



San Antonio, TX Patient & Family Forum – November 18, 2017 - Session 1 **Page 1 of 20**

Speakers:

Roger M. Lyons, MD, FACP
Virginia E. Aguilar, NP

Audrey Hassan: ... Foundation and I want to welcome all of you today. Just a few housekeeping rules. We are taping this program for those that are unavailable to come today. It'll be up on our website following our program. So, if you could put your cell phones on vibrate that would be great. Please help yourself to food during the program. We want you to feel very comfortable. It's very informal. There will be an opportunity to ask questions. So, at that time on your microphones on the desktop there is a... right in the middle you'll see a face with a speaker coming out of it. You'll have to press that button to be heard and then toggle it off and whoever is speaking there will be a red light. So, you'll know when it's ready. I want... it's an honor and a pleasure today also to have Dr. Roger Lyons here from Texas Oncology who donated his time today to be here. We also have Ginny Aguilar, his nurse here. So, it's an honor for us to have you here today.

So, without further ado we'd like to get the program started. Please help me in welcoming Dr. Lyons.

(Applause)

(No audio 1:28 - 3:35)

Roger M. Lyons, MD: ... and because of the reporting is very poor. Those numbers are really numbers that I took from Sweden and Finland where they have better registries than we do and I think it's in that range. That's people will argue back and forth, but this is a common disorder now. Still called rare, but it's becoming more common as our population ages and we are allowed to develop other diseases, survive other illnesses. Median age is in the senior range, the more experienced group of people and this a clonal disorder. So, clonal we mean it comes from a single clone of cells in the blood usually at the stem cell level, the earliest cell that's being developed in the bone marrow and these clones grow and they get multiple genetic defects and as you get more genetic defects the cells change and they tend to have other activities, which we try and attack. So, we'll go through some of that and so when you look at a bone marrow the bone marrow is full of cells, but the cells are not coming out. They're ineffective. They're dying inside the bone marrow. There is a side pipe where the bone marrow is suppressed and it's a little bit different but the majority of people have lots of cells and if you look at them say why aren't they in the blood? They're not.

So, this is old slide, but still very nice, very valid. It shows you the incidence with increasing age, this huge jump as we get into the 60s and above and more common in men than women. Don't know why. This is sort of a pathophysiology. The way we think about cell development.

So, the very earliest cell is called the stem cell. In the bone marrow this cell can then develop into any other blood cell. It can develop into white blood cells, red blood cells and platelets, the cells to make platelets, megakaryocytes, and then those cells continue to grow and become normal, but in this disease what happens is there is a mutation that occurs very early on and so you get all the defects in the way cells grow and differentiate, turn into more mature cells, how quickly they grow and this word apoptosis which means programmed cell death. All cells within them have a program that they're not supposed to live longer than they should and they die and that's called apoptosis and these cells no longer have normal apoptosis. They tend not to die. They continue to live. That's cancer and this is a cancer and as these cells grow they get additional mutations and sometimes turn to leukemia or just stay at myelodysplasia or turn into something called myeloproliferative disorder. Myelo is bone marrow. Proliferative is growing too fast. So, a cell a different subtype of blood disorders where the cells are actually growing too quickly and the blood counts tend to be quite high. As that happens the normal cell production decreases and we develop low blood counts, red cells, white cells and platelets. So, when I first see a patient the patients are usually sent to me, I would say 80 percent of the time because their primary care doctor or somebody else noticed that a blood count was low, usually anemia and about a third of the time it's a low white blood count or a low platelet count and when I go back and I dig out blood counts for five years – 10 years ago I'll often find some minor abnormalities that were there that nobody would pay much attention to and I wouldn't pay much attention to because it's a retrospective look, but you can see in the background there's probably something going on for a long, long time.

So, this is a long list of things. You don't have to read it, but we go through a routine of what we have to look at. We have to look at the blood. We have to look at it under the microscope. We have to measure how many cells are being produced. You have to do a bone marrow. You have to look at it and see how many immature cells are there, blasts, immature cells, leukemia type cells. You can't tell looking if a blast is a leukemia cell or normal cell. So, we just call them blasts and then we do all the things that we like to do in terms of iron stains and how much fibrous tissue, we're taking tissue then we look at the genes, the cytogenetics. They call it various things, cytogenetic karyotype chromosomes. We can do that in by actually looking at them, crushing them and looking at them or you can do this FISH test, a nice name, fluorescent anhydrous in situ hybridization where you can take a look at a fluorescent dye and it tags all these chromosome abnormalities. So, they're easier to see if you know the specific one you're looking for and now, of course, you've all heard about these next generation sequencing machines where you throw a little bit of stuff then seven days later you got your whole gene comes out or we can target the genes that we want. So, that's called next generation sequencing and we do different sets either small sets or larger sets or the whole gene depending on what we want to find here and we do iron studies and B12 and so on and then we have to classify patients' disease based on the way it looks under the microscope. The original system was the FAB, the French-American-British System, and then there's a WHO, World Health Organization, classification which just got updated last year. Gets more complicated every year... every time they update it and then we have these prognostic scoring systems. The original one was the IPSS,

the International Prognostic Score, and then more recently there's a revised form of that and I'll show you those in some detail because it gives you when you look at them a feel for what we're trying to look at to give us an idea of what's going to happen, what's the appropriate treatment.

So, we're not going to go through this.

This is World Health Organization criteria and you can see there's that you need actually pretty low blood count, hemoglobin less than 10, lower limit of normal for a man is 14, woman is 12. So, it's lower than 10; a low absolute neutrophil count. That's actually a normal one and a low platelet count, lower range for normal is 150. So, you really have to have to low blood counts to make the diagnosis unless you have a specific gene abnormality and then there's all these criteria that we (inaudible 10:01), but if you see one of these genes in... then you have an automatic diagnosis of myelodysplasia. There's multiple different genes here. They have different prognostic indications. This 5Q- or the where the long arm of the fifth chromosome is cut off is almost a separate disease with a separate response rate. It's the most common genetic abnormality seen in MDS. It's only about five percent, but when you see it and I'll show you the data after the response rates to a specific drug are quite remarkable and persistent. So, we look for these chromosomes and say even if those blood counts don't fit the criteria you see one of these genetic abnormalities you've made the diagnosis.

