



Speakers:

Maria Baer, MD

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(People near recorder speaking over presenter 0:00 – 3:10)

**Maria Baer, MD:** I'm going to cover medical aspects of Myelodysplastic Syndrome. So, what Myelodysplastic Syndromes are, how they're diagnosed, how they're sub classified, treatments, new treatments and I'm going to allow plenty of time for questions because I guess all the medical questions should come to me. So, I'll be sure to answer it. Try to answer everybody's questions of medical sort. So, that's the University of Maryland just a few blocks away.

So to talk about Myelodysplastic Syndromes, we first need to talk about normal blood cells and bone marrow cells so then we can talk about how Myelodysplastic Syndrome is abnormal and I assume there's a wide breadth of amount of knowledge and so some of this may be very elementary, but I'd rather cover elementary things than assume that people know them and then maybe people who don't. So, these are normal blood cells and there are three kinds of blood cells, the red cells, the white cells and the platelets. So, these red cells are the red cells and they carry oxygen and if people don't have enough red cells that's called anemia and symptoms of anemia are tiredness, shortness of breath with climbing stairs. So, that's anemia. And these are normal white blood cells. These are called neutrophils and they fight infection and these little cells here, these little tiny ones are called platelets. They're the third kind of blood cell and they clot the blood. So, when somebody cuts themselves, the platelets go to the site of the cut and immediately stop bleeding. They're like a band aid and then after that clotting factor proteins come in also and kind of seal it, but they're the first defense against bleeding. So, this is what a normal blood smear looks like with plenty of red cells, with these mature neutrophils and with platelets and the blood cells are made in the bone marrow. So, the bone marrow is the inside spongy part of the bone and in adults it's primarily the iliac bones here and the breast bone or sternum. Children also have bone marrow in their long bones, their arms and legs, but the bone marrow is where the blood cells are made. So, when the blood cells are abnormal and it's not some obvious thing like iron deficiency or something then you need to look at the bone marrow which is the factory because often something's wrong in the factory that's not producing enough blood cells or producing abnormal blood cells. So, this is what a normal bone marrow looks like. So, this is bone marrow. This is fat or kind of empty space and normally the bone marrow occupies 40 percent of the space inside the bone marrow tissue. So, this is normal and it has precursors or the cells that make red cells, white cells and platelets. So, these little dark things are red cell precursors and these more pink cells here are white cell precursors and these great big cells here are megakaryocytes. They're the cells that make platelets. So, a normal bone marrow has kind of the right amount of bone marrow tissue and has all the right precursors, the red cell precursors, the white cell precursors and the platelet precursors or megakaryocytes.

So, what are Myelodysplastic Syndromes? What is the definition? So, the kind of technical lingo. It's a clonal blood stem cell disorder characterized by ineffective blood cell production. So, what does this mean? We like lingo. So clonal means that it arises in a single blood stem cell in the bone marrow. So, it starts in one cell and that cell becomes abnormal. There's often damage to DNA in a single bone marrow stem cell and it becomes abnormal and it has an advantage over the other cells and it gradually takes over the bone marrow and that's similar to what happens in a cancer but in such as a leukemia, but in Myelodysplastic syndrome the cells don't behave in a cancerous manner at least when it's Myelodysplastic Syndrome. So, clonal arises in a single cell and the behavior of that cell is that it has ineffective blood cell production. So, whereas a cancer often it grows very fast and that's not the behavior of an affected stem cell in Myelodysplastic Syndrome. It results in ineffective blood cell production Myelodysplastic Syndrome. It results in ineffective blood cell production. So, what that means is that the precursor cells are present in the bone marrow, but they do not produce normal numbers of blood cells. So, I showed you what a bone marrow looks like in the cells that should be there and they are there, but they just don't produce the right number of blood cells. So, normally the body kind of a well-tuned organ and it makes enough red cells, it makes enough white cells, it makes enough platelets and in fact if somebody, for example, has bleeding then the bone marrow cranks out more red cells to compensate. If somebody has an infection, it may crank out extra white cells to help fight infection, etc., but it loses those regulatory mechanisms and it doesn't produce enough blood cells. Is that clear? Please stop me if something's not clear. Okay?

**Q1:** Are the precursors the same as the stem cells?

**Maria Baer, MD:** So, there are stem cells that generate red cell precursors, white cell precursors. So, they're very early cells. Good question and that'll be important when we talk about transplant as a matter of fact.

So, Myelodysplastic Syndrome you have the right numbers and kinds of cells in the bone marrow, but they don't produce effectively. So, consequently the presentation of someone with a Myelodysplastic Syndrome they have low blood counts because the blood cells are being produced effectively and you can have one or two or three low blood counts. So, red cells, white cells, platelets. Most of the time people with Myelodysplastic Syndrome are anemic. So, 85 percent of patients with Myelodysplastic Syndrome are anemic. Fifteen percent aren't. So, occasionally people have low white cells and/or low platelets but they're not anemic and often anemia is the major blood count that produces symptoms. It produces fatigue and shortness of breath with trying to do things. So, low red cells which is called anemia. Low white cells which is called neutropenia and if the white cells are low there can be difficulty fighting infection, preventing infection and fighting infection when it occurs and then low platelet count and we have big words for everything. That's called thrombocytopenia. Thrombocytes are platelets and penia means not enough. So, Thrombocytopenia and when the platelets are low there can be a tendency to bleed with gum bleeding, nose bleeding. Also, these little red dots often on the shins called petechia. Though the platelets have to be pretty low for all that to occur. The platelets get

down around 20,000, 30,000, 40,000 and not have a lot of symptoms, but certainly if they're below 20,000 there are symptoms. So, one or more low blood counts. So, one, two or three usually including anemia.

So, how do you diagnose Myelodysplastic Syndrome? So, somebody presents with one or two or three low blood counts and you look for the obvious other causes which we'll also go through in a minute, but certainly if someone presents with anemia, make sure they're not iron deficient or if they have all their blood counts are low make sure they don't have B12 deficiency or some obvious other cause, but if you can't find another obvious cause then you need to look at the bone marrow. So, that's where you have a bone marrow aspirate and biopsy to look at the bone marrow and see what might be wrong there. So, in a Myelodysplastic Syndrome you have one or two or three low blood counts then you look at the bone marrow. The bone marrow has cells in it. We call that a cellular bone marrow and it has red cell, white cell and platelet precursors and the other feature is that you have dysplasia. So, dysplasia means that the cells look qualitatively abnormal. Literally so, plasia is like plastic like plastic surgery refers to appearance and dys means abnormal. So, it's funny looking, abnormal looking bone marrow cells and that, as you can imagine, can be somewhat subjective. It can be anything from very subtle abnormalities that may or may not be there to, frankly, bizarre cells and sometimes the early kind of subtle can be difficult to call and in particular there are pathologists. So, pathologists are the doctors who look at biopsies. There are pathologists who specialize in looking at bone marrow and called hematopathologists and often a specialist is required someone with a lot of experience and a good eye to make this diagnosis.

So, just to show you what I mean by that. So, this is a bone marrow with normal cellularity. So, normal proportioned cells around 40 percent. Here is a bone marrow that's empty. So, that's aplastic anemia. So, if somebody has low blood counts. You do a bone marrow. It looks like this. They have aplastic anemia. This is consistent with a Myelodysplastic Syndrome. This is where you have too many cells and that could be a myeloproliferative disease or a leukemia, but this just to show you visually when I say normal cellularity this is what I'm talking about as opposed to this or that and, again, this is the same slide just to show you, again, that red cell, white cell and platelet precursors need to be present and then so what is dysplasia look like? So, just to show you some examples. This is a red cell with four nuclei and that's not normal. A red cell should have one nucleus. So, that's dysplastic. It's abnormal looking. This is actually a blast. It's a large immature white cell with something called an Auer rod. These are abnormal white cells. They're not staining appropriately. Here's another red cell with two nuclei. This is something called a ring sideroblast. So, it's a red cell precursor with a ring of this blue stuff is iron. So, you do an iron stain. It's a ring of iron around it which is abnormal and these are abnormal megakaryocytes. So, this has many, many megakaryocyte lobes... lobes in the nucleus which is abnormal. So again, it's really an experienced hematopathologist makes these diagnoses.

So, as I said you have to evaluate for other causes of low blood counts and of dysplasia which somebody might have one of these other causes instead of a Myelodysplastic Syndrome, but also

someone with Myelodysplastic Syndrome the counts may be worse because of one of these other causes either at diagnosis or if you're... if we as physicians are following someone with a Myelodysplastic Syndrome and suddenly their counts are worse. You don't want to just assume that oh, well, their Myelodysplastic Syndrome got worse. Maybe one of these other things happened as a superimposed cause. So, one needs to be kind of at least kind of on top of this and think about these things. So, certain medications can cause low blood count. Certain medications can actually cause dysplasia in particular chemotherapy for something else would be one thing, but other medications. Low vitamin B12. Poor nutrition can cause low blood count. Some autoimmune diseases, infections. If someone has an enlarged spleen for whatever reason it traps the blood cells and the blood counts can be low. Alcohol. If you drink enough alcohol it can lower the blood counts and make the cells dysplastic. Recent chemotherapy. So, sometimes people get a Myelodysplastic Syndrome having had chemotherapy for some other... for a cancer usually or an autoimmune disease and that can be difficult to sort out as to when the things just look abnormal because of chemotherapy or when it has created the Myelodysplastic Syndrome and then etc. Every patient is different and one has to be thoughtful and creative.

So, the other finding that you commonly see about 60 percent of the time in a Myelodysplastic Syndrome that can help establish the diagnosis is chromosome abnormalities. So, this is a chromosome spread here and this is a woman, actually, because there are two Xs. If it were a man there'd be an X and Y and normally you have either XX or XY, you're female or male, and you have 22 chromosomes with two copies of each chromosome that look the same. So, here's two copies of chromosome one, two copies of chromosome two. This one is a little bent, but it's basically normal, but here this is an abnormal chromosome spread. So, this is missing part of chromosome three, it's missing part of chromosome five, missing what's called the long arm of chromosome seven, chromosome 12, a whole chromosome 14 is missing here, etc. So, if you have abnormal chromosomes in the bone marrow and you have several cells with abnormal chromosomes that tells you that there's a clone with abnormal chromosomes and it's consistent with a primary bone marrow disorder and it otherwise looks like a Myelodysplastic Syndrome and you have this then you say well, this is part of the Myelodysplastic Syndrome and it helps to confirm the diagnosis because sometimes if someone has low blood counts and they have very subtle dysplasia sometimes we can't totally or we'd say we think it's a Myelodysplastic Syndrome, but we need to watch or whatever, but if they also have abnormal chromosome then yeah, it's a Myelodysplastic Syndrome.

**Q2:** Where do the letters come into play? Like they analyze things that I'm missing part of the P and the Q. Where does that come into (inaudible 19:22)?

**Maria Baer, MD:** So, P is the short arm and Q is the long arm and these two arms are somewhat similar but for example chromosome seven here, P is short and Q is long. So, actually so you can remember P is actually for petit which means short or small in French and then Q is the letter after P. That's how that...

**Q3:** Or mind your Ps and Qs.

**Q4:** When they talk about five deletion, what are they talking about?

**Maria Baer, MD:** Very good. It's right here as a matter of fact and I'm going to focus on it a little bit more. So, this is a normal chromosome five and this chromosome five is missing part of the long arm or the Q arm. So, it's chromosome five deletion or 5Q- is the other...

**Q4:** That's prevalent isn't it?

**Maria Baer, MD:** It is. It absolutely is. Absolutely both by itself and as part of multiple chromosome abnormalities and I'm going to show you a little bit more about chromosome five deletion as a matter of fact.

**Q5:** (inaudible 20:33)

**Maria Baer, MD:** Prevalent. It's common. It's one of the more common chromosome abnormalities and it actually in a certain setting has its own treatment and we'll talk about that. So, those are chromosomes. Here we go as a matter of fact. I forgot it was the very next slide, but this is to show you FISH or FISH stands for Fluorescence In Situ Hybridization. So, if you don't know what kind of chromosome abnormalities somebody's bone marrow might have, you do the chromosome spread like in the last slide and you look at all the chromosomes, but if you're looking for specific abnormalities so sometimes there's certain abnormalities that are common such as this is exactly the deletion 5Q or 5Q-. So, there's something called an MDS FISH panel. So, you might have heard of it that's why I thought I would mention it. So, it's looking for specific abnormalities that are common in Myelodysplastic Syndrome. So, usually there's a probe for the long arm of chromosome five or 5Q. Usually seven, three copies of chromosome eight is common, loss of long arm of 20 or 20Q deletion is common. Usually, those are the main four that are part of the panel, but just to show you how it works. So, these are fluorescent probes to specific chromosome regions. So, this green probe here is the green fluorescence is conjugated to a probe for the short arm of chromosome five or 5P. So, here you see there are two copies, but the long arm... so this red fluorescence is conjugated to region that's part of this long arm region that's commonly deleted and you see that here it is deleted. There's only one signal. So, that's a quickie look. There are two Ps and one Q. So, there's a 5Q deletion that's part of an MDS FISH panel.

