been going back and forth MDS and aplastic anemia, but without anything through the biopsy showing other than my... all my levels are low, abnormally low. So now, just this week I... about 2 months ago was the first they were recommending a transplant. I'm going to be 66, but healthy, but now they're coming up this week the diagnosis was now again aplastic anemia and we're going to try the Cyclosporine and possibly (inaudible 59:03) around it depending... Have you heard other cases where you keep getting negative biopsies (inaudible 59:10) what they call systematic?

Steven Allen: I can't... It's hard for me to discuss your individual situation without actually seeing...

Q10: Are people like without having diagnosis?

Steven Allen: It's not that uncommon. We see that frequently. People are pancytopenic and they're having trouble with the bone marrow saying yes it MDS or yes it is aplastic anemia but if it's hypocellular and it looks aplastic anemia, again, it doesn't much matter. Immunosuppressive therapies is excellent in people, mid-60s, immunosuppressive therapies as good as transplant.

Q10: Is as good?

Steven Allen: Yeah.

Q11: Cyclosporine. What conditions might warrant the use... a trial of cyclosporine as...

Steven Allen: That hypocellular MDS where the bone marrow looks empty.

Q11: Exclusively that?

Steven Allen: Yes.

Q11: It wouldn't help in patients that don't have particularly empty cells?

Steven Allen: No.

Q12: I have MDS (inaudible 1:00:30) I'm on red cell transfusion. It's new medication Rigosertib is supposed to be treating that or used for treating that?

Steven Allen: Well, they're looking... They're studying it in people who are a failed Azacitidine. It's not at the point where they're trying it in people who have never been treated. So, if you're (inaudible 1:00:56) just red cell transfusion dependent, if it got to the point that you need a treatment, I'm sure your doctor would recommend Azacitidine or Decitabine first. Ultimately if Rigosertib is as good as it appeared to be in the phase 2 trial, once they get... once the company gets FDA approval for advanced people who already failed treatment, the next thing they'll do is a trial newly diagnosed people and generally if a drug is a homerun and people have failed standard treatment and you move it up front it's even better. So, but that's probably going to be a few years down the road.

Q12: Do you have any other insights into trisomy because it's one of the things that you didn't mention.

Steven Allen: It's the most common... It's one of the most common cytogenetic abnormalities.

Q12: Thank you.

Q13: You gave some statistics about median survival rates that were in the 2 to 3 year range for people in (inaudible 1:02:06). What is the spread and is there any insight into what causes the tails certainly on the longevity side of things?

Steven Allen: You know, there's no answer to that. The numbers I gave you were median which means that 50 percent of the people do better. I have MDS patients I've been following for 20 years. One fellow who had chromosome 7 abnormalities, he's like 25 years out and I... for 20 years I told him he was about 40 when he got diagnosed and I was telling him, "You need a transplant," and he always says, "Not yet, not yet, not yet," and if I transplanted him and he lived all this time, I said, "Gee, it's a good thing we transplanted you," but here he did great.

Q13: There seems to be a lot of question about...

Steven Allen: But he did just get transplanted.

Q13: Oh, he did. Okay. There seems to be a question about transplants and timing. You suggested people over 60. They're still not recommending it or is that changing?

Steven Allen: The age is moving up. People will do donor transplants to the mid to high 60s now if you're in good shape.

Q13: And how does one make the decision at what point to do that? I understood that the survival rate is lower if you have a few symptoms and then, of course, it extends your life if you're further along and somewhere in the middle you have to decide how do people make that decision?

Steven Allen: (inaudible 1:03:38) individualize that decision. It depends how people are doing, what their cytopenias are, what their cytogenetic abnormalities are and you try to time it since transplant is not easy. Like the phrase you hear all the time is, "I feel like I've been run over by a truck," and you don't get back to feeling normal for about six months and then there's all the problems with graft versus host disease that can arise. So, you try to time it but you do it at a point where if you don't do it the patient's likely to run into big problems and I always try to do it before they've had a major complication. If somebody starts getting life threatening infections, life threatening infections that'll make it much harder to safely do the transplant. So, there's no straightforward answer. It's all a balancing act and try to give the person as much time as you can without doing the transplant and then once things are leaning the wrong way try to get the transplant as quickly as possible. I would frequently have people have a transplant consultation so that the transplantors know about them so that they have donors lined up and we're ready to go.

Q14: If you have a sibling does it make sense early on to test for compatibility and freeze blood?

Steven Allen: Absolutely.

Q14: Oh, it is.

Steven Allen: Yeah.

Q14: And what is that process? How does one go...?