Well, this is sort of hard disease because MDS is overlapped with all sorts of other things. Diseases actually (inaudible 11:02) I mentioned model proliferative disorders, aplastic anemia where the marrow is totally wiped out and this rare disease of paroxysmal nocturnal hemoglobinuria, an immune disorder of lymphocytes and so on and you often see these together and so we have actually a formal classification now of something called mixed myelodysplastic/myeloproliferative disorder. There's actually a formal designation because that's reasonably common and there's different genes that you see there. We're not quite sure the treatments are much different yet.

Again, I'm not going to go through this. This is the World Health Organization classification. MDS is on this list and what I want to point out here is we keep talking about lower risk disease which is in this area and then there's a set of higher risk disease and we base that partly on this classification really almost totally based on the number of these blasts. If it's less than five percent it's lower risk. If it's between five and 19 it's higher risk. If it's above 19, it's leukemia. It used to be that 20 to 30 was also myelodysplasia. They just changed that. So, now 20 to 30 is acute leukemia, but we don't think about it that way. We call it now low blast, low blast AML and actually people get treated just as if they have myelodysplasia with that. So, the pathologists keep fiddling with this and there's good reason for it, but it doesn't change our thought process about treatment.

So, here's this IPSS score, Peter Greenberg, still around, still working hard and put this together and he also is the author of the new... of the revised form. Took only three criteria – the number

of these blasts in the bone marrow, the chromosome, the karyotype and the number of cytopenias, the number of cell lines that were decrease. White cells, platelets, red cells and you added these up and you got a score and... so, you got a score and with this score you could split people into different risk groups. You would say either lower risk, intermediate, intermediate-2 or high. The important thing is these two are lower risk and these other two are higher risk and actually this separated people out in different groups. You can see that the lower-intermediate and the high are... differ with survival and change to acute leukemia. Now, only about 20 percent of people develop leukemia. Most people don't die of leukemia. They die of either bone marrow failure or some other disease. As we get older we could still have heart disease and lung disease and strokes. You're not excluded from other diseases just because you have MDS and so this is the survival group. When people look at that and say oh, my God I better dig, 5.7 I'm done. Of course, these are ranges and the line is very broad and you'll see later on as we look at some of these curves they seem to go on forever because many people really don't die of this disease in the lower risk group.

And we don't have a slide there, but here's the revised portion. So, this is more complicated and it's more complicated because we realize that there is some more subtypes that we can put in here to try and separate people out in terms of the risk and so the differences here are that there are different some different points given for different reasons. So, now for these chromosomes there's a very good and a very poor instead of just three groups. For the number of blasts there's now a two to five. It was just five, less than five before. For the red count, the hemoglobin, it's now less than 10 and less than eight. That adds another half point. Platelet count at various levels adds points depending on how low it is and the white count, the low .8 is the neutrophil count adds more points and then you can get all these scores and you can see, again, a very good separation in the different groups in terms of survival.

So, what causes this? This is a little complicated slide if I can get it. Can I get it? There we go, but it's very pretty. Just look at the top and you'll see my color... I'm a little color blind so I have a little trouble with this slide and it's small, but on this side these are normal cells. So, you get a normal cell and it grows and if you follow its color along you will see that the normal cell either gets smaller or larger. So, the width of each of these suggests a clone. So, what happens is there's a mutation and the mutation and then that subgroup grows and you can see at different times it gets smaller or larger as additional dots appear in here and these additional dots are additional mutations. So, the whole idea, again, is you got the stem cell, it produces the earliest white cell which we would see as look as a blast under the microscope. It's going along and then it gets a mutation randomly and then it's probably doesn't do anything with one mutation. There's only a couple of mutations that where you get a single one that you're getting disease and then you start getting additional mutations and when you get these additional mutations then then the cell develops additional characteristics where it has growth advantages and survives longer and then you end up with acute leukemia with this intermediate step of myelodysplasia where there's only a few mutations and when you get to acute leukemia there's many more mutations. Does that make sense? It's a little complicated, but it's really the core thought process

here. A mutation that occurs randomly, starts the disease off and then you start to acquire more and more mutations. Each cell line, each clone can grow or shrink and you may have one cell line that's so tiny you can't even find it and... So, I'll tell you a story about this. This is I was at Foundation One. I don't know if you know they are the first people to develop the whole genome and we're talking with a group of people trying to advise them on what to do and we said, "We can tell you all these different clones based on their genes," and the fellow beside me from Sloan Kettering, he said, "Well, you did that for me and I found somebody with acute leukemia whose major gene had a drug that we knew we could get to, we could target that gene. I gave it to them and they died." I said, "That's horrible. What happened?" He said, "I killed that one, but there was a little one in the background that as soon as that big one went it exploded, the big gene, the big clone was suppressing this tiny clone and when the big one was gone the tiny clone grew very quickly and there was nothing to treat it with." So, you have to be careful here. So, we're all about looking for targets now, but we have to be careful what we're doing. It's not really that easy.

So, this is really great data. So, there were two studies back to back in the *New England Journal*. That there were 25 to 30,000 patients all together. Normal. I say patients they were not... these were normal people walking down the street. They did a genetic profile looking for genes associated with blood cancers, myelodysplasia and leukemia. So, normal. Have normal blood counts, no complaints, normal people and they looked for a single whether or not they had a gene abnormal. You can see here by the age of 70, 10 percent, one in 10 of the entire normal population has at least one gene abnormal. So, this is occurring in us all the time. What does that convert to? Well, it converts to... I think I may have this out of order a little bit. So, it converts to a slight increase incidence of acute leukemia, but look at these percentages. These are really tiny. This .04. So, it may be a one in 100 change of getting acute leukemia every year when you have one of these gene abnormalities. You have to have more gene abnormalities and so these people were normal, nobody would have had any idea. Well, what do we do with these people who have a gene abnormality but don't fit the criteria of myelodysplasia? What do we say? Well, some of those people do have low blood counts. They don't fall to that criteria of less than 10 and so on that I showed you, but they're low enough that they end up on my doorstep and we now have another disease as we call it CHIP. So, this is what we call people who have these gene abnormality but don't have myelodysplasia. So, this is clonal hematopoiesis of indeterminate potential. Sort of a weird name, but you happen to have an acronym otherwise nobody remembers and so they put this together and it's nice and so there's a variety of things in here but focus on this CHIP. There's a clone if it's abnormal, but when you look at the cells in the microscope you can't see any abnormalities. They look fine. There's no... the blood counts aren't significantly decreased. There's no increase in blasts in the bone marrow and these... and people do well. So, I see a lot of people. I actually try not to do the gene studies because I can't... I say, ah, there it is. I'll see you in six months. We're not going to do anything about it, but if you do them for some reason people will have this disorder. So, as I said, there's a little increase in leukemia, but what's also interesting here is that overall survival is decreased even though there's only a slight decrease in... a slight increase in acute leukemia. So, this kind of