So, the other entity that's coming increasingly into play. This is kind of an evolution, but is mutation. So, these are not chromosome abnormalities, but they're mutations in particular genes. So, you can't see them with a chromosome spread. You can't see them with FISH. You see them with a molecular analysis and there are a whole slew of genes that can be affected. So, I kind of categorized them by their roles in the cell and these are the genes. So, I don't know if you've

heard of these, but TET2, DNMP3A, IDH1, IDH2, some of the splicing genes. TP53 is another one.

**Q6:** Question. Sloan Kettering up in New York they run this as a normal process of yours, but now another cancer center they don't run that. Why is that?

**Maria Baer, MD:** So, they may not run it in-house. They may send it out, but there are a lot of labs that do this. So, Sloan Kettering has their own lab and they do it in house, but for example at the University of Maryland, we don't do it in-house, but we send it's called... We send it to Quest Diagnostics just different hospitals contract with different labs or whatever, but it's called a myeloid mutation panel and the Quest version of that is Luke Advantage is what it's called.

**Q5:** If they don't do that is that an omission that they should do?

**Maria Baer, MD:** So, it has come into play increasingly. So, to...

**Q5:** As a recent.

**Maria Baer, MD:** Exactly. So, two years ago we didn't send them routinely. Now, we do and the reasons that we send them are 1) so I was saying that the diagnosis can be really subtle and you may have very subtle dysplasia, but then if you have a chromosome abnormality you can say yeah, that's what this is, but often if dysplasia is really subtle you may also not have abnormal chromosomes, but you may have one or more of these mutations and... but it's a little more complicated than that. Let me get to that in a minute, but so it can help clinch the diagnosis. Also, there're increasing targeted treatments targeting these mutations. So, for example, their IDH2 and IDH1 inhibitors. So, they're clinical trials. So, if someone has an IDH2 or an IDH1 inhibitor they can go on a clinical trial. They're also... and I'll cover this at the end when I talk about clinical trials, new treatments, clinical trials, splicing mutations. Spliceosome inhibitors targeting them. So, that's... So for diagnosis and for also prognosis. So, prognosis means predicting how things are going to go whether this is likely to kind of idle along or become more aggressive and some of that we'll get into prognosis in a minute. In fact, the scoring systems, some of that helps decide whether to treat immediately or watch and wait and also whether to consider transplant.

So, right now these are so new that they're not part of the scoring systems, but there have been some scoring systems proposed that include mutations. So, it's exciting that the field is moving along so much and honestly two years ago we did not do this routinely. Now, we do and it is informative. However, here's the however. Some of these mutations can occur in the absence of disease. So, some of them occur with normal aging and so if you look at the whole population in particular older people you may find these mutations and it doesn't mean they have a bone marrow disorder. Some of them might mean that they're more likely to get a bone marrow disorder, but so you can't... so in particular TET2 and DNMT3A...

**Q5:** My perspective they did this up at Sloan Kettering and they did relate some of that to age.

**Maria Baer, MD:** Right. So, it's complicated though because you don't want to peg someone with having a bone marrow disorder if it's just a normal aging. So, if you have several mutations that's more likely to be a bone marrow disorder, but it's exciting that this is new knowledge and it's nice that... The field really moves along. So, giving this talk now it's different from the talk I would have given a year ago and some of it's the same, much of it's the same, but some of it's new and hopefully it'll be more different in another year or whatever. Some of these then result in additional knowledge that helps tell us who needs treatment and what kind of treatment and who needs a transplant and then some of these as we have targeted treatments, hopefully, they'll be helpful and represent...

**Q6:** Is this the same cytogenetics?

**Maria Baer, MD:** So, cytogenetics is chromosomes.

**Q6:** Oh, it's the chromosomes. Okay.

**Maria Baer, MD:** So, this is molecular.

**Q6:** And what is this called?

**Maria Baer, MD:** Molecular. Molecular analysis.

**Q6:** And you're finding out (inaudible 27:51) as a matter of (inaudible)

**Maria Baer, MD:** It kind of is these days. It's really changed in recent years. So, five years ago probably no one was doing it routinely.

**Q6:** What is the unit of analysis? Your marrow?

**Maria Baer, MD:** Yeah. So, you send...

**Q6:** Bone marrow biopsy.

**Maria Baer, MD:** Aspirate.

**Q6:** Or the aspirate. Are those percentages the likelihood of people having that?

**Maria Baer, MD:** Yes, this is the incidence. Sorry, I should have put that there. So, each of them is kind of rare actually, but...

**Q7:** I was diagnosed many years ago. The first thing that came up was MGUS. If MGUS comes up today does this come into play?

**Maria Baer, MD:** So, MGUS is different. MGUS is an abnormal... or an increase in a certain... in an immunoglobulin in the blood and it is somewhat common particularly as people get older and many people just smolder along with MGUS. It can if the protein is going up over time, it can turn into multiple myeloma and both MGUS is common in older people. Myelodysplastic Syndrome, it's not common, but occurs more frequently as people age. The other... if somebody has MGUS and then gets myeloma, multiple myeloma and gets treated for multiple myeloma sometimes they can then develop a Myelodysplastic Syndrome. Does that make sense? Myeloma there's a set of chromosome, a FISH panel for myeloma and myeloma has different mutations than this. These are myeloid meaning white cell mutations.

**Q8:** You mentioned the term aspirate. What does that mean?

**Maria Baer, MD:** Very good. So, when we do a bone marrow procedure we do an aspirate and a biopsy. So, the aspirate... Bone marrow, I'm sure many of you know this and can tell me about it. Usually, bone marrows are done in the posterior iliac crest here. In the old days they were done in the sternum, but so you go in and you pull the liquid part of the bone marrow kind of like drawing blood but from the bone marrow and that's the aspirate and then you go in... (inaudible) so you go in and carve out a piece of tissue, little cylinder of tissue and that's the biopsy and the aspirate is the best way to look for dysplasia and is also what you send for chromosome analysis and molecular analysis, but the biopsy is the best way to cellularity and so those are biopsies I showed when I showed you aplastic anemia versus those are biopsies you can see cellularity and architecture and then sometimes you can't aspirate. Some people it's hard to aspirate so then you only have the biopsy.

**Presenter:** Sorry I forgot to mention something earlier. We are audiotaping today so if you move your mics a little bit closer to you so the others can hear a little bit better.

**Maria Baer, MD:** You didn't tell me you were audiotaping. (Laughing). So these are just statistics. So 20,000 – 30,000 estimated new cases of myelodysplastic syndrome in the United States each year. The average age is 76 years so this is typically a disease as people get older. It's more common in men than in women, almost twice as common for whatever reason, and then acute leukemia develops in 25 percent of people with myelodysplastic syndrome. So, a lot of the purpose of treatment is to prevent development of acute leukemia and we'll talk about that with an early low-risk Myelodysplastic Syndrome that's much less likely, but in Myelodysplastic Syndrome that presents as a more aggressive or becomes more aggressive then it's more likely.

And, what is acute leukemia? The bone marrow has blasts in it. Everybody's bone marrow has blasts in it and normally they're well regulated. You have less than five percent. A normal person



has less than five percent blasts in the bone marrow, but as part of the dysplasia that can occur in Myelodysplastic Syndrome, you may develop increased blasts and if it's five percent or more, that's abnormal. If it gets to 20 percent somewhat arbitrarily, that's called acute leukemia. Actually, this changed about seven or eight years ago. The cutoff used to be 30 percent, but arbitrarily it's 20 percent. So, that's what that means is that the blasts go up and it becomes 20 percent.

**Q9:** There's something that has developed recently, I understand there are cures for acute leukemia and with MDS you're trying to prevent getting to acute leukemia. Seems my engineering logic would say well let's get to acute leukemia and treat it.

**Maria Baer, MD:** I see how you can think that.

**Q9:** And if the acute leukemia that goes too is treatable, then do not seem to be, and I know you're going to touch on this, but there don't seem to be cures other than transplant for MDS itself.

**Maria Baer, MD:** That's a very good question. Acute leukemia is curable, but it is not cured in everybody unfortunately. Sometimes it's curable just by chemotherapy, sometimes by transplant, but some of the features of acute leukemia that make it much less likely to be cured are evolving from a Myelodysplastic Syndrome and being over age 60, which most people with Myelodysplastic Syndrome are and then the chromosome changes in acute leukemia are predictive of how it's going to respond to treatment and often the kinds of chromosome changes that you have in Myelodysplastic Syndrome when they occur, when they're present in leukemia, it means the leukemia is less responsive. In fact, ironically, the deletion 5Q that's good in Myelodysplastic Syndrome is actually bad in leukemia, but I see how you would think that. So, this is just the age related incidents just showing you graphically that kind of peaks in the 70s, actually goes down in the 90s, but anyway, but it's something to look forward to, but it's not relatively rare in adults.

So, having talked about and I'm probably actually going to long as a matter of fact, so I'll try to be... but having talked about how you diagnosis it, then classifications. So, one set of classification that we don't use so much but you may have heard of it so I thought I'd include it is the pathology classification. It used be the FAB classification. The current one is the WHO and that was actually this used 30 percent for acute leukemia, this uses 20 percent. I guess it was 17 years ago, not eight years ago, but this is not so useful from a practical point of view, but the prognostic or predictive classification is really important and there are two of them that we use. One is the International Prognostic Scoring System or IPSS, which was published in 1997 and then there's a Revised or R-IPSS that was published in 2012. These are really important so whenever we diagnose Myelodysplastic Syndrome we go through this risk stratification and it determines whether to treat immediately or watch and wait and whether to think about transplant.

I'm just showing you sort of how this is set up. I don't expect you to memorize it and, in fact, I need to look it up each time. It's very difficult to remember.

**Q10:** Discussing and mentioning transplant, there are some obstacles. Do they change age wise?

**Maria Baer, MD:** They have. I'm going to talk about transplant at the end and get into that, but the age has extended upward.

**Q10:** Has been extended?

**Maria Baer, MD:** It has, but still it's a challenging decision whether to have a transplant or not, even if it's feasible and I'm going to talk about that, but yes. So, at our institution for example, it's 75, meaning 76 minus a day, but we have had some fit 76 or 77 year olds that we've transplanted and some institutions actually don't have an upper limit anymore.

**Q10:** The reason I ask you, when they determined that I had myelodysplasia, my age prohibited even thinking about a transplant.

**Maria Baer, MD:** Should I ask how old you were at the time?

**Q10:** At the time I was about 70.

**Maria Baer, MD:** Okay, yes, 70 is... you think about it. It's not like, oh let's go transplant every 70-year-old, but 70 does not preclude transplant, but it's a difficult decision whether to proceed to transplant and I'll try to cover that.

But this is the IPSS so it incorporates three factors – the percentage of blasts in the bone marrow, the chromosomes and how many low blood counts there are. So either none, although by definition you sort of have one, or two or three. So, again the red cells, the white cells, the platelets. So you score all this and you come up with a... so these are the number of points that you get for each. So the more blasts, the more points. Good chromosomes you don't get any points as you have other chromosome changes that are less favorable you get points. So, you total up those points and if you have 0 to 1, so 0.5 or 1, it's lower risk. If you have 1.5 to 3.5, it's higher risk, so we stratify into lower risk, higher risk, and that's really important.

This is the Revised IPSS which is basically the same thing. It just breaks it out a little bit more, so you actually plug in the actual blood counts and the actual bone marrow blasts as opposed to a range of blasts and then chromosomes get split out five ways instead of three ways and have more categories here. So, these are the numbers from very low, low, intermediate, high, and very high.

**Q11:** A quick question. I just spoke about this with my doctor, the diagnosing physician and she said she doesn't use this because it's out of date. She said don't worry about that, it's different. We don't look at age the same way. We don't look at these things the same way and I said well, everything I'm reading says I should be classified. I didn't get this information.

**Maria Baer, MD:** So, we don't look at age. There is actually an age adjusted, but we don't ... but we do ... I mean it's somewhat common sense basically if someone's kind of doing okay and their bone marrow's not that aggressive, they have lower risk disease, so this is a way of formally ... conversely if someone has really problematic blood counts and their bone marrow looks pretty aggressive and that's higher risk and they need treatment. It's somewhat classifying things that are common sense. If you're doing okay, you probably can have watch and wait, but if you're having problems then you need treatment. So it's somewhat classifying common sense, but we do classify.

**Q11:** It's worth it to push so that I can at least know where I stand.

**Maria Baer, MD:** Yeah.

**Q11:** I'm recently diagnosed and I'm secondary MDS from chemo. Initially when they gave me the news they said we know you're at least intermediate, but then when I pushed her to see am I high risk, she said you have a lot of chromosomal abnormalities and then we walked through the whole PQ thing. I never really got an answer and I feel as though going for other opinions it's going to be difficult if I don't have this.