Steven Allen: It's just a blood test and they look at your tissue type and your sibling's tissue type and if you match on the most basic levels then they can go and do much more sensitive testing, but that kind of testing is very involved and expensive. The original screening is very straightforward.

Q14: And you can freeze that blood for periods of time or keep it, let's say...

Steven Allen: No, they wouldn't collect the stem cells.

Q14: They would not. They wouldn't. Okay.

Steven Allen: They'd just... They would identify a donor.

Q14: That has to be at the moment of the...

Steven Allen: Or fairly close.

Q14: I see. Okay.

Q15: I thought I read that they're doing transplants up until the age of 75. You said the upper 60s. So the ones... the institutions that are doing it up to the age of 75, are they doing like mini transplants or not...?

Steven Allen: At that age they'd be doing mini transplants and that's on a trial basis. It's not standard.

Q15: Could you describe what mini means?

Steven Allen: It's lower doses of chemotherapy drugs and different classes of drugs than the standard transplant approach. It's more tolerable. The concern has been engraftment and survival of the donor cells. Everybody's very encouraged by it, but it's in a relatively early stage.

Q15: And could you just say something about the difference concerning blasts versus sideroblasts in your words?

Steven Allen: Well, blasts are the most immature precursor cells that you can see in the bone marrow and they have a characteristic appearance that hematologist or pathologist will recognize when studying the marrow. Sideroblasts refers to a subset of red cell precursors and you're probably referring to ring sideroblasts which are... there's a lot... you have iron in the red cells because that's where your hemoglobin is made and iron is at the center of the hemoglobin molecule and part of the synthetic process for hemoglobin goes through an organ L structure inside the cell called mitochondrion and in ring sideroblasts the mitochondria fill up with iron and you can do a special stain on the marrow and you can actually see the iron filled up mitochondria called ringed because the mitochondria tend to be around the outside of the nucleus. So, it's very pretty actually to see this ring of blue granules around the outside of the nucleus and by definition it has to be more than two-thirds of the circumference of the nucleus to call it a ring sideroblasts and that's refractory anemia with ring sideroblasts is one of the subtypes of Myelodysplastic Syndrome. It's in the low risk group and...

Q16: Some of the drug treatments that you said you have something called complete remission and a percentage. Could you explain the difference between complete remission and cure?

Steven Allen: Well remission means whatever disease, the disease isn't there anymore. Cure means it never comes back. We don't... we can't cure Myelodysplastic Syndrome with any of these medical treatments. The only potential cure is to get rid of all of your blood stem cells and replace them with the donor's.

Q16: So complete remission looks like a cure but it's possible that it comes back. Is that the difference?

Steven Allen: I would say complete remission looks like things are normal. A cure is at 120 you get run over by a truck.

Q17: But just as somebody lives until, let's say 50, 60 or 70 "normal" and then MDS develops, couldn't somebody who has transplant live for a number of years "normally" and then MDS just might have developed anyway in the person that's giving the blood. Do you know what I mean?

Steven Allen: Yes.

Q17: Is that a possibility?

Steven Allen: It's occurred.

Q17: Oh, it has.

Steven Allen: Of course.

Q18: What is oldest person (inaudible 1:09:40) with MDS?

Steven Allen: I've had patients in their 90s with MDS.

Q18: It's possible to live long enough.

Steven Allen: Or to develop in the 90s.

Q19: You mentioned about 30... 30 percent of MDS eventually go to a change to leukemia.

Steven Allen: Yes.

Q19: What happened to the other 70? Do they continue having...?

Steven Allen: Unfortunately, eventually they may die of complications of the MDS, the low white count. People get infections, the low platelet counts, they get bleeding complications.

Q20: Can you put the slide back that that shows the pie of percentage of the IPSS score and the different low risk, first intermediate, second intermediate? Thank you. You just had it. Okay.

Q21: I'm curious about the iron issue. What are the symptoms of high iron and what happens if it's not treated because the treatment seems to be fairly unpleasant?

Steven Allen: Well, the main things we'd worry about are heart problems. Usually, arrhythmias, the heartbeat becoming irregular, atrial fibrillation, things like that. You worry about the liver, people can get cirrhosis. People can develop diabetes. They can get hypothyroidism, low thyroid function.

Q21: And that's when they get up in that over 1,000 range?

Steven Allen: Yeah.

Moderator: If anybody else have any other questions, again, feel free to reach out to MDS Foundation and again you can field the questions through that avenue if you should think of any other and we can have Dr. Allen or myself or other nurses or other physicians that are part of the organization answer your question. So again, this does not mean that we stop right here. It means that you can continue your questions further on. So, we're available. Thank you, Dr. Allen, very much.

(Applause)

Moderator: Anybody want to take a five minute break to use the restrooms and stretch a little bit or...