curve if you're we'll see again and again you can see this is a sort of (inaudible 21:43) so one... if it's less than one in this thing that means that people will live longer. If it's above one it means a shorter survival and so there's a slight increase... a slight decrease in survival, hazard ration of 1.4. So, that's real statistically real. Why is that? Well, it turns out people have CHIP for reasons we have no idea, have an increased incidence of death from coronary heart disease and stroke. I don't understand that and, of course, so there's something else going on. It's not just a mutation in the gene that affects the blood. There's something that is affecting blood vessels or clotting or something else.

So, what do we do with treatment? So, we think we now start coming back to this thought process of lower risk versus higher risk based on the number of blasts and the IPSS score and for the... the old IPSS when there were only four groups that was easy. With the revised it's in the middle group we have to split in half. Don't worry about that. I'll do that for you, but it takes a little bit of a calculation. So... sorry... If I can make it go backwards. Went to the beginning. That's not good or did I go to the end? I'm not good at pushing the right button here. So, when we're talking about treatment for lower risk disease many patients don't need anything at all. I mean, they have mild anemia, hemoglobin may be 11 and people don't have symptoms. You've made the diagnosis and you don't do anything. You just say tell me if you don't feel well, if you start being fatigued or bleeding or having increased infections and come back then. So, this is this group here that quality of life is normal and you don't do anything. You just wait and watch. Early intervention does not alter the outcome and then there's the second group of patients whose hemoglobin is less than 10. There's no other obvious causes for anemia, you corrected iron deficiency or B12 deficiency or bleeding or whatever and they're still anemic and they're starting to have symptoms and with that situation we start treating with erythroid stimulating agents. The kidney produces a substance called erythropoietin and the erythropoietin and it does that because there's a sensor in the kidney that sense oxygen when the oxygen goes down you... oxygen content goes down you make more erythropoietin. That stimulates red cell production. We have that stuff in a bottle. We've had it for a long time. We have short acting, long acting, different, generics, all sorts of stuff and so we use that. Well, how do you know if it's going to work? You can actually have a pretty good idea if it's going to work. This is Dr. Lindstrom from Sweden who's done a lot of working this area. This is an old paper, but it's still valid. What she did is she separated people with lower risk. Now, this is based on the way they looked. This is the old FAB classification and based on the erythropoietin level, serum erythropoietin level and the number of transfusions people were needing you could have either a 74 percent chance of response or seven and so people look at this, but frankly I'll take a seven percent, too, because it's so easy. So, most people will get erythroid stimulating agents, but you can guess ahead of time whether or not they're going to have a good response and we play with doses and you can add on other agents as well. So, that's the first thing to do and in lower risk people response rates are really excellent. Higher risk they're not very good.

So, what do you do once that fails because it doesn't last forever? You then come down to adding on another drug. Dr. (inaudible 25:55) likes to start with Revlimid. I am not so sure that

it's the right starting drug. There's two groups of drugs that we'll talk about. Either Revlimid, Lenalidomide is the original name is the non-trade name or Azacitidine or Decitabine which are hypomethylating agents. They strip the methyl groups off the DNA, so the DNA can express itself. This disease is associated with a slimy coat of methyl groups, CH₃, on the DNA. When that gets added on with time and if you take those off the DNA starts to work again and you start to make more blood cells and I'll show you some of that data.

So, here's Lenalidomide. It's actually this is the Thalidomide story. Lenalidomide is the second generation of Thalidomide. You remember Thalidomide was the drug that was used for women for sleep disorders when they were pregnant in Germany and caused all those defects. It was taken off the market. Obviously, never came to the United States and probably now 25 years ago a patient in the University of Arkansas who had multiple myeloma was doing very poorly and his wife found some research done by somebody at Harvard that said that Thalidomide stopped blood vessels from growing and if you look at the bone marrow, people with multiple myeloma, there's lots of abnormal blood vessels and she persuaded the Art Vorlage who was the head of that group to apply to the FDA to use Thalidomide in her husband. They agreed. I don't know if they agree now. It worked and Thalidomide was back in. Of course, not given to pregnant women and then this is the next generation developed largely for multiple myeloma but works and I'll show you good data how it works or not how it works, but it works here. So, it's approved in MDS and it's approved in multiple myeloma.

So, here's Alan List's data. This was a tremendous finding. He was studying... he's now Head at Moffett. He was in where was he? He was in... not in Phoenix, but he was in Arizona at the time and he studied patients who took this drug and gave it to everybody and found that this small subgroup, these people with the long arm of the fifth chromosome when received this drug had an unexpected response and then did additional studies and had saw this unbelievably good response with huge responses. This was his... people were transfusion dependent became transfusion independent and there was some minor responses and even the chromosome went away in some people. So, there's this dramatic increase in hemoglobin, five grams, time to response very fast, average duration of response is actually about four years, really an amazing treatment. So, how about the people who don't have that mutation? So, these responses are much lower in the complete responses here are only about 26 percent in total about 43 and we see in the lower risk patients with myelodysplasia we see actually higher response rates with Azacitidine and we've had arguments back and forth which drug you use first and people have tried to use them in combination and that's been disappointing. So, and here's the increase in hemoglobin. It's significant. Time response is great, very short term response rates.