**Maria Baer, MD:** Although the other... So, I often do second opinions and I basically get the primary information, so I have the blood counts. We always get the bone marrow slicing and we have some terrific hematopathologists, so we get the bone marrow reviewed and I have the chromosome information. So, even I don't, if someone gets referred for a second opinion it says this is the risk we always recalculate it. It's usually correct, it's not something usually wrong or anything, but that's part of the second opinion is actually doing all that including looking at the bone marrow.

**Q11:** Alright, thank you.

**Maria Baer, MD:** Sure absolutely.

So this is kind of an overview of treatment. We do divide into lower risk and higher risk as far as treatment. So, lower risk and I'll go through each of these treatments, but lower risk, if the primary problem is anemia, one thing we do, so someone with lower risk Myelodysplastic Syndrome, major symptom problem is anemia, we look for the, well, we look for it anyway, but people who have the deletion 5Q, the one you're asking about, the Lenalidomide or Revlimid

can be effective, as frequently effective in improving anemia in this situation, so that would be the treatment. Otherwise if there's no deletion 5Q or 5...

**Q12:** Is that Procrit?

**Maria Baer, MD:** No, so this is Procrit here. So, what we did if somebody has the abnormal chromosome five and you're dealing with lower-risk disease anemia, then Lenalidomide or Revlimid. If they don't then you measure what's called the erythropoietin level. So, erythropoietin is a hormone that the body makes to tell the bone marrow to make more red cells and if it's less than 500, if it's low, then you treat with erythropoietin which is Procrit. So, erythropoietin is Procrit. Epogen, Aranesp, sorry, so that's this. If somebody has a really, they're cranking out a lot of erythropoietin on their own though, they're probably not going to respond to erythropoietin treatment or Procrit. Sometimes there are people who would respond to immune treatments like for aplastic anemia. It's relatively rare, but if not either anemia, for which none of these are indicated or you've tried them and they didn't work or they stopped working, the kind of standard treatment is demethylating agents so that's Azacitidine or Vidaza or Decitabine or Dacogen which I'm sure many people have heard of or experienced. Then if you have lower-risk disease and you have low white count and/or platelet count, if that's the major problem, it's not going to respond to treatment for anemia, so you go right into this.

Higher-risk disease, there we assess whether the patient may be appropriate for transplant and, again, I'll get into transplant at the end. If they are appropriate for transplant often if it's higher-risk disease you need to get the disease under better control and you would go with Azacitidine or Vidaza or Dacogen and then go to transplant. Not a transplant candidate, then you go to Vidaza or Dacogen. However, and I'll say that I'm going to conclude with this, but clinical trials are really important. There are all sorts of clinical trials and really encourage clinical trial participation because all of these treatments arose from clinical trials and actually they arose recently enough that I remember when they were in development. So, when I started my career there were no FDA approved treatments for Myelodysplastic Syndrome. You basically transfused patients and you're nice to them, there wasn't much to do and now we have all sorts of things all of which were developed in clinical trials. So, I encourage the next generation of clinical trials.

This is Lenalidomide or Revlimid. So, this is, again, the deletion 5Q, so a patient with lower risk primarily anemia, here's a nice response. This is the hemoglobin level. Here this patient is getting transfused, they get treated with Lenalidomide or Revlimid which is pills, so pills are nice as opposed to shots and they improve very nicely. It's not a cure, but it is a nice response and it can last a good while. So, 76 percent of patients with deletion 5Q lower-risk anemia respond. In the absence of deletion 5Q, you can still try it for anemia, but it's a lower response rate. They don't respond as well and it doesn't last as long, but sometimes we try it. It's worth a try.

This is erythropoietin or Procrit or Epogen or Aranesp and sometimes we augment it by also using GCSF or Neupogen which is a white cell growth factor, but if you have someone with lower-risk disease anemia who's needing less than two units of transfusions a month and has, again, this erythropoietin level less than 500, they have a 74 percent chance of responding to Procrit. If you have either one of these criteria, but not the other, 23 percent, and if you have someone who's needing a lot of transfusions and has a higher erythropoietin level, it's really unlikely they're going to respond and we wouldn't try.

**Q13:** Can you define the differential between Procrit, Aranesp?

**Maria Baer, MD:** Sure, so Procrit is shorter acting and it's given at least once a week. Aranesp also called, the proper name is Darbepoetin, is longer acting. It's just a modification of erythropoietin, so it's longer acting and it can be given every two weeks. Sometimes when it's not working well enough, every two weeks you still try it every week. They're the same thing, so different practices use different ones and sometimes if one isn't working, you can try the other. It's rare that if one isn't working the other one works, but it's sometimes worth a try.

**Q14:** Excuse me. Is it true, I'm to getting (inaudible 47:12) shots and they don't give them every week because they're afraid of my hemoglobin getting too rich.

**Maria Baer, MD:** That's a good problem to have.

**Q14:** Is it?

**Maria Baer, MD:** Yeah.

**Q14:** Because they say they're afraid of strokes.

**Maria Baer, MD:** Yeah exactly. That's exactly right. When erythropoietin became available which was probably 15 or 20 years ago, I kind of lose track of time, but it was used fairly indiscriminately including people getting chemotherapy. You'd just boost their blood counts. Then it was discovered that it had some downsides. Now, it has these black box warnings and you're not supposed to drive people's hemoglobin above 10. So, that is correct. So, normal would be 12.5 or 13. You should not drive the hemoglobin to 12.5 or 13, but it's a really good problem to have to be responding to Procrit and needing less of it. That's a good thing.

**Q15:** (inaudible 48:14) deletion 5?

**Maria Baer, MD:** Yes.

**Q15:** And you said responding? What do you mean by that?

**Maria Baer, MD:** So responding, so talking about anemia. So, it means that the hemoglobin is going up. It's like, let me find this picture. This is a nice response. Here you have someone who's anemic, meaning their hemoglobin is around seven, whereas it normally should be around 12.5 or 13, or for a man even 14. So, they're anemic and the blood count is going down and they're needing transfusions so that's anemia needing transfusions. You give this treatment and you see that the hemoglobin is going up over time. They stop needing transfusions. So, here's the transfusions and here no more transfusions, and here the hemoglobin comes up to 13.

**Q15:** What's the timeframe for that?

**Maria Baer, MD:** Usually it takes about three months, so actually this started in March and last transfusion was late April and hemoglobin became normal like July, so it's a gradual response.

**Q15:** But this medicine, the side effects are to have the white and red and platelets drop?

**Maria Baer, MD:** It can make the platelets drop and then they come back up. So, you have to watch people closely and check blood counts at least every week initially and often the people who are going to have good responses, it drops the other blood counts and then they come up, but yes, absolutely. If then the other counts are staying too low, you may have to reduce the dose and there's a whole standard approach to how to adjust the dose.

**Q16:** Is that more effective than Vidaza?

**Maria Baer, MD:** It's a different situation. This is anemia with lower risk disease, anemia and the chromosome five deletion or 5Q-. So the response rate is 75 percent which is higher than Vidaza and I guess in this situation if you can take pills rather than coming in for shots five days in a row or seven days in a row, that's a good thing. Then you could always if it doesn't work or stops working, Vidaza down the road. Vidaza is kind of the fall back, but if you have... and similarly for Procrit, if you respond that's great. It's for anemia, but if you have lower risk disease with low white count or low platelet count, these treatments for anemia are not going to help. Then you need Vidaza or if you have higher risk disease, you need Vidaza. Does that make sense?

**Q17:** Would you recommend having them both? Vidaza and Revlimid? At the same time.

**Maria Baer, MD:** There is a clinical trial actually looking at, there's a national clinical trial a few years ago, looking at Vidaza alone versus Vidaza with Revlimid versus Vidaza with something else, another category of drug called an HDAC inhibitor and they were pretty similar. I don't routinely give them together. It was tested and the response rate wasn't higher giving them together, but it's not wrong to give them together. Is that a good answer?

Just to mention if you have lower risk disease and you're getting transfusions, iron overload is an issue. The serum ferritin which measures iron stores can go up over time and these days we have treatment for that. It used to be that you only had infusions and it was kind of difficult, but there is this oral medication. This is Exjade which actually gets dissolved and you drink it and there's a newer, even more expensive version called Jadenu and that's what that looks like. Those are pills that you take. So, in that situation this is important. These can be difficult to get covered by insurance which is an issue, but this is something to be aware of.

So having covered the treatments for anemia, now we're going to talk about demethylating treatment which is Vidaza or Dacogen. In Myelodysplastic Syndrome, as well as in some cancers, there is a phenomenon called gene hypomethylation. So, these are methyl groups, these are genes, these are methyl groups. So, methyl is CH<sub>3</sub>. It's just a chemical and they occur in the regulatory part of certain genes and when there's increased methylation the gene is silenced meaning it's not expressed. It was thought that maybe having these genes being silenced correlates with not making blood cells well and if you could get rid of the methyl groups maybe the bone marrow would behave better and that's sort of the theory.

Methylation, so this is a methyl group here, this is cytosine which is one of the residues of DNA. This is a methyl group and when you have methyl on here, if you have enough methyls the gene that the cytosine is part of doesn't get expressed so you treat with cytosine analogs, Azacitidine, Decitabine, which have nitrogen's instead of carbon and nitrogen can't be methylated. So over time you have a bone marrow that has cytosines with methyl groups that can't be methylated, so you decrease methylation of DNA in the bone marrow. So, that's the theory.

**Q18:** What is methylation exactly?

**Maria Baer, MD:** Methylation is having methyl groups sitting on your cytosine. This is methyl. CH<sub>3</sub> is methyl. It's somewhat of an arm wave the explanation. That's part of how these things work. They probably work in other ways also, but just to give explanation for how they work, yeah, it is more complex.

The initial trial of Azacitidine or Vidaza was actually a national cooperative group trial, which I remember well which was published in 2002 and showed that... so patients were randomly assigned to get Vidaza or not to get Vidaza and the Vidaza was kind of the classic regimen of 75 mg. per meter square under the skin as opposed to IV for seven days every four weeks and responses were assessed after four cycles. So, seven percent of patients achieved complete remission which means normal blood counts, normal bone marrow, 16 percent had partial remission meaning the bone marrow looked a lot better, 37 percent had improvement in the blood counts, but significant improvement meaning they had been needing transfusion, but now they weren't, so that's a pretty high overall response rate. Actually people who got Vidaza survived longer. In fact the way the trial was designed if you went four months without Vidaza and you weren't responding, then you could get Vidaza, so it minimized the survival different

because everybody ultimately could get Vidaza but even with that it showed that people lived longer if they got Vidaza than if they didn't. There was a subsequent study that also confirmed that.

**Q19:** I was in the clinical trial for Azacitidine.

**Maria Baer, MD:** The original?

**Q19:** Here at Johns Hopkins as well and after... actually it was a story that many people might be interested in. At the time the way of administering was a lot different than we have today and one of the things is I didn't have a port but I had a tube hanging out of my body and I developed blood poisoning from that. Took care of that and I went into remission for about a year. Then it cropped up again. I've been treated since. So, as far as Azacitidine is concerned which is Vidaza, I think it did a great deal for me. Anybody on it could be very positive.

**Maria Baer, MD:** Yeah, it helps a lot of people and it does if people get it and are doing well, they do well longer, so I totally agree with you on a lot of it, really a lot.

The original clinical trial was giving it under the skin for seven days in a row every 28 days. Then when it got FDA approved, there were all these practices that weren't open on weekends, so they couldn't give it seven days in a row. Some private practices got together at a clinical trial group and compared just giving it for five days versus giving it for five days, take the weekend off and then give it for two days versus decreasing the dose and going five, weekend off, then five, and the results were pretty comparable to each other and pretty comparable to the seven days, so it's okay if you go to a practice where they only give five days rather than seven days. We're open seven days, so we give it seven days, but five days is okay. Then just to be equal opportunity, Decitabine or Dacogen, this was the initial study using five days of Dacogen and the response rates were similar. So either drug works well.

**Q20:** Why do they choose one over the other? Is it your diagnosis and the details levels that you've talked about in the past?

**Maria Baer, MD:** There really is no particular rhyme or reason for choosing one over the other. Azacitidine or Vidaza, there have been two studies showing that it prolongs survival, that people live longer. I'm sure Decitabine does the same thing, but the way they've designed their study, they couldn't show it, so Azacitidine is kind of the classic, but Decitabine works fine. We actually use a lot of Decitabine for acute leukemia in people who can't get intensive chemotherapy, but both are fine. It's good for an individual physics or practice to kind of get used to what they're doing and do the same thing and know how people react, so it's good to be consistent, but they're both good. It just that Decitabine they didn't design the study quite as well.



**Q20:** So one of the things, I don't know how many people are from the Philadelphia area, but I'm about to start a clinical trial with Decitabine and it's Fox Chase Cancer Center working with MD Anderson and they're combining Decitabine with arsenic.