So, Azacitidine. This is a whole list of things. This is one of these groups of drugs called hypomethylating agents. We're stripping the... cleaning the DNA of the methyl group so that the DNA gets reactivated and it's approved for virtually all kinds of myelodysplasia. There's a very similar drug called Decitabine, which they look very similar in terms of their structure. They

have some different activities. Decitabine is more toxic to the bone marrow and but the... probably if used properly fairly similar in benefit although that's never been proven.

So, this is a study we did looking at the lower... largely lower risk patients. The original way the Azacitidine was given seven days in a row by Lou Silverman who's in New York. Everybody thought he was crazy. This is an old drug, a drug that was pulled off the market because it was too toxic in the doses used. He believed if you used tiny little doses probably a tenth of the doses that were used before it would help myelodysplasia and everybody laughed at him until it worked and it did work, but he used seven days in a row. I asked him why he picked that. He said, "No, reason. Just picked it out of the air," but nobody can do seven days in a row because it's hard to get people, nurses and pharmacists, to work on the weekends and so we actually did a study looking at different regimens either the five days with two... the weekend off and then two more, five-two-five or just five days in a row. The results are about the same but with very good response rates in the 50 to 65 percent range and that's what you see with the Azacitidine and all the other studies show the same thing.

Well, people are looking at all sorts of things with this Azacitidine and Decitabine. So, five days worked good. How about three? Three may work, too. The recent study from Dr. Garcia-Manero at Anderson shows that it works very well. Unfortunately, he didn't compare it to anything and there's we now have an oral form of the Azacitidine and maybe it works better if you take it every day and that study's ongoing. There are studies published where you take it every day for three weeks out of four. That looks pretty good. There's all sorts of variations on this theme and there's actually some... an oral form of the Decitabine as well now that's in study and we'll have that study up hopefully soon, I hope.

So, what do you use first? Well, we have a paper in publication now looking at this and the authors did not agree because we don't know. So, we don't know what you use first. So, Azacitidine is more effective in the non-5Q-. Revlimid is less effective, but it's a pill not an injection. People like that, but if it's a pill your co-pays a little higher. So, there's some financial issues and in addition in just one study retrospective people who failed Azacitidine, Revlimid didn't work if you failed Revlimid. It worked... Azacitidine worked in a small percentage of people. There's not really an answer here. Actually, Azacitidine is better tolerated than Revlimid. Revlimid has about 20 to 25 percent of people can't tolerate it because of rash and stomach upset. So, nice to have two drugs. Well, why don't you just put them together? Five studies now all failed putting them together. Toxicity profile is too high. Maybe the doses were wrong, maybe they were given in the wrong way. I'm still hopeful that that will come back, but it's been looked at largely in the higher risk group patients.

So, let's come back to this. So, this is a little touchy because this, the FDA, would probably put me in jail for this slide, but it's not my slide. So, I'm better... So, low platelet counts what do you do? Well, we have two drugs marketed for immune thrombocytopenic purpura low thrombocytic... low... thrombocytopenic low platelets purpura the little red spots you get when

your platelet count is low. We were actually involved in the original studies. Great drugs that you give either in an injection or a pill to bring the platelet count up. We studied it in MDS and the FDA shut us down and says it causes leukemia. Here's the data. It doesn't cause leukemia and here's the data and they don't care. Nonetheless everybody who treats patients with this agrees that those drugs work in MDS and we don't really have a lot of other things until you go to Azacitidine which actually helps in many patients as well. So, multiple studies and one study here if you look in people who had platelet counts of less than 20 where we often give platelet transfusions people on the platelet agents had less bleeding where above 20 where we don't usually give platelet transfusions it was less bleeding. So, it clearly works and in terms of leukemia here how many years now? This is years, seven years out following these patients. Absolutely no increase in (inaudible 35:29) leukemia. The FDA is not interested in talking to us about this, but they're going to have to because we don't have anything else.

So, this is really an interesting situa... Some people when they arrive have high iron levels and we measure that with a serum ferritin which is sort of a measure of the total body iron stores. It's an iron storage protein that leaks out of the liver and really easy to measure. We get the results in our office within an hour and when the ferritin level is high, the question how high maybe over 1,000 or over 2,000, upper range of normal is about 150 for women and maybe 400 for men. When you give patients a medicine to lower the iron levels and there's several different kinds. The one we use most often now is (inaudible 36:25) is easier to manage as pill you sometimes lower the iron, sometimes don't, but if you look at these patients that you do give this agent to the survival is dramatically improved. So, this is our study. Sorry for showing just ours, but there are many others and you can see these are people who got these agents. They were chelated either for more than six months or even less than six months, brief exposure compared to patients who were very similar who did not get it, almost doubling survival, and this is not just our study. Look at this. This is a compilation. This is a little older slide because there's more studies and see this is this hazard ratio, again. Above one is benefit and when you take all these studies together you can see pretty dramatic benefit with this drug. So, people don't always think about this and we're not quite sure how this works. So, I reviewed a paper this morning from Austria to trying to decide on how to give the drugs and I'm not sure they got the right idea. They are going to stop the drug if the ferritin doesn't go down. I have no idea if this drug works by lowering the ferritin or not and it may work by some other mechanism of removing iron and maybe not even iron. It removes copper, it removes a few other things and alters metabolism. So, this is a very, very important thing that many physicians don't even remember because it seems like it's a side supportive issue.

So, higher risk disease. Higher risk disease. So, these are people who I can't even see it... So, these people... the first thought here is transplantation and I'll show you a little bit of data about survival. The reason being is bone marrow transplantation is curative. There's nothing else that's curative, but when we calculate the total number of people eligible for bone marrow transplant I'm talking about getting bone marrow from somebody else, it's probably less than 10 percent because of age, comorbidities, personal preference, side effect profile, cost and so it's not that

many. So, the first thing we do usually with these higher risk patients are to, again, to make sure there's nothing else going on you can fix. Check the copper levels, check the B12. Those people with copper deficiency look like they've got myelodysplasia. Fix all those things and then usually you go right into a hypomethylating agent or if you have a research study available you certainly want to do that first if you can and so we'll go to these hypomethylating agents and there is a various response rate. It's not as good as we'd like. It's probably only about 40 percent response. Some people who respond can respond five or six years, but that's not the most common thing. The average response time is about a year – year and a half and then you're stuck and I'll show you some of that data. So, again, you try and get everything else ready. There are a few people who are healthy enough or as you'll see later on have specific gene abnormalities that you want to treat more aggressively. So, even as we get older and our healthier population we don't have an age cutoff anymore for more aggressive treatment. We'll treat anybody who is strong and healthy and has a very good performance status, but again it's a very small proportion. I would say it's less than 10 percent of patients who really want to spend like really up to three months in the hospital, maybe little breaks in between to get a response rate that may be in the 20 percent range, but it's there.

So, this is a calculation of... did the colors come out? Did the colors show there? I don't see colors. No colors. Well, I'll show you numbers. I don't know why the colors don't show. So, this is a... it's a called a mark off calculation of what you would predict survival would be with transplantation and you can see either at diagnosis or at progression and so you can see for lower risk people this low and Intermediate-1 that if you transplant early you don't do as well if you transplant late, but it's just the opposite for higher risk people. Transplanting early has a better survival than transplanting late. So, it's just a reason why we don't transplant early in MDS. I don't know how this one got torn, but there it is. So, in hypomethylating agents interestingly since these drugs don't work like regular chemotherapy it really doesn't wipe out the marrow. The marrow is suppressed. About 80 percent of people who respond by the sixth cycle, but another 20 percent respond after the sixth cycle. So, you have to be very persistent. When the first treatments were done with these agents some places said oh, 10 responded after two treatments. That's a failure. Well, this missed about 70 percent of the patients who were going to respond or 60 percent that are going to respond. You have to be persistent, have to stay on time and have to just go right through the low blood counts and you can almost always do it and when you get a response you just keep going until it doesn't... you don't... until you lose your response. Well, here's this very interesting trial from Pierre Fenó from France. None of this was done in the United States. It was all done in Europe and this was a design looking at Azacitidine and they did the seven days in a row. You can give an IV which we prefer rather than subcutaneous and what they did they said before you start the trial patients are going to get randomized, you don't know to which to either the best treatment available or to the Azacitidine and you... but you had to pick which best treatment. You couldn't play with it after and so it made it a very good study. People could not manipulate... the physicians couldn't manipulate where their patients went and those best treatments were transfusion only, low dose cytosine arabinoside, which the Europeans still like for this and there is a small response rate. We don't

do much of that here or standard acute leukemia treatment. These are high risk patients. What they saw was an almost doubling of median survival, 15 to 24 ½ months really remarkable and it was all subgroups and so with this study Azacitidine became the standard of care. Decitabine on the other hand was used and this... against the investigator's advice and I wasn't involved in this study. They picked this regimen which didn't work and it was predicted it was going to be too toxic and it didn't show any survival advantage. Some of the newer ways to give it may be better, but there's no control study. So, what happens after the Azacitidine failure? So, these lines are different kinds of things either transplant if you... sometimes you come eligible after Azacitidine because you get better, the blood counts get better, people get healthier, they feel better and we beat on them to fix their heart problems and lung problems and you sometimes will have people who become transplant eligible who weren't before or who didn't want to do transplant and now have rethought that or a research study and these two that occurs this the best survival was transplant and the second best was investigational going on a study. So, don't have a tremendous amount after the Azacitidine fails.

So, what's new? There's a lot of stuff new. So, there's a BCL-2 inhibitor. We'll go over that. BCL-2 is something that prevents apoptosis that programmed cell death I mentioned. This is old but reapproved, another FDA attack on us that they finally gave in on where if you look at the surface of these cells they're covered with proteins and we give those proteins all a name, common designation numbers and this is CD33 which is present on most leukemia cells and so this is with one of these targeted therapies where there's an antibody and a toxin attached to it and then there's a reformulation of the standard treatment of the cytosine arabinoside and the donamicin (sp? 45:31) now put into little lipid packet in the exact right combination and it has some advantages and then there's really new targeted therapies just out in the last couple of months for these things called IADH2 and FLT3 and we're still as I said I personally haven't given up on these combinations and there's these really exciting immune system manipulations.

So, I showed you this before, but just to remind what's happening here is as cells get more and more abnormal the BCL2 level this protein inside the cells, the BCL2 increases and so it becomes a very high level and we actually measure BCL2 in all sorts of cancers, but BCL2 is high in lymphoma, for example, that's bad. So, here's this Venetoclax, this BCL2 inhibitor and this is, again, not a great slide and the numbers are small, but you can see here that these are the response rates in various doses in people with either Decitabine or Azacitidine in combination and they're really pretty impressive results in patients who had acute leukemia and who were older and so that's now FDA approved. It's FDA approved in combination with cytosine arabinoside, the Ara-C (? 47:01) which is in low dose or standard dose whichever you want and you can see here that these are pretty good response rates. So, the overall response rates are when you add all these together are pretty good. So, that's a pill. Take it at 4:00 a.m. and then we have to monitor your blood counts during the day because sometimes it works too well. In lymphomas and leukemia where chronic lymphocytic leukemia where it's released sometimes the cells just pop. They just disappear and when that happens the debris from

the cells and the uric acid can be life threatening illness and so you have to monitor people after the first dose and it's true for this disease as well.

So, this is a really neat agent. So, lots of names for it. So, this is Mylotarg, gemtuzumab ozogamaicin. You like that one? GO. So, this is this monoclonal antibody that targets the surface of the cancer cell of the leukemia cell and it has a poison attached to it. The cell swallows it. The poison is released, the cell dies. Interesting. We've got all sorts of agents that do that now. So, the immunotherapies, targeted immunotherapy. So, these are studies that were done in England. In England the Medical Research Council really controls all patients treated for elderly acute leukemia, actually all leukemia, and they did these studies showing repeatedly over and over and over again survival advantage, but this was not the dose that was approved in the United States. This drug was available in the United States. It was one-quarter of the dose. When we first saw these papers we reusing the drug. We immediately dropped our dose. There was another study published with a higher dose, too much toxicity. FDA pulled the drug and it just came back. So, this is almost what 12 years ago we've been without this drug. Well, this is really a San Antonio drug. Got a neat story to it. So, here's this... the poison what does that remind you of? Calicheamicin is the name of the poison. Calichi. So, the story is that the pharmaceutical company told all their employees when you go on vacation bring back some dirt. Okay? So, they're in New Jersey and there was a young couple who were on vacation in Curville (sp?) of all... I don't know why and they dug up a little dirt and they brought it back and they grew a bacteria out of the dirt that produced this poison and they named it calicheamicin. So, it's really our drug. So, yes it worked. Take it off the market by the FDA and but two recent studies from French showed survival advantages are using the drug alone or in patients in combination with chemotherapy really pretty good survival advantage and so it's back on the market and we've got it for older patients with better chromosome abnormalities. There we go. So, that was the second study. I won't show you that.