**Maria Baer, MD:** I know that group because we collaborate.

**Q20:** And they're finding that ...

**Maria Baer, MD:** That's a very nice trial. I've seen the data.

**Q20:** It is, it is. I'm starting Monday and they're saying that completely clean bone marrow rates have doubled.

**Maria Baer, MD:** That trial looks really good. I've seen the data presented.

**Q20:** Do you know Dr. Croft?

**Maria Baer, MD:** I do because we're part of the Stand up to Cancer thing where we do, so yeah.

**Q20:** She's my doctor.

**Maria Baer, MD:** She's wonderful.

**Q20:** She is. Very assertive woman. I was five minutes diagnosed and she's shoving the clinical trial paperwork under my nose.

**Maria Baer, MD:** And she's the one who didn't give you your risks.

**Q20:** Yes, exactly. She's like doesn't matter, we're just doing this.

**Maria Baer, MD:** And that's fine. You said it's treatment related and you have multiple abnormal chromosomes, I agree with what she's doing. It's fine. It's all good. Say hi to her for me. It's a small world. We all know each other.

**Q20:** She's said that, she said that. She was thrilled that I was coming here today.

**Maria Baer, MD:** Oh excellent. She's wonderful. She's very entertaining, too.

**Q20:** She is, she is, she is.

**Q21:** I'll just speak in favor of Vidaza myself. I was diagnosed July of last year and right away, I'm too old for a transplant and that sort of thing. I'm 75 and so they got me on Vidaza right away and we started studying and I'm not too old, I have a transplants, been transplanted.

**Maria Baer, MD:** Oh, wow. I was going to say is 70...

**Q21:** I'm brand new blood.

(Audience applause)

**Maria Baer, MD:** You look so wonderful actually. You look so well.

**Q21:** I took seven cycles of Vidaza and I dropped from 17 percent to zero.

**Maria Baer, MD:** That's fantastic.

**Q21:** In about seven months.

**Maria Baer, MD:** That's fantastic, and had a transplant too.

**Q21:** Then we went to MD Anderson and got the transplant.

**Maria Baer, MD:** Fantastic!

**Q21:** Other... allogeneic. Someone else. Bone marrow transplant. A stranger in Europe. God bless him.

(Audience applause)

**Q22:** By the way 75 is not old.

**Maria Baer, MD:** Yeah, 75 is fine for a transplant in someone who's fit and motivated and we'll talk about that and you look wonderful.

(General conversation)

**Q22:** To confirm that, someone asked a question earlier, that it is a good idea to take the Vidaza in preparation for a transplant if you're contemplating that eventually. You want to get your blasts down.

**Maria Baer, MD:** Exactly, so that's what I tried to show because if you have higher risk disease you want to get it dialed back to lower risk and doing well going into transplant and in particular

people who are 75, older people getting nonmyeloablative transplant, it can take a while to work, so you definitely want your disease under control. Sometimes people even get Vidaza after transplant for a while.

**Q22:** Yes, as a clinical trial, I'm in that. I was chosen to be in the null group.

**Maria Baer, MD:** Well, you look great. Whatever they're doing is turning out great.

**Q23:** I was diagnosed with MDS three ½ years ago and their primary concern at that point was the white blood cell, that was down in the just over one, low ones and was at risk level two on the IPSS and was immediately put on Vidaza and starting and it seems to have had no noticeable effect, positive or negative, and starting a year ago this past June my hemoglobin started going down and my initial transfusion was four months apart and then it was three months apart, and now it's down to about a month, and I wondered if that's something you see in MDS. I've been on the Vidaza during this whole time. Initially, I was 69 ½ they said well we got about six months to decide if you could be transplanted. That was sort of the time when that issue was changing, went for a second opinion and they said well you know we've done 500 transplants here up in Boston and the oldest person was 76 and so it went from six months to see to six years, but I do have this situation that's degrading, if you will. The Vidaza and I've asked the question, well if I hadn't been doing the Vidaza, would it have been any different and they said well, we don't know.

**Maria Baer, MD:** I don't know your exact situation, but as a general, when people are on Vidaza, sometimes the counts go down over time and there are a couple things that can be happening, and again I don't have all your so, so it's a general point, one is that the disease isn't responding as well and is getting worse and maybe you need a different treatment, but the other is that the Vidaza can gradually suppress the bone marrow and the counts can go down over time and sometimes people need, not that infrequently, actually, a lengthening of interval between treatments and/or a decrease in dose. Obviously, I don't know your situation, but sometimes, I hate to tell you this, but sometimes we do a bone marrow to reassess and see how the disease is versus if you're seeing that the cellularity is lower, maybe we call it, we have words for everything, cumulative myelosuppression meaning all that Vidaza over those several years is suppressing the bone marrow.

**Q23:** They did a follow-up bone marrow not too long ago and everything seemed about the same. In the last few weeks I had all my records sent to NIH and I'm going to be evaluated on November 1 for possible clinical trial.

**Maria Baer, MD:** Great, excellent, that's great. That sounds really good.

**Q24:** (inaudible 1:06:42)

**Maria Baer, MD:** First of all the Vidaza injections, there are two ways of doing it. One is under the skin and the other is intravenously and we don't know that there's a difference because that's one question. So, the oral Vidaza, the pill, is not FDA approved yet. It's been in development, so there've been clinical trials, but you cannot just prescribe it because it's not FDA approved yet. Hopefully, it will be because if it works as well, obviously, people would rather take pills than come get shots five or seven days a week, but it can't be prescribed. There have been clinical trials. I know Hopkins had an oral Vidaza clinical trial and hopefully it'll get FDA approved one of these days, but I personally don't know when.

**Q25:** Talk about using the subcutaneous for Vidaza versus having a port installed. I've been getting to the point where I don't want to get another into the veins.

**Maria Baer, MD:** The original clinical trial, the one that was published in 2002 was subcutaneous. That's kind of the classic regimen is subcutaneous and it's seven days. So, I showed you that five versus seven days probably doesn't make a difference. There's never been a comparison of subcutaneous and intravenous. The national clinical trial was subcutaneous. Some of the research before that actually was intravenous. We think they're equivalent. So, I really prescribe it as a convenience thing so if somebody doesn't want to have a line, I also have people who are working who just want to get in and get out, so subcutaneous. Someone who wanted IV and then he was getting streaks up his arms, so we went back to subcutaneous. We don't know that there's a difference and they've never been directly compared and probably no one will ever compare them. I do it as a convenience thing if someone wants to get in and out in a hurry we do subcutaneous. If someone already has a port and they want to get IV, they're leery about the injections or sometimes people get injections and have red lumps that occur, so we don't know actual data that there's a difference.

**Q26:** Is there a difference between a port and a PICC line in terms ... I wanted to get a PICC line instead of a port.

**Maria Baer, MD:** No, they're the same. They're both intravenous access so the advantages a port is under the skin and if you're not using it, it only needs to be flushed once a month. On the other hand if it gets so if someone has low white cells, first of all with low platelets you can get, you shouldn't ideally, but it happens, get a what's called a hematoma meaning a big bruise and also if it gets infected it creates a nasty tissue infection and has to be taken out. A PICC line is external so if you were wearing what you're wearing now, your PICC line would be... which is fine you can actually put something nice around it or whatever to make it look fashionable, but anyway. It needs to be flushed daily, so that's 1) it's external and visible, 2) it needs to be flushed daily. On the other hand, if it gets infected, you don't pull it out, but the doctor pulls it out.

**Q26:** And my MDS is low white blood cell count so I'm worried about infections and for my chemo, because this is secondary from my cancer treatment, I had a PICC line and I just found

that to just be, I felt more in charge of that. Do you know what I mean? I could keep it clean on my own.

**Maria Baer, MD:** Also it's not as painful as sticking a port. Some people are very sensitive and need topical lidocaine. It's a personal preference.

**Q27:** Dr. Baer, is there a difference in the infection rate? PICC versus port?

**Maria Baer, MD:** No. Ideally neither one gets infected, so not that I'm aware of and I don't think so, but if a port gets infected, it usually has to be taken out and you have a wound and you need lots of antibiotics whereas a PICC, either you can get positive blood cultures and sometimes you can just clear that with antibiotics, but if it's not clearing or certain kinds of bacteria, you do need to take the PICC out, or sometimes the PICC site can get infected and sometimes that can be cleared with antibiotics, but sometimes it needs to come out. To my knowledge there's not a difference.

**Q28:** What level of degradation (inaudible 1:11:27)

**Maria Baer, MD:** What level of what? I'm sorry.

**Q28:** (inaudible 1:11:33)

**Maria Baer, MD:** So, you mean how low the blood counts ... it's more putting together the risk score, so how many blood counts are low, which blood counts, how low, but also the increased bone marrow blasts and the chromosome. Sometimes somebody's blood counts ... I have a current patient, for example, her blood counts really weren't all that bad, but she had 18 percent blasts in the bone marrow surprisingly, but went ahead and treated her and she's doing well actually. It's the risk score, it's the whole thing. If the blood counts aren't that bad and there aren't increased bone marrow blasts then I would watch and wait. If the blood counts are quite low and/or the bone marrow blasts are significantly increased.

**Q29:** That relates to this table that you showed (inaudible 1:12:35)

**Maria Baer, MD:** Right, so it is. Lower risk you only treat if the blood counts are causing problems, so either anemia or if the white count is really low and you're worried about an infection or the platelets are really low, those would be the indications for treatment, that's lower risk, but higher risk in general you treat because it's more likely to be more aggressive and to ease into a leukemia. I was just telling you about my patient who really her blood count, it was sort of an incidental pickup. It wasn't that she was having symptoms and her blood counts weren't that bad, but she had 18 percent blasts. So, I thought that was an indication for treatment. Conversely if she had not that many blasts, but her blood counts were really problematic, I would treat, but every patient is different, but it is good to have the risk scoring because you have some

kind of framework to make a decision. That said, everybody's different and the decision is definitely...

**Q29:** Thank you.

**Maria Baer, MD:** Sure.

**Q30:** Can you have the port?

**Maria Baer, MD:** Forever, as long as it doesn't get infected. There's no limit. Similarly a PICC, we've had people have them for several years as long as they're well taken care of and don't get infected.

**Q31:** I'm wondering if you can discuss the state of (inaudible 1:14:09)

**Maria Baer, MD:** I'm going to touch on it at the end.

**Q31:** Gene targeted immunotherapy?

**Maria Baer, MD:** I'm going to touch on it at the end.

**Q31:** And who's doing it and where they're doing it.

**Maria Baer, MD:** Sure. So just going through standard treatment. I think I'm almost done with that. I'm going to talk about transplant and then I'm going to talk about clinical trials, or maybe it's the other way around. We'll see which way I did that, but I'm going to definitely talk about clinical trials including immunotherapy which is certainly a hot area for lots of diseases including Myelodysplastic Syndrome.

This was just to show you that Decitabine ... oh here we go, we're going to talk about clinical trials, then transplant. I forgot which way I did that.

So testing new treatments, so again clinical trials are really important because 20 years ago I wouldn't have any of that to talk about any of those treatments to talk about, but now we have them, they're FDA approved, everyone can get them, but we need to do even better. So, we test new treatments and there are kind of two settings in which new treatments are tested, at least for higher risk disease. You can test them with... you can have your backbone of Vidaza or Dacogen and add the new treatment. Test them at the same time to try to increase the response rates or you can test them in patients who do not respond to Vidaza or Dacogen or who lose response. Sometimes respond well, but then after it varies, a number of months or several years. You were talking about how the blood, in fact you're a perfect example, you're saying how your blood counts have gotten worse and they did another marrow and now they're referring you for a

clinical trial, so that's this situation, but we do have some situations where... and there's a lot of activity, really a lot of clinical trials right now, so that's a good thing.

These are some of the new treatments. This isn't even all of them, but this is a lot of them and they make changes all the time, so some of the new treatments. There's a new demethylating agent called guadecitabine. It was initially called SGI110 and now it has a somewhat ugly name which is guadecitabine, so Decitabine is Dacogen, this is gua. It's actually kind of a modification of the Decitabine molecule, but it has been tested and in fact some of the testing was at Fox Chase, as a matter of fact, and it was published in *Lancet Oncology* about a year ago and it looks relatively promising so that's coming along. There's signaling inhibitors. So, one of them is called Rigosertib and this is what we've participated in these trials and currently have one actually. So, kinases are proteins that mediate signaling like growth signaling and kind of perpetuate the blood cells and Rigosertib also used to be called ON1910, but now it has a name which is Rigosertib. It inhibits multiple kinases and it is being tested for patients who, actually this is initial fairly broad testing and it got positive enough results that it got in a fairly prominent publication, but now they're testing it in the group that responded the best which is patients from 18 to 80 years of age, not over 80 for whatever reason, who do not respond to Vidaza or Dacogen. So, not the people who responded and then lose response, but the people who never respond and they can only have had nine months of, I have to remember all these criteria, I think I have them about right, only nine months. If it's longer than nine months, so anyway, it's a fairly targeted trial, but anyway, we'll see how that goes. They're working on an oral form. The currently version has to be given by an infusion pump for 72 hours and you have to come in and get the infusion changed every 24. It seems like every patient we treated lived at least 1 1/2 hours away so it was challenging, but anyway we'll see how that goes. There's another kinase called pim kinase which is an important mediator in cells and there's this drug called LGH447. It's being tested in a variety of bone marrow disorders including Myelodysplastic Syndrome and it's fairly early on. Then there's specific mutation. I mentioned earlier IDH1 and IDH2, which can occur in Myelodysplastic Syndrome or in acute leukemia and they're IDH1 and IDH2 inhibitors that are being tested. Then I showed you spliceosome mutations when I showed you all those mutations. There's just a little bit of work on spliceosome inhibitors. That's fairly early. There's a nuclear export protein. There's a mediator that cranks mediators out of the nucleus and maybe helps abnormal cells grow so there's this export inhibitor which looks interesting. It's being tested also in multiple bone marrow disorders.