So, this is this lipid package. This is CPX whatever 351. So, this is the cytosine arabinoside and Donamisin (sp? 50:31), a little lipid exactly the right combination and, again, you can see it's a survival advantage here, but the toxicity and the toxicity is slightly lower than other treatments. So, it means it's a little better tolerated in older people. If you've got \$100,000, we'll give it to you because that what it costs.

This one's really neat. This is called...it's an IDH2 mutation for IDH2. So, everybody remembers their Krebs cycle from... So, this is the Krebs cycle. This is 2-hydroxygluturate. This is just the Krebs cycle that you all learned in high school or wherever. It turns out the 2-hydroxygluturate is produced in excess because if mutation in the IDH2 gene and 2-hydroxygluturate causes leukemia. God knows... So, it does and so about seven percent of people with myelodysplasia and about 12 percent of people with acute leukemia have this mutation and this drug is now available. The IDH1 mutation does the same thing. That drug should be out next year or the year after. If you give people the drug your IDH1 level... IDH... I'm sorry. Either 2-hydroxygluturate level goes down and the cells don't disappear. They turn

into normal cells. They turn into normal cells. Now, there's a differentiation process with that and it's like similar to giving retinoic acid to acute promyelocytic leukemia (sp? 52:15) acute leukemia. The same thing happens. You can get really sick early on with this and so you have to watch carefully insert other treatments perhaps with steroids and so on to get through that first week where you can get all this toxicity.

So, these are some results, again, in red and you can see these overall response rates and there's leukemia and MDS pretty good response rates. Very small numbers, but very good response rates. Duration is not entirely clear. It's some are a year, some are less and then you get this differentiation syndrome that you have to watch for carefully that as the cells turn into normal they release all sorts of hormones and you can get into pulmonary problems and so on. You have to use hydrocorticosteroids and stop the drug. So, it's not take this pill and go home. It's take this pill and we're going to watch you like a hawk.

So, this is really also something you've all heard about. It's really kind of a pretty picture, but it's kind of weird. So, here's this cancer cell sitting in the middle surrounded by lymphocytes that would love to kill it. Okay? They'd just love to kill that cell, but they can't see it. It's hidden. It's cloaked. It's covered with something called PD-L1 which is here. Where's it show it? So, I don't know if you can see it but it says PD-L1 here. So, these cancer cells, leukemia cells, myelodysplasia cells have a protective mechanism. They're pretty smart. They protect themselves from being attacked by these lymphocytes. This was only discovered six or seven years ago and within a couple of years there are, I think, there's four drugs on the market now that either hit that PD-1 or something or related things and wake up these cells and so you give these PD-1 inhibitors, these lymphocytes, these killer lymphocytes see the cancer cell and attack them. There's almost no cancer that this not being tried in now. It's most effective in cancers that have some immune basing like melanoma, but there're trials active in myelodysplasia with this and we're hopeful that they'll be positive. Really exciting new stuff.

So, these are... this is one trial, a very small trial. So, the one they looked at two different agents, one Nivolumab and the other Ipilimumab, Ipilimumab (sp? 55:06) and they didn't see anything at all by itself, but when you add it to Azacitidine you have this really 69 percent response rate. Now, this is again these were treated patients these were untreated patients, but a very interesting comment that this may be something in the future and we have a study for this up and running much too early to tell if it's going to do anything.

So, what do you do with this? So, again, we try and split people into lower risk disease, higher risk disease and usually think of these low blast AML patients who are in the same thought process in the lower risk people need any treatment? No, don't treat. Use erythropoietin or platelet growth factors, red cell or platelet growth factors, iron chelation. 5Q- you treat with the Revlimid upfront if they're symptomatic. If that fails you can go to Revlimid or Azacitidine or immune therapy. I didn't mention this but some of the bone marrow patients who have bone marrow that is not full but looks empty sometimes respond to the sort of treatment we give for aplastic



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anemia where we give anti thymocyte globulin or cyclosporine the sort of drugs they use to prevent transplantation rejection and there's a significant response rate there.

And then, of course, if that fails you go to transplant or study and hope that you have a good study available. For the higher risk people who if you can't transplant you go straight to a study or Azacitidine or Decitabine. My preference is Azacitidine and then transplant.

So, we went 25 years with nothing new and now all of a sudden in the last year we have all these things that we've just talked about, the Venetoclax, the Mylotarg, the liposomal drug, the IDH2 and then something we didn't mention, Midostaurin for FLT3 because we don't see that in MDS, just acute leukemia and there's these things are right on the cusp of being approved and we'll see what happens with those.

So, that's all I've got for you today. Any questions?

(Applause)

Q1: Thank you, doctor.

Roger M. Lyons, MD: You're welcome.

Audrey Hassan: Please remember to toggle and a red light will go on. You're ready.

Q2: Hi. I just wanted to ask if you could comment on why do the medicines stop working because you mentioned the Revlimid might stop working and the AZA and I don't really hear about medicines stop... I don't hear about people with diabetes, their insulin stops working or blood pressure pills stop working or...