Here we are with the immunotherapies. There are some molecules that are trying to enhance program cell death of myelodysplastic cells. There was a drug called birinapant that was tested and that wasn't a homerun. So there's a new one called venetoclax. It's actually approved in chronic lymphocytic leukemia. It's being tested in both settings actually in conjunction with Vidaza for new treatment for people who have not been previously treated and then also for people who got Vidaza or Dacogen and it didn't work or it stopped working trying it. So this looks quite interesting.

Then here's the immunotherapies. Enhancing the immune response and this is an extraordinarily hot area in cancer therapy certainly. It is thought that part of the reasons that cancers evolve is that the patient's immune system is not recognizing the abnormal cells and saw the same thing for Myelodysplastic Syndrome and there's a PD1 which is a protein and then PDL1 is the ligand to the protein that prevent recognition of these abnormal cells. So, if you use antibodies to PD1 or PDL1, you may block that kind of blinding phenomenon and allow the T-cells to recognize the abnormal cells and in fact transplant is a form of immunotherapy. We'll talk about that in a minute so there is certainly evidence that the immune system is important.

These are being tested in a variety of places and settings. Hopkins had a study, I think it's closed now, we have and it closed and now it's reopening, a study of the MedImmune drug actually. There's not one center that I can identify that kind of "the center for," but a lot of these are pharmaceutical trials for that matter. So that one's MedImmune, it's either Merck, I can't remember which one it is, or BMS, it's one of the two. I forget which, but anyway.

**Q32:** Does this mean that hematological clinicians, researchers and doctors are working with immuno specialists now as opposed to just keeping it in the hematology department? I know there are specialists that are working on other things for the immune response. How does that work? How do you guys get access to the immune intellectual property? Do you know what I mean?

**Maria Baer, MD:** Yeah I do, so there are several ways. So, certainly immunology has been there and immunotherapy. Immunotherapy wasn't all that promising until recently, but every cancer center has an immunology, so our cancer center for example, we have five programs and one of them is tumor immunology and immunotherapy. One of our laboratory researchers is extraordinarily dynamic and productive and interactive, so he's a Ph.D., but he totally interacts with clinicians who are trying to move things forward. At our place also there's someone who's more of a clinical person who has done a lot of immunotherapy trials. So, certainly in terms of developing things at individual institutions, then pharmaceutical industry in addition to making expensive drugs, does a lot of research and well, it's true. So, they offer clinical trials. For example, MedImmune which is actually a company in Maryland. In fact it's been, maybe because it's September and it's after summer, I'm getting tons of E-mails we're having this trial, do you want to participate. I guess they choose centers that have enough patients and that are known to do clinical trials well.

**Q32:** So, it wouldn't be a bad idea for us if we're shopping and getting opinions to look at somebody who has a well-developed core of immunology studies or people or clinicians or something, right?

**Maria Baer, MD:** Yes, for in-house, but also some real nice trials are pharmaceutical and so the Medimmune trial, I forget where else it is, but it's multiple institutions. So, one of the things to go on is [clinicaltrials.gov](http://clinicaltrials.gov). Are you all familiar? It's a website called [clinicaltrials.gov](http://clinicaltrials.gov) and you



could put in Myelodysplastic Syndrome. I think the MDS Foundation is good at helping people find clinical ...

**Presenter:** (inaudible 1:24:35)

**Maria Baer, MD:** Yeah and actually I know that works well because I know I've gotten emails from the Foundation saying they have a patient looking in this geographic area. So yeah, they are very helpful.

**Q33:** Two questions: First of all will we have access to these slides and possible the audio after we leave here?

**Presenter:** The audio will be on our website and we'll have the (inaudible 1:25:02).

**Maria Baer, MD:** I don't mind. There's nothing proprietary. Actually, they're on the laptops so I wouldn't forget to take my flash disk.

**Presenter:** Anyone (inaudible answer 1:25:17)

**Maria Baer, MD:** I don't mind. There's nothing proprietary on there, so I'm okay.

**Q33:** The other items are the speaking in this clinical trial thing and so forth, we learned that aplastic anemia and MDS Foundation last one here in Rockville that five of the major centers like Dana Farber and Cleveland and Anderson have gotten together, they have a problem finding enough patients with a particular set of criteria to do a clinical test, so they sort of collect from all over the place. Is that a common practice and how do you get into that kind of an environment versus any particular center?

**Maria Baer, MD:** I guess I'll answer, for any given (inaudible 1:26:15) it's kind of the flip and if this doesn't answer it, so our center for example, we have national cooperative group clinical trials that are at multiple institutions. We participate in pharmaceutical trials, so some of them, so Phase three trials for example are in multiple centers, but for example we started participating in an IDH1 inhibitor clinical trial that I think is five centers. So, for example I had a patient who had an IDH2 mutation last year and I sent her to Sloan Kettering because we didn't have a trial and they did. We all know what each other are doing and I guess, for example these IDH inhibitors, you have them at a few centers. If it looks really good and you want a large population then it'll open either a large trial at multiple sites or it'll go to the cooperative group, although the cooperative group that's a whole other issue, but they're less well-funded and there's less going on. Sometimes there are investigator, for example we're part of this little group Stand up to Cancer with Fox Chase as a matter of fact for investigator initiated because we may participate in that trial also. Sometimes we'll pilot something at an individual institution and there also your patients are right there. You can really study in detail what's going on with the bone marrow

cells. Then if it looks good it gets more generalized. Does that answer your question sort of? Okay, are you sure?

**Q34:** Dr. Baer, you diagnosed my husband back in 2012 and you put him on the Vidaza and for about 3 ½ years he did wonderful. He had excellent normal counts. Then he was involved in an ATV accident and could not take his chemotherapy and then from there it's been downhill all the way. His levels are extremely low. He usually has to have about two units of blood every week, so that's about eight units a month. Would he be a candidate for the new trial?

**Maria Baer, MD:** So, there are a couple things. One without getting into your particular, but one thing that we looked at was transplant and certainly if that were to become an option, but yes, we have so in fact he's coming back to see me in a couple weeks and I had actually said to his outside hematologist to wait a little bit because we would have new clinical trials and we have these clinical trials opening, so yes, but I can't say specifically which clinical trial. We'll have to see what's what, okay?

Transplant, there we go. We're almost done so I'm really running over, but I really appreciate all the questions. I'm really happy to be able to answer everyone's questions. I'm glad you're interested. It would be bad if I were talking and you were all asleep.

Transplant is currently the only treatment that is known to be able to cure Myelodysplastic Syndromes, but not everyone that who has a transplant is cured and the number gets better over time, but has been sort of less than 50 percent. So, you look fantastic and I'm sure you're in the good 50 percent.

So, historically transplant has been applicable to only a minority of Myelodysplastic Syndrome patients because of age. We talked about that. Years ago the upper age limit for transplant was 50, then it was 60, now it's, at least at our place, 75 but we'll go above 75. I know for example Minnesota there is no upper age limit, so part because transplant has gotten easier and better so that's getting better.

Co-morbidities are a big word to say for other medical issues. If you have someone who has myelodysplastic, typically people with Myelodysplastic Syndromes are older and older people can have other medical conditions like heart problems or kidney problems so if you have bad enough other problem or multiple other problems, it may not be a great idea to go to transplant and there are cutoffs. It gets precisely studied and makes sure all the other organs are working reasonably well.

Then donor availability so early on the major source of donors was tissue-typed siblings or brothers and sisters, so tissue-type identical brothers or sisters. For each brother or sister who are same mother same father, the pair has a 25 percent chance of matching, so it's only one in four and then as people get older maybe they don't have as many brothers and sisters or the brothers

and sisters have medical problems. Now, first of all, unrelated donors became available and now half-match transplants are becoming more and more routine. That's really been a development in recent years, so most older people have children who could be half matches and also your siblings have a 50 percent chance of being a half match with you so that really opens up the donor pool.

Partly using this non-myeloablative approach that I referred to earlier, so it's a more gentle transplant so older people can go through it more easily. That has made transplant available to more patients with Myelodysplastic Syndrome and then alternative donors meaning in particular half-match donors, for example, has helped made it more available. This is just a transplant in one slide.

What is transplant? First of all we're talking about allogeneic transplant. Allo means from someone else. Allo is I guess Greek that means 'other so it's from someone else because in other situations sometimes people have autologous transplant meaning from their own cells, but not in someone who has an abnormal bone marrow. We're talking about allogeneic, and it's called hematopoietic stem cell transplant. It used to be called bone marrow transplant a lot, but these days we get stem cells from the blood, so hematopoietic stem cell means the stem cells that make blood cells, whether they're in the bone marrow or the blood. So, the basic procedure is high-dose chemotherapy and sometimes whole-body radiation therapy. Again, with reduced intensity or non-myeloablative you use a little bit more gentle regimen. Then the transplant, you all probably know this, but most people don't. The transplant is actually a transfusion so you basically collect cells and we'll talk about how you do that from the donor and you give it as a transfusion usually into the PICC line or Hickman catheter. So it's not a transplant like you transplant a heart or a kidney or liver. It's a very special transfusion.

So, again donors can be related donors, either tissue-type or HLA is the formal term for tissue-type. Tissue-type matched or these days, half-matched, and then matched unrelated donors. Again the source could be the bone marrow. This is a bone marrow harvest in the operating room. You used to take patients to the operating room and collect usually like a quart or a quart and a half depending on size, under anesthesia, but these days most of the time it's done by leukapheresis which is collecting blood. So, the donor gets shots of G-CSF or Neupogen that mobilize stem cells into the blood and then they get a couple of IV lines placed and you circulate the blood through a leukapheresis machine and siphon off the fraction that has the stem cells, give back the red cells and the plasma and then sometimes that needs to be processed if particular people are ABL incompatible, but that's how it's done for the most part. It's certainly a procedure, but it's reasonable for donors and donors donate for strangers and, obviously, if it were compromising to their health they wouldn't be allowed to do that.

**Q35:** Are any statistics about the relative efficacy of the source?

**Maria Baer, MD:** There are some data and there was actually a national randomized trial a few years ago. With peripheral blood you get more graft versus host, but that also gives you more graft versus leukemia or graft versus Myelodysplastic Syndrome. So, on balance they're about the same and most places are using blood. Hopkins tends to use marrow. They may be shifting out of that, but they're one of the exceptions. People with aplastic anemia where you don't want graft versus whatever because they don't have whatever then you need to use bone marrow.

**Q35:** Mine was marrow, but it was a foreigner that we don't know where (inaudible 1:36:11) and they said he was young, but he was not suitable for apheresis.

**Maria Baer, MD:** That's interesting.

**Q35:** And so they made him do the bone marrow which is, of course, more arduous, but God love him, he did it.

**Maria Baer, MD:** Absolutely, and I don't know why he wasn't suitable for apheresis, but obviously it worked out great. Sometimes donors have preference, but it's usually a preference for apheresis rather than bone marrow harvest.

**Q36:** The donor did prefer the apheresis and when he was (inaudible 1:36:40) likely unsuitable they talked him into doing (inaudible 1:36:44) at MD Anderson and I was in fact prefer the bone marrow, but they very rarely get it.

**Maria Baer, MD:** Interesting.

**Q37:** What did you mean by graft versus leukemia? I understand graft versus host a little bit, but what were the other two things you said?

**Maria Baer, MD:** So, how does transplant work. One way that it works is that you're giving high dose chemotherapy plus/minus radiation therapy that kills the bone marrow. So fine, kill the bone marrow, give someone a new bone marrow and that's that, but it's not that simple. When you transplant new bone marrow or blood stem cells, you're actually transplanting in a new immune system. So, after a transplant you don't have your own bone marrow. You also don't have your own immune system and that's good and bad. The analogy if someone has a heart transplant or liver transplant or kidney transplant, you worry about rejection, right? So you worry about if I give you a new kidney, your immune system's going to say, whoa, that's not my kidney, that's foreign, I'm going to get rid of it, so you have to be on medications to prevent that from happening and actually for a solid organ you're on life-long medications.