Roger M. Lyons, MD: Well, most cancer drugs stop working. There's some exceptions, for example, for chronic myelocytic leukemia if you get a good response you're there, but for most cancers these cancer cells continue to mutate. They get new mutations and those mutations, those new clones may have a resistance mechanism. The body itself has... may change its metabolism. So, we see drugs that seem to work and then a month later you can't even measure them in the blood because the metabolism in the liver changes and you can't get enough of the drug in anymore. There's a couple of pathways that are notorious that the cell has bypass pathways that you turn something off and within a month or two that same cell then opens up a pathway that was quiet and goes around it. So, there's hundreds of different mechanisms that these cancer cells, leukemia cells have to overcome treatment and so it's extremely rare not to have some mechanism of resistance. Even in these immune based treatments where you say oh, my God. You now turned on the immune system. It's going to kill all the cells. Some of those cells find a way to get around that. So, not everybody has a cure or a long lasting treatment. You've heard about CAR T cells? Everybody heard about CAR T cells and what these are? It's sort of an

immune mechanism where what you do is you identify the marker on the cell surface like the CD33. You take the patient's cells, take them out, send them to a laboratory and the patient's lymphocytes are harvested and then... and a T cell is engineered with a virus to recognize the abnormality so those T cell lymphocytes are engineered to recognize the CD33, for example, and then ship back and you give it to the patient. Well, that has cured some children with childhood leukemia. It's just been released now for acute... for large cell lymphoma. The problem with leukemia is that the CD33 is on the stem cells. So, if we have a CD33 that's really stronger than the Mylotarg. Mylotarg's fairly weak. You have CD33 that's stronger you may kill all your blood cells and not recover it. We just closed a study with a much stronger CD33 monoclonal antibody with a different stronger toxin. We had to close it. It's oo much toxicity. So, these car T cells may actually have some cure because those lymphocytes then may live forever, but for most situations the cancer cells find a way to get around that and that's so transplantation... remember what you do with transplantation from another person is you're giving a big dose of chemotherapy to kill off as many cells as you can and then giving patient... somebody else's immune system which then attacks the cancer from the immune system. So, it's really an immune treatment.

Q3: So, I was diagnosed with low risk RARS May of 2016 and I have a blood draw every three weeks. If my hemoglobin is below 11, and it always is, I get an injection of Aranesp and mostly I'm feeling pretty well, but what I'm wondering is what I should expect going forward. Should I expect to maybe stay stable over time or will it progressively worsen and if it does worsen or change does it change from anemia to a white blood cell deficiency or platelet deficiency and what would be the timeframe for any changes I could expect and the frequency of the change?

Roger M. Lyons, MD: So, refractory anemia with ring sideroblasts is a subtype that was in there that we didn't talk about. If you look at the red cells in the bone marrow they have nuclei and around the nuclei there's little dots of iron. Sidero is Greek for iron. So, little dots of iron around the nucleus. It's a particularly good subtype of myelodysplasia with a specific mutation called SF3B1. There's a couple of other less common and these are what called spliceosomes. So, for reasons we don't fully understand people do much better with refractory anemia with ring sideroblasts, much longer survival and tend to respond better to treatment, but the long term is still the same. Eventually the stimulation of Darbepoetin that you're getting which is the long acting kind of erythropoietin tends to work less and sometimes you have to increase the dose, you have to, again, be sure that there's nothing else going on, but eventually it develops into various possibilities. One is it stops working and then you have to go to Azacitidine or a research study and there's a risk of leukemia still with that little less than the other subtypes. It's about 10 percent and then there's a risk of just the bone marrow just getting tired and wearing out and you look and you say oh, gee, there's just not much going on here. The cells are just not working and so the survival is better than most other people with myelodysplasia with RARS, but it is still a fatal disease. There's no cure. Does that help?

Q3: Yes, but I was wondering what is the timeframe... five or 15 years?

Roger M. Lyons, MD: No, it's in the five to seven year range, but everybody's different. Remember these curves are averages that if you look at a survival curve you have no idea where you are on that curve. Some people die two months in of a heart attack. Other people we have that iron study that I showed you. Some of those patients were 30 years out and we don't... we can't fully predict who's going to do what.

Q3: So, the death within those averages or those curves that's from all causes not necessarily death from MDS.

Roger M. Lyons, MD: Correct. That's survival curve. That's all cause survival.

Q3: Thank you.

Roger M. Lyons, MD: I mean, we can do curves where it's survival related to MDS, but we don't really know anymore what... how to classify that because remember I pointed out to you that heart disease and I didn't show you some of the curves from our study. Heart disease is actually higher in people with MDS. So, and I'll show you that with the mutation. So, we're not quite sure what to attribute everything to.

Q3: Okay. Thank you.

Roger M. Lyons, MD: But you will not know how you're going to do until it happens.

Q4: Hi, Dr. Lyons. What you said to the first question how you address the first question kind of, I think, is answering mine, but just to make sure we hear about immunotherapy and lots of times when I read it says instead of taking chemotherapy that can be very toxic in the future you could be taking immunotherapy, but now hearing you speak about how our own bodies will react, immunotherapy doesn't mean that you may not have severe toxic reactions.

Roger M. Lyons, MD: Yeah and I actually really object to that. I think it's marketing.

Q4: It's marketing.

Roger M. Lyons, MD: It's...

Q4: That's how I felt.

Roger M. Lyons, MD: I may be an outlier, but chemotherapy means chemical therapy. Chemical therapy is therapy and everything you use has some side effect. There's no such thing as a non-side effect drug. So, the immunotherapies have a different set of side effects. Most of them... no, you don't lose your hair. Yeah. Most of them... many of them, not all, the blood

counts don't get really low, but some of them they do, but there's a whole set of other side effects. These PD1 agents are notorious for reactivating. So, think about it. You're suppressing the immune system or in one area. If you suppress the immune system you have an increased instance of infection. If you activate the immune system such as with PD1s if you have a hidden immune disease, rheumatoid arthritis, lupus, some of... and there's hundreds of these subtypes those disease get reactivated and they're very threatening. There's a very high incidence of loss of thyroid function. There's a very high instance of pulmonary disease, inflammation in the lungs which is life threatening. It's a whole different set of side effects. They're different and no, and some of them don't cause nausea, some do. I think it's sort of a fallacious argument. These are strong agents. They have a different toxicity profile, but many of them are very toxic. So, don't believe every ad you see on TV. Anything else I can help with before Ginny tells you the real stuff?

Q4: Let this gentleman go.

Roger M. Lyons, MD: Go ahead.