An allogeneic blood or bone marrow transplant, you're transplanting new bone marrow, also a new immune system. So, there you don't worry, well you can have rejection, but it's relatively unusual and not such a concern. You worry about graft versus host which is the new immune

system looking around saying, whoa, this is not my body, I'm going to reject it and graft versus host can be very serious and people need to be on medication to prevent it, though usually they're able to come off after six months or a year or somewhere along in there. And when it manifests, it manifests rash, gastrointestinal problems, liver, it can be very, very severe although transplants gotten so much better you don't typically see a lot of severe graft versus host. So, you think that's a bad thing, but actually the donor's immune system also reacts against the recipients bone marrow so it helps prevent the Myelodysplastic Syndrome from coming back. It's called graft versus leukemia because there was more transplant for leukemia before myelodysplastic or graft versus tumor. So how do we know this? There are two ways that we know that it's a good thing, well at least two ways. One is if someone, there aren't a lot of people with identical twins, but some people have identical twins so you think that's great, that's the perfect transplant donor, but actually if you transplant from an identical twin the relapse rate is much higher because there's not that immunological (inaudible 1:39:39). It's kind of interesting. It's counterintuitive. The other thing is that people did large studies looking at a lot of transplant patients and patients who had more graft versus host had lower relapse rates, so graft versus leukemia or graft versus Myelodysplastic Syndrome is a good thing.

I was saying earlier in some other context that transplant is an immunotherapy. I think you were asking about immunotherapies and I was saying there is a role for immunotherapy. We know that because of transplant because transplant is in part an immunotherapy.

**Q37:** So what I'm hearing even before today is that a little bit of graft versus host isn't a bad thing.

**Maria Baer, MD:** Right, it's a good thing. Absolutely.

**Q38:** I'd like to know how many units possibly for stem cell, how many units are needed from donors?

**Maria Baer, MD:** It's number of cells. There's a couple way that you do it. When we used to do bone marrow harvest you would calculate the volume based on the patient's size and the donor's size. With collecting by apheresis you often check CD34 count. So, CD34 is a protein on stem cells and you want to make sure you get enough stem cells, so you get an adequate CD34 count and usually one pheresis, usually just one day of apheresis is enough, but sometimes people need two and I can't remember the exact CD34 number. I just don't remember.

**Q39:** What about four hours pretty much?

**Maria Baer, MD:** Yeah, that's about as long as it takes, and actually you can't usually collect and then check your CD34 count and then say, yep, we got enough and usually from a normal donor you get enough with one pheresis. Sometimes if you're doing autologous, people are

giving for themselves which is not relevant to Myelodysplastic Syndrome. It may be more of an issue.

**Q39:** The other question is only about the DNA. The DNA is only changed for the bone marrow, is that correct?

**Maria Baer, MD:** Yeah, so if you have a transplant, you have your donor's cells in your bone marrow, so it's interesting. If you have a transplant from a male donor, your bone marrow is male. It's XY, whereas the rest of you is female. Sometimes when we forget to tell the chromosome lab that someone's had a transplant and here's this female patient and they're getting XY and we get this phone call saying what?

**Q40:** Which bathroom do they use? (Laughing)

**Maria Baer, MD:** She looked perfectly female, but she had male bone marrow and blood cells.

**Q41:** Is that why they prefer, they found a woman that matched me exactly, 10 out of 10, but they chose the man.

**Maria Baer, MD:** Sometimes women have more antibodies because they've had pregnancies, although either one is fine. If you have several options, that's a wealth of choices.

**Q42:** Definitely (inaudible 1:43:00)

**Q43:** I wanted to ask a question about immunity. The shots, measles, chicken pox, I've been told two different things. Sometimes the body remembers and immunizations are not needed again. So what is, this seems to be changing and it seems to be different between where you go as to having immunizations again. At this point there is no immunity for me. My body seems to remember and so I've been fine.

**Maria Baer, MD:** Usually we do re-immunize so you wait until people are off immunosuppression because usually you can come off at six months to a year though everybody is different. Then you re-immunize, but you can check titers and see if immunities are already present and there's a whole list of things.

**Q44:** Don't our donors have immunizations? Everybody in the world has basically unless you're in a third-world country.

**Maria Baer, MD:** Yes, but the immune system has to redevelop. That's a good question. You would think I just told you you're transplanting the immune system so you should be perfect immunologically functional right after transplant, but no. The new immune system has to reestablish and develop in your body not to mention that you're also on immunosuppression. It

takes a while to be fully immunologically normal. In fact it takes several years to be fully immunologically normal and we typically do re-immunize, but the alternative is to check titers and if there are titers that are okay, then don't re-immunize.

**Q45:** Some cancer therapies are now taking T-cells out of the body, subjecting them to intensive chemotherapy (inaudible 1:45:14) and then reinjecting them into the patient without having to reduce the patient's immune system to zero. My question is that happening in MDS? And if it's not, why not?

**Maria Baer, MD:** Those are CAR T-cells. You're talking about CAR T-cells and actually they genetically engineer them. There's been some successful work in acute lymphoblastic leukemia in particular, some in chronic lymphocytic leukemia. There's some trials in lymphoma. I am actually not aware of any work in Myelodysplastic Syndrome nor in AML, actually interestingly. It's not to say that there isn't any, it's not been very visible or, and why not, that's a good question.

**Q45:** (inaudible 1:46:17) stem cells.

**Maria Baer, MD:** Right, one reason is that Myelodysplastic Syndrome bone marrow cells do not necessarily have antigens or proteins that are different from bone marrow cells. For example, you're really making me think here, so acute lymphoblastic leukemia you sensitize the T-cells to CD19 which is an antigen on B-cell ALL which you don't have a lot of CD19 positive cells in normal bone marrow, so you can target the ALL cells and leave the bone marrow intact, but there might be some antigen changes, but we don't know what they are and I guess that's the major reason, but yeah, there could be in the future certainly. That's a good question.

**Q46:** What the experience of the wrong 50 percent? The ones that this doesn't work for. What happens to them?

**Maria Baer, MD:** Several things can happen. One, transplant is difficult to go through and there can be complications of a variety of sorts and sometimes people don't survive either early on or later on though statistics are better and better, much better than they were years ago. The other thing is that the disease can relapse. You can go through the transplant and one of two things either the disease doesn't go away although that's relatively rare or it goes away but then it comes back. In particular with Myelodysplastic Syndrome, you're using non-myeloablative or reduced conditioning, so it can take a while and that's so the clinical trials were giving Vidaza after transplant or to kind of keep treating it and allow the immune system enough time to rev up and do the graft versus Myelodysplastic Syndrome. It can be both complications of therapy which can be, rarely early complications, if someone just doesn't tolerate the high-dose chemotherapy the part that you test people carefully. That's why you don't take people whose hearts or livers or kidneys aren't working or whatever and early complications, graft versus host, though again that's much less of a problem than it used to be, the immune system is down you

can get an infection and if it's a bad infection that could, so most people get through, but it's not a guarantee. The other thing, I think I bring this up in the subsequent slide, but I'll go ahead. So, you measure someone's age, how old they are, that's easy, and you measure heart function, liver function, kidney function, but there's also something we call performance status which is just how well they are. It doesn't necessarily correlate with age. There are people who are older who are extremely fit and there are people who are 50 who are train wrecks, right? So, you try to assess that. It's also just how well someone is and then there is some there are these scoring systems, but that helps determine who's going to get through successfully.

**Q47:** If one should relapse after a transplant, is Vidaza then to be resumed or is it useful?

**Maria Baer, MD:** It varies. It can be. Sometimes if someone is relapsing you try to give some more donor T-cells, so that's an option. Vidaza, depending on the history with Vidaza, if someone hadn't been responding you can start it again if they had been resistant to it. It might work, but you'd be a little more pessimistic.

**Q48:** We were told that once he goes off it (inaudible 1:50:43), that he would in fact he would need to get all of his immunizations over again, but none of the live vaccine ones could ever have again.

**Maria Baer, MD:** Right, so that's what a lot of places do. That's what you were asking about, whether everyone just gets re-immunized or whether you test. In my experience we just re-immunize, but if you test and somebody has immunity I guess you don't have to re-immunize. There's no downside to re-immunizing except it's a bunch of shots often given at the same time, but you would not get live vaccines. Because the immune system is compromised and a live vaccine could, unlikely, but could produce the disease that you're vaccinating against. It's all pretty standardized.

**Q48:** So you wouldn't be able to get a flu shot?

**Maria Baer, MD:** You can get a flu shot, you should get a flu shot, well I don't speak to you personally, but one should get a flu shot, yes.

**Q48:** Isn't the live?

**Maria Baer, MD:** Yeah, there's like polio, there's a live and, don't ask me which one is which I can't remember, there's a live and attenuated, so definitely polio is an issue. That's the main issue I think although.

**Q48:** Shingles?

**Maria Baer, MD:** Yeah, shingles, good point, very good, you're absolutely right. And what?



**Q50:** MMR (inaudible 1:52:09)

**Maria Baer, MD:** Okay, very good.

**Q51:** They're using, speaking of polio, they're using polio as a treatment for some cancers.

**Maria Baer, MD:** I've seen that.

**Q51:** Is that applicable to MDS at all?

**Maria Baer, MD:** Not to my knowledge. I think they were using it glioblastomas or something.

**Q52:** Yeah, glioblastomas and Fox Chase is using HPV on melanoma now.

**Q53:** Could you repeat what you said about glioblastoma?

**Maria Baer, MD:** You asked about whether polio, there's some research and clinical trials using polio as part of the treatment and he asked whether that was relevant to Myelodysplastic Syndrome and I said not to my knowledge, but I said the trial that I am familiar with was in glioblastoma. It might have been at Duke, but don't hold me to that.

**Q53:** It was on CBS like on "60 Minutes."

**Maria Baer, MD:** I know because that's where I saw it. I saw it on TV. I think one of my patients told me about it.

So transplant, I'm just going to talk briefly about considerations about decision making for transplant. So, IPSS is really important. The risk scoring system is important. I mentioned it's important in choosing treatment and I've mentioned several times that it's important in deciding about transplant. So, this is a little bit of a complicated slide and it's about a 12-year-old study, but these are patients who are low and intermediate ones. This is lower risk. This is the IPSS, intermediate two and high is higher risk. No transplant, transplant. So, you see that the people who are lower risk who don't get a transplant actually live longer than those who do. People who have lower risk disease, they may have anemia and low counts, but they don't have anything acutely life threatening usually and to put them through a transplant you may shorten their survival. On the other hand people who are higher risk do tend to have more complications to develop leukemia. Their disease poses more of a risk to them and transplanting them they do better than not, but this is an average and everybody's different and, for example, I had a patient a few years ago who was lower risk but he had one low blood count, but it was low platelets, and he didn't respond to platelet transfusion so that was really life threatening so we transplanted

him. They're totally, everybody's different, but on average you would not rapidly transplant a lower risk patient and you would try to get a higher risk patient to transplant.

So, the transplant decision. That's a very complicated one and a very personal one. So certainly in terms of the disease, Myelodysplastic Syndrome, there's the risk status as I just said. Within risk status chromosomes can additionally play a role in the decision making and now there are new data on mutations also, again, it's really new data then whether there's a donor and who the donor is obviously important. For the patient, the age, but we've talked about how age is not, is much less important than it used to be. Medical problems and I actually forgot to put performance status which is really key whether you're a well 75 year old or a chronically ill, out-of-shape 50-year-old or whatever. Support system, I'm sure you can vouch for this, no one can go through a transplant by themselves, so it can be pretty overwhelming and you absolutely need a support system. It's key. Then really there's personal choice. So, people have different life situations and they have different personalities and I experience this all the time except for the same or comparable medical facts, you have someone who will say, you know what? I'm not a risk taker, I'm doing fine right now, let's leave well enough alone and if something else comes up we'll deal with it and then you have someone who says, the other extreme, this is hanging over my head, I want something done about it, I want definitive, just different. Then you have people who may have a personality somewhere in the middle, but say the most important thing to me is to get to my daughter's wedding this summer and after that I'll think about transplant. So, everybody's different so that makes life interesting, but it is very much a personal decision in addition to all the medical stuff.

We got through the slides, that's my summary slide. It's treatable, new treatments change the disease course which wasn't true 20 years ago, how you treat depends on the presentation on the abnormal blood counts and the risk score, transplant can cure but the indication depends on the presentation of the disease and lots of patient specific factors both medical and personal, there are FDA approved treatments all of them approved in the last roughly 15 years based on clinical trials. So again, 20 years ago we had none of this. I just to tell you, again, how important clinical trial are, please consider participating in clinical trials.

**Q54:** I have a question, what do you think about clinical trials, stem cell clinical trials?

**Maria Baer, MD:** So doing transplant as part of the clinical trial?

**Q54:** There's one right now.

**Maria Baer, MD:** I think that if the patient qualifies for the trial and if you understand what the question is and it seems like a good question then I would do it because transplant has gotten much better over time.

**Q54:** It doesn't seem much different than the traditional clinical trial. I mean the traditional stem cell transplant. It's actually a little better.

**Maria Baer, MD:** I really encourage clinical trials. You should know also that clinical trials get extraordinarily heavily scrutinized at every level. So, a lot of clinical trials, the FDA has to weigh in, CTEF which is part of the government has to weigh in, then at each institution there's a clinical research committee that looks at the science and says does this make sense and then there's this thing called the IRB or Institutional Review Board that reviews the ethics. So, anything you're being offered has been very heavily scrutinized at multiple levels. It's not just someone saying oh, I think I'll do this or whatever. As you know, 50 years ago there was a history, that was not the case, but if anything it's gone totally to the other. So, anything that you're being offered that anyone's being offered has been very carefully looked at and inspected and for science, for ethics, informed consent and I'm old enough I remember when transplant was the rare patient and we didn't have these treatments and it's all been because of clinical trials and for all of these treatments somebody was the first patient. Some first patient got Vidaza, or not for that matter, but somebody said yeah, I'll do this. I encourage clinical trials. On the other hand if you as an individual, if it's a clinical trial for whatever reason, in fact we bend over backwards to say we're offering you this clinical trial, if you don't want to do it that is absolutely your right and it will not compromise your care or your relationship with your team. So, that's important.

**Q55:** Especially about the trials if you've been on Vidaza, maybe of them rule you out of, clinical trials if you've been on Vidaza and yet Vidaza's the only drug approved to treat the disease. Is there more interest in trying to find clinical trials that are compatible with people that are on Vidaza?

**Maria Baer, MD:** Most of the clinical trials are either up front try something else with Vidaza or Vidaza plus or minus something else, but almost all of them are for people who got Vidaza and it either didn't work or it stopped working because Vidaza, because it does have a good response rate, to say we're not going give you Vidaza, unless for example it's the guadecitabine, the SGI110, is a similar drug that is potentially better. It's going to be in randomized drug, but so that's not giving you a Vidaza equivalent that's been chemically modified and may be better than Vidaza. But to say that I'm going to give you some totally different and not have you, unless it's something to try something for a couple months and then get Vidaza, but I don't know of any trials like that. So, most of them are Vidaza plus or minus something else or something else for someone who has had Vidaza. Does that make sense?

**Q56:** With the clinical trial is there kind of a way to do it or one or two places or do you just shop everywhere you can think of to find a clinical trial?

**Maria Baer, MD:** There's different ways of looking at that. So, one is you live in a particular place and there are X many institutions around you and you might want to know what's going on

locally. On the other hand, for example, if you had an IDH1 mutation, you would want to know and if it were time to try something different, look up which institutions have IDH1 inhibitor clinical trials and try to find the one closest to you. I guess if you're looking for a particular treatment or CAR T-cells, for example, though that's not for Myelodysplastic Syndrome, you would look at which institutions have them, but otherwise if you don't have a particular bias towards a particular clinical trial, certainly in this area there are lots of institutions.

**Q56:** I mean you don't necessarily know what you're looking for, if you will, what mechanism is there to decide that for you?

**Maria Baer, MD:** One thing is I would talk to your doctor who hopefully knows you well and is well-informed. Each of the academic institutions have websites that are more or less easy to navigate, so you go into the particular institution, clinical trials, Myelodysplastic Syndrome and see and, hopefully, they're easy to navigate and they're being kept current. I can't say that with certainty. Then you could talk to the MDS Foundation because they are very helpful in terms of knowing what the clinical trials are and where they are and then if you're kind of interested in what the broad landscape, go to [clinicaltrials.gov](http://clinicaltrials.gov) and type in Myelodysplastic Syndrome.

**Q56:** Is NIH a good place to look?

**Maria Baer, MD:** The NHLBI, the National, the blood part, yeah they've had some good trials for Myelodysplastic Syndrome. And they just take people for clinical trials so they'll take you if you're eligible for their clinical trial, but they don't do general treatment.

**Q57:** I have low-risk disease. I'm being treatment at Eisenhower in Rancho Mirage. The treatment that I've had is exactly what looks like your presentation would recommend. I had Vidaza for 8 months, 55 mg. My question is about the Centers of Excellence and the treatment that I'm getting is not at a Center of Excellence. How concerned should I be about that if at all?

**Maria Baer, MD:** The Centers of Excellence I guess are certified based on expertise and having chromosome labs in-house.

**Q58:** (inaudible 2:05:43)

**Q57:** I just have one more quick question. I spoke with the doctor yesterday who said I don't know why you would do Decitabine or Vidaza, why don't you just go straight to transplant? I would send you straight to transplant. So, that was a curveball.

**Maria Baer, MD:** I don't know your particular situation.

**Q57:** Just really general, and I know you can diagnose on the spot, but I have a lot of chromosomes involved like at the bottom of my cytogenic it says poor prognosis MDS. I'm

secondary, so I'm going to progress. It's not like being diagnosed as an elderly person where I'm going to progress to leukemia. So, I was so blown away by that and I actually called Dr. Trish's PA and I said, "Why not? Why don't I just go straight to transplant? I'm super healthy right now. I'm not stressed out by all the transfusions and all that stuff. My counts are really bad" and he said, "No we want to get your bone marrow as clean as possible before transplant."

**Maria Baer, MD:** So, one thing I would want to know is your percentage of blasts in the bone marrow.

**Q57:** I'm less than 10, so I'm at like 7.

**Maria Baer, MD:** I would give you therapy first. If you could go to transplant with less than five and possibly better looking chromosomes.

**Q57:** The only thing that he said is sometimes transplants don't go as well once you've been given, like there's some impact on the transplant process when you've been given Decitabine and/or Vidaza. I mean, I'm not hearing that makes any huge difference and he said there's no numbers.

**Maria Baer, MD:** I agree and not just because you're being treated by my friend, definitely if you can get the blasts down and know these treatments are gentle and in fact sometimes they're even continued after transplant.

**Q58:** You can talk to me. I'm in the same situation.

**Q59:** Actually my question is do you have any data on the percentage of people post-transplant who do continue on Vidaza. We were randomized into the null set so we're not getting it. Should we ask for it (inaudible 2:08:28).

**Maria Baer, MD:** Sure, there are no data. There was a clinical trial looking at tolerability and in particular what dose could be tolerated after transplant because you can't just come in with 75 per square meter because the new bone marrow doesn't tolerate it so well. This may be the randomized trial.

**Q59:** It is.

**Maria Baer, MD:** So, maybe that will ... with clinical trials and this is important for clinical trials in general also if we clearly know that one arm is better than the other arm, we can't do the clinical trial. So, if it was known that it was better to get Vidaza than not, then it would not be ethical to offer you that, it is absolutely not known. In fact at our place, we have people who've responded to Vidaza or Dacogen and are able to go transplant and we're thinking they had problematic disease to begin with, transplant takes a while, the immuno part of the transplant,

takes a while to work, let's do this, but it's not, so hopefully this randomized trial will answer the question. Everybody's so different. Everybody's disease is different, everybody's different. Sometimes clinical trial might say clearly this arm is better than that arm or it may be like I was telling you about that Rigosertib trial where, well if you're between 18 and 80 and have gotten nine months of therapy and haven't responded, that's a little subset, so it may be that they do enough patients they may figure out which subset benefits, if that makes sense. But, no, if they knew for sure that it was better to give you the treatment, they could not ethically do the clinical trial and it's not just the doctors doing the clinical trial, but as I said it gets reviewed by everybody.

**Q60:** Is it conceivable then that after let's say after two or three years of clinical trial, it isn't just the (inaudible 2:10:23) testing Vidaza after and if that turns out that there is a preference that is (inaudible 2:10:30), no reason I couldn't start it then.

**Maria Baer, MD:** That's true. On the other hand if you go two or three years without relapsing, you're probably home free.

**Q60:** I like that, good.

**Maria Baer, MD:** And you look terrific, you really do. So thank you all so much

(Applause)

**Presenter:** Hi everyone. I hope you've enjoyed lunch. We're going to get started now with Donna. So, I'll do a brief introduction, very brief.

**Donna Cetroni:** Hi, I am so glad to be here. It was kind of last minute, like I don't know, what, Thursday night as I was driving to the city at 5:00 pm, but my feeling is when opportunities arise there probably is some reason why you have to be wherever you're supposed to be. Thank you for having me and I'm very glad to be here and I learned so much about MDS from Dr. Baer. I am a nurse at heart. I was an emergency department nurse for so many years and I saw that people did better when there was an integrative approach to care versus Western medicine and Eastern medicine or alternative or complimentary care. I don't really believe in any of that. I believe that there is Western and medicine that we can rely on and thank God because some of those medicine, many of us may not be here if it wasn't for the amazing miracles of Western medicine. On the other hand having a team approach and having the ability of people who really understand how the mind and the body and the spirit work on a physics plain as well helps the person, and myself, to another place of healing. Healing isn't always curing.

Just a little tiny bit about myself. I don't want to spend a lot of time because we have a little bit of time, but why I would be speaking to you and maybe why you want to listen to what I have to say. So, emergency department many years, went for a Baccalaureate degree at Rutgers and then

I moved on to patient safety and quality and that's what I do in the Western world now every day. I work with the medical staff. I work with the oncology staff. I work with emergency department. I work with now (inaudible 2:13:39) surviving sepsis campaign, so I'm right in the middle of Western medicine. I know all of the criteria for certain things that have to happen because when I'm reviewing a chart or having a conversation at grand rounds, I really need to know that. That's why I'm so happy about being here and learning so much about what's may be happening for some of you. Then I went for a Master's in Holistic Health Studies and a second Master's in counseling psychology, so I did it all at like 40 the degree at Rutgers, 50 the degree at Georgian Court and 60 the degree at Monmouth University. My message there is learning can never stop. Lifelong learning can never stop. I do one course at a time. People wonder why and I say well I don't really want to go to bingo or play bocce. I mean that may be good for you and I'm okay with that, but I really enjoy being in a classroom and learning from people who are more learned about me and learned in a subject more than I am so that I could bring that to people like you.

If you don't pay attention to all of who it is that you are, we call it whole person processing, you may have a cure of your disease, but you still may live a life that's unbalanced and unsatisfying because you may fear that the disease may come back and I do believe this, I have to say, healing is always possible and miracles happen every single day. With your stories I listened, I observed, I wasn't deciding, I wasn't judging any of you, but this room is filled with just a loving presence of caring and empathy and compassion and expertise and commitment in a way that I don't see every single day working in a hospital. So, I really want to say, does anybody have a problem with me using the word 'God' or the symbol. You could believe whatever you believe. If I use the word 'God' and you don't believe in God just replace it with whatever you believe, whether it's Buddha or Nature, is that okay? Is that an agreement that we have? I'm just looking around the room, alright. So I'm going to say 'God' or whatever you believe should send a multitude of blessings to every one of you.

Now I'm going to show you a video of someone who is one of my main teachers at this point, Dr. Joan Borysenko. She actually was a Harvard cellular biologist just at the time Herbert Benson was discovering the stress response, so she was 20-something years old and she's working in the lab and she's looking at cancer cells and she's seeing how they respond to like an acidic environment versus a non-acidic environment and she actually birthed with Herbert Benson that information that stress affects our physiologies. I just actually spent the weekend with her a week and a half ago, and she's just an amazing being because then what she did is she got a bunch of post doctorates and a few of them were in psychology, spirituality and I always say she lives at the right hand of the Dalai Lama because she does hang with him. So, when I'm with her I feel like I have everything. She has the Western world, the day language and she has the night language. You will get a lot out of this video.

I would like you to put your feet flat on the floor because this video could be available to you online. Take a deep breath, in through your nose, all the way down whatever that means to you,

and just scan from the top of your head to the tips of your toes, any areas that may be tense or, there was a lot of information, scientific information, certainly valued, but I want to get out of your prefrontal cortex a little bit and go into the whole body, so I want you to really be connected with your body right now. Any cell phones just maybe turn them off or take them out of your attention. This hour, I think we have 55 minutes, this is for you. This is a gift for you. The MDS foundation is smart enough to know that it takes a team, it takes a village, to help people come to a place of healing and if you want your medication to work you have to be in love with it. You can't be afraid of it. If you are afraid of your medication, it just will not work. It is proven. There is evidence that says that. If you say thank you so much for this medicine and medicine can you take away or give me whatever it is that you're supposed to do. The whole body changes, we know this through neuroscience, we know it through epigenetics, we know that the brain will put out neurotransmitters that help us to a healthy and joyful life, or prevent us from having health and joy.