Q5: Just to make a comment. You were talking about different side effects for different people. When I was put on Revlimid as my starting thing and what was funny is we had... I had been feeling bad for so long going downhill I just couldn't hardly function and sleeping all day and all kind of stuff. When they finally got me to an oncologist and he found this and got me on Revlimid within a few months I started feeling better, but before I got to him in October of last year I broke out just almost immediately with psoriasis all over my body especially in my head and along with that psoriatic arthritis really, really bad. Couldn't hardly shake anybody's hand or anything. When I was put on this drug a side effect was it cleared up almost immediately my psoriasis and my arthritis.

Roger M. Lyons, MD: Good side effects.

Q5: It was a good side effect and the doctor kind of goes, "I've never heard of this." He says, "I might have to write something up." You know.

Roger M. Lyons, MD: Yeah. You have to be careful. So, when Dr. List did that original studies he's a great guy and he had no idea what the dose should be or what was going to happen and the dose that they put patients on totally unexpected only for the 5Q- patients was about a seven or eight percent death rate and despite that the death rate was because he said, "Oh, this is an easy drug. We don't have to monitor people. Come back in a couple weeks." Come back in a couple weeks there was no bone marrow because in 5Q- patients the bone marrow is essentially wiped out in the first couple of weeks and then you have to recover. You have to watch people like other acute leukemia treatments and he didn't know that to start with and so the whole thought process about how you use the drug changed. So, that's, I guess, not a chem... I don't know what you call that but it's an immune modulator of sorts. It works through something called cereblon

and we're not quite sure how that works, but it's some of these drugs are very toxic and sometimes in very unexpected ways.

Q5: One other side effect that I wanted to see if this Revlimid could be responsible for is a neuropathy in both of my legs that showed up just in the last couple of months.

Roger M. Lyons, MD: It's more common with Thalidomide than Revlimid, but... and Thalidomide has been tried here, too, but it does occur with Revlimid and you'll often have to modify dose sometimes even interrupt. Anything else?

Q6: If nobody else because... So, there's a gentleman here that his wife told me he used to have MDS and I said how do you used to have... and she said he had a stem cell... he had stem cell treatment or transplant.

Roger M. Lyons, MD: That's bone marrow transplant.

Q6: That is what?

Roger M. Lyons, MD: He had a bone marrow transplant. You had a bone marrow transplant and as I said that's the only curative treatment.

Q6: Oh. Okay.

Roger M. Lyons, MD: And with a significant mortality and significant in some people long term side effects. I have people who had a bone marrow transplant and are back at work at four months and have no symptoms ever and I've had some people who have bone marrow transplant and are... they have so many side effects from graft versus host disease that they regret having had it done and most are someplace in between, but it's the only curative therapy but it's a significant risk.

Q6: And is it not available for people over a certain age because of the risk?

Roger M. Lyons, MD: No, we don't do that anymore. It used to be there was an absolute cutoff. We now use sort of performance status, comorbidity evaluation. There's a formal classification for bone marrow transplant that I think is 20 or 30 things and what's your heart function is, how fast you can walk, what's your pulmonary tests look like, what your psychiatric/psychological status is. This requires some steel in your spine to get through, what your support is from your family. All those things are thrown into this formula to try and figure out what your chances are of getting through. So, these comorbidity evaluations are not... there's an age portion in there, but in our population 80 is the new 60 or whatever.

(Laughter)



Roger M. Lyons, MD: Yeah.

Q7: My transplant was done at (inaudible 1:12:39) Medical Center and I'm 20 months out

Roger M. Lyons, MD: Good. Congratulations.

Q7: And their criteria is your physical condition (inaudible 1:12:48) virtually (inaudible)

Roger M. Lyons, MD: Good.

Q7: They put me through a physical just short of an astronaut physical. If there was anything in here that wasn't working perfectly they'd have known about it. That's what their criteria is. (inaudible 1:13:00) is 68. Sixty-eight. (inaudible)

Roger M. Lyons, MD: Age is secondary. I guess my oldest patient got transplanted was about 76. So, we don't worry about age as much.

Q8: When he went through it no side effects of the transplant. You know, we heard all this stuff about it. Everything's great. The numbers went up to normal. Everything was good. Right before 100 day relapse. The MDS came back at seven percent blasts. Within three weeks it was 32 percent blasts. It came back with a vengeance and went right to AML. They had nothing for us. So, they sent us to MD Anderson. They said (inaudible 1:13:46)

Roger M. Lyons, MD: What did they give you?

Q8: Seven plus (inaudible 1:39:49) they're salvage (inaudible)

Roger M. Lyons, MD: Standard chemo.

Q8: (inaudible 1:13:52) chemo. They checked his environment (inaudible 1:13:55) about 60 days.

Q7: And part of the population didn't test on the (inaudible 1:14:03)

Q8: Put him on (inaudible 1:14:04) all the mutations IDH2 (inaudible)

Roger M. Lyons, MD: So, you lucked out here with your mutation. So, it's the seven and three after transplant failure is pretty dismal and having the IDH2 mutation has done you worlds of good. I think that probably be more than (inaudible 1:14:25). So, we have to look for all these things now and some of the insurance companies don't like us looking. So, yeah.



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Q9: One of the (inaudible 1:14:35) he gets bone marrow biopsies every year (inaudible) average every 28 days (inaudible) Not only is the IDH2 gone all the submutations are gone (inaudible)

Roger M. Lyons, MD: That's wonderful.

Q9: (inaudible 1:14:55)

Roger M. Lyons, MD: So, we have a little different approach... we're pretty good friends with the Anderson people, but we don't believe in doing bone marrows unless there's an indication. They like to do them because they like to do them.

Q9: (inaudible 1:15:06)

Roger M. Lyons, MD: You come to my office.

(Laughter)

Roger M. Lyons, MD: Come to my office.

Q10: (inaudible 1:15:14) down there in three years. We were down there and they were (inaudible) after effects, not sore, not anything.

Roger M. Lyons, MD: It's like a surgeon. Some people are better than others and you can get pretty slick at it and or not so slick and the more you do the better you are. Any other questions because Ginny's just chomping at the bit.

(Laughter)

(Applause)