*[Video]*

*We all need to be able to develop resilience because the world is in a tremendous time of change and even that aside our personal lives are always changing. It's just the nature of life. One thing dies away, something else comes up and you've got to be able to be comfortable with that kind of flow.*

*So, resilience has been studied in a number of contexts. People who are sick, who's resilient and who crumbles, people who unfortunately have been prisoners of war or in concentration camps, kids who have come from really disadvantaged abusive backgrounds, so even corporations, resilience in corporations, is a big area of study. And, do you know what? Whether you're an individual or a corporation, the basics of resilience are the same.*

*So, let's talk about five things that you can do to become a more resilient person. I wasn't a resilient person myself so I know these things up close and personal because I've been working on them for years personally and I can tell you, you will change your brain circuits and you can become resilient no matter what your family history was, no matter what your brain wiring is now, these are skills that can absolutely change your brain, change your attitude and change your life.*

*The first thing that we know about resilience is that resilient people are realists and I'll give you a corporate example of that. Remember there was a first bombing of the World Trade Center years before the planes actually crashed into the towers. At that time one company which was Morgan Stanley said, "We better recognize we are in a very high value target and this is not likely the last attempt. Sooner or later the terrorists will come again to destroy these towers and we have to be ready." That's what a realist does. They're ducking with the head in the*



*sand, no wishful thinking, just like hey, we have to pay attention here. What they did was to get a wonderful resilient Vietnam vet as their head of security and do drills constantly so that their people, over 7,000 of them, knew how to evacuate from that tower. Then they also got three offices off-site so that were the towers to go down, they'd be able to continue their business. Well, what happened on, and it was so sad, during the planes crashing into the towers on 9/11 is that it paid off for them. Even though their floor took a direct hit, fortunately they were in the second tower so that they had some time that the security got everybody out but seven people. The head of security actually perished because he was getting everybody else out, but it's extraordinary that they were able to evacuate virtually everybody from those offices. So we all have to be realists. If you're living in a lousy marriage, if you're living with an abusive person, you have to be realistic. It's unlikely that person is going to change. You're going to have to make a radical step toward your own freedom. Or if you've lost your job, it's not a good idea to sit around and do aforesations and expect a job to come to you. You need to get out there and be a realist and take charge. So, that's the first part of being resilient. Do something, actually face things head on, eyes wide open, heart wide open, ask your friends for help, and that really is important.*

*The second aspect of resiliency is that we're meaning making animals, human beings are. I often think of the soul as the organ of the creation of meaning, and if you're going through a hard time you have to be able to create meaning for that so that you don't become depressed. For example, many people have had difficult marriages. If you say to yourself the meaning of this is I'm a no good person, I don't deserve love, you're not very resilient. But if you say to yourself, I have faith and trust that this aspect of my life, like so many others, is a place where I'm learning and I'm growing. Yes, it's a difficult time, but I'm facing it head on and I will be different now. I've learned so much from this difficult relationship. That's faith and trust. So, for some people it's religious faith, but for many of us it's simply faith that life is meaningful and good.*

*The third aspect of resilience. We've looked at realism, we've looked at faith and meaning the third aspect is that resilient people tend to be radically creative and this is really, really, really important. Radical creativity means that you think outside of the box and so for example, instead of saying well I've lost my job, this is terrible, the economy's bad, I'm not going to get another one and then declining into your box, into your rut and feeling depressed, you start to say to yourself, okay, I can't do perhaps what I've always done before, but what is it that I find most interesting now? What am I most curious about? Then you say to yourself, well I've always been curious about geology, or I've always been curious about photography and as much as it may not make sense to you at the moment, you go and you participate in something that you've always been curious*

*about. Maybe you get an internship somewhere or you volunteer somewhere and that leads you to a new job. It means you approach things from a different point of view and as I know we'll come into a discussion of mindfulness together, but instead of mourning what you don't have, mindfulness means appreciating what you do and often it's through that deep appreciation that resilience comes up new ideas and creativity comes up.*

*The last two little hints for resilience, and now we've looked at three. We've looked at being an optimizing realist, optimizing your situation by looking at it head on. We've looked at trust and faith. We've looked at creativity. The last two are social support and a great sense of humor and the absurd. You have to have your friends and your family around you to help you, to cheer you on, to give you ideas. A study of POWs found that in one camp, the POWs have found a way to tap almost like Morse code and that allowed them to communicate and talk with each other. That gave them resilience. They shared where they were at.*

*And the last thing is humor. A sense of absurdity is great. So, for example in the 2008 Presidential Elections, John McCain was running for office. It doesn't matter what your politics are because that's not what we're discussing here. We're discussing the fact that he was in a POW camp for five years and is clearly a resilient person. After all, he's a Senator, quite functional, ran for President and, if you watched "Saturday Night Live" during that time, not only was Tina Fey great as Sarah Palin, that Senator McCain was great as himself. He has a wonderful sense of humor and the sense of absurdity lifts you out of your box. It lifts you out of the limits of your own thinking and it expands your perspective and that leads to resilience. So remember, even if the genes were not stacked in your direction, even if you came from a pessimistic family, you can change your brain wiring through these simple five tips.*

**Donna Cetroni:** Joan Borysenko.

So, now we have to find ... alright here we are. So this happens to be my dad after three strokes two years ago and he was 92 and we had to go to an event by ourselves because my mom was ill and someone snapped this photograph and I have to tell you I never realized how much I loved my dad, so I want you to go home and I want you to look at those photographs. The photographs that have meaning to you and while all of you are together here right now I want you to look at each other and especially the person who is needing care and the person who is caring for you and say thank you so much for being here for me. Kissing is allowed, not too long though. I don't want to get in trouble here. Then I want you to look at each other and I want you to say to each other that I, okay I want you to say this, miracles are happening every day and healing is possible.

So what is quality of life? Tracy asked me if I would come here and talk about quality of life. What is it? Anyone? How your everyday life goes.

(Attendee), what's quality of life?

**Q61:** A sense of peace.

**Donna Cetroni:** A sense of peace.

**Q62:** Living to your highest potential.

**Donna Cetroni:** Living to your highest potential. How do we know what that is?

**Q62:** You feel it. It's a gut feeling.

**Donna Cetroni:** Okay, wonderful. Anyone else?

**Q63:** What you make of it.

**Donna Cetroni:** What you make of it.

**Q64:** What you do and who you surround yourself with.

**Donna Cetroni:** What you do and who you surround yourself with. We have these things in our brain, like they're called brain cells, and there are these neuro neurons that take on literally what it is that you see, smell, hear, taste. So if you're hanging around with a bunch of negative people or you're working with people who are very pessimistic, negative energy is scientifically proven to be like eight to nine times stronger than positive energy. You have to do nine times whatever it is that you experienced in the negative to turn that around. Breathing is a good way to turn that around, so we're all breathing, but you know what? We're breathing from here. We're breathing right from here. All of you right now are breathing from here. None of you are, including myself, are breathing consciously where you're thinking about the air coming in. It's an automatic response. We breathe air in and the breathe air out. Unfortunately because we life in a stressful environment, usually I mean most people we're moving, moving, moving, running, running, running, we're not thinking about breathing. If you could take a really slow deep breath, while you're driving, every red light, think about it because we sit at red lights many times. What are we doing? We're just worried about getting to the next place all stressed and my son's in the back blowing the light out, so it turns green, or my grandson now. Well that's probably good because it's a breathing exercise, blowing. Taking a deep breath, bringing it all the way down and then just really consciously thinking. You don't have to modulate it a lot, you don't have to work hard, bringing that breath up to your shoulders and then breathing out, feeling that cool air going in and the warm air going out. Three minutes of that kind of exercise will totally change

the physio logics in your body from one of epinephrine and cortisol to endorphins and oxytocin which will help you feel relaxed. It's the product of the parasympathetic nervous system. When you stimulate the parasympathetic nervous system your organs say, alright this is good. When you're getting your treatments, taking long deep breaths, focusing on the inside, your inner continent and really connecting with the healing part of you. Whatever it is you believe, if it's a God that lives in your heart, if it's a God that lives in your church and if it's a God that lives everywhere, a God that lives in nature, if it's nature, if it's a tree, whatever it bring you hope. I've studied all traditions and in Chinese medicine, Chinese believe that the energy runs from Heaven to Earth or from the sky to the Earth. Native Americans believe in nature, the healing powers of nature, the healing powers of community. There are different philosophies and cultures that can bring you to the same place. Christianity believes in God, so for myself because I've been brought up in the Christian tradition, Mother Mary I wouldn't help but go to Mexico City one year and go to the Feast of Guadalupe with other 100,000 Mexican people who were in line waiting to go to the chapel. It was an inside drive. I didn't have a choice. I said I'm doing this, it happened and I mean it was just beyond all reality really, whatever drives you to a peaceful place and spirit is really the universe informing you about how to make your life better.

So, we do best in nature. Many of you, maybe if you're going through treatment or you have some weakness when you wake up in the morning, if you're just not feeling at your best. This is a Chinese tradition, walking 100 steps after each meal, slow mindful steps. Tec (sp?) Han who was a Vietnamese sage, will say when you're washing the dishes, wash the dishes mindfully and say as I'm washing the dishes I feel happy, as I'm washing the dishes I feel happy rather than, oh my God, I came home, every time I come home there's dishes in the sink, why can't they clean the sink out after they wash the dishes? That just brings negativity from the top of our heads to the tips of our toes and it definitely changes our physio logics. So when I'm washing the dishes, I'm washing dishes. Listen, none of us are perfect. This is the 80/20 rule. There are times I'm at work and I'm going, mmm, right? Really feel, smell and taste the beauty of nature. When that picture was taken, actually when I was with Joan Borysenko at Kripalu and I took my camera and I was out in the back on the grounds, I just found this daisy that was like staring at me, so I took my camera and snapped it and wanted to share it with you. But look at the light that's actually coming from the daisy in the middle, just amazing how when you're walking by the daisies you would never really appreciate that.

So, this is my grandson, Cristian, he's nine. He knows not to eat poison food. My daughter wants to probably kill me at times because he'll say, "Mee ma, can I have Oreos?" I go, "Oh yes Cristian, you can have two Oreos maybe sometimes, but you really can't eat them too often because they're not doing anything except making you feel good and making you happy." So now he comes over he says, "Mee ma, can I have three organic apples and can you juice them for me?" and my daughter's like, "What? He wouldn't do that at my house." I go I just trained him from young that there was poison food and food that helps you. So, again, the 80/20 rule, think about what you're eating. Would you put bad gas in your car? I love cars, so anybody have really interesting cars here? I'll be your best friend. I love cars. What do you have?

**Q65:** Electric car.

**Donna Cetroni:** You do, very nice. I would never put bad gas in my car. I won't even kind of change gas stations because actually I could feel it in my car. Maybe it's subconscious or not, like I go, oh no I put Costco gas in my car. My car's not liking it because I paid 10 cents cheaper, but I can feel it. So it's the same thing your body. You're feeding yourselves, so do you want to feed yourselves in a healthy way, especially if you're going through treatments? They say that bodies that are more alkaline than acidic are healthier and will take treatments in a better way. Look online, there's plenty of opportunities to figure out how to eat in a better way and I was just mentioning to Dr. Baer, there is this woman who I really am in love with. Her name is Kris Carr. She was a New York City director of plays and graphic designer and she ended up getting this very, very rare cancer and she was literally told that she will die in a very short period of time. So I think she sold her New York City apartment and she had her parents support her and she went and she interviewed all of the sages in the disease and also in spirituality, so Andrew Weil and Mark Hyman and she became buddies with them and she actually put out a documentary called "Crazy Sexy Cancer," so I'm not sure if any of you are interested in watching that, but I would definitely look into it and she's written so many books about food and how to help your body accept the treatments in a better way. So, "Crazy Sexy Cancer," Kris Carr.

What I want you to do is hold your hands over your chest like this. If you hold your hands over your chest for about three minutes mindfully, you could actually even lock your thumbs, so like a butterfly. Breathe into that area of your chest. Three minutes of that exercise, it's a yogic exercise. This is a hand mudra, will produce oxytocin. Oxytocin is the hormone that's produced when a baby is breastfeeding, so it allows the mother to be more comfortable and calm during the breastfeeding experience. This will do the same thing for you. Oxytocin will help you feel calm and safe, somewhat comforting that inner child, the place inside of us that gets scared, it's just human nature, it's the human condition, we all have fears and we all have love, everything else lives in those buckets. A really good book, "Love is Letting Go of Fear". And just think while you're doing this about all the people in your life that you love and send love to them and then just imagine them sending love to you. Also imagine all those people that you feel like you tolerate or they tolerate you and send love in your imagination, your mind is like Memorex, what you imagine is real, to them and just imagine that they're sending love to you. Then also think about that person that really pushes your buttons, just knows exactly what to say or do and send love to that person and have that person send love to you. Breathing in and breathing out.

Now, I just want to around the room and in your microphones I want you to put your name and one word about how you feel right now, one word.

**Q66:** (Attendee), Peaceful

**Q67:** (Attendee), Peaceful

- Q68: (Attendee), Kind
- Q69: (Attendee), Blessed
- Q70: (Attendee), Thoughtful
- Q71: (Attendee), Joy
- Q72: (Attendee), Relaxed
- Q73: (Attendee), Serene
- Q74: (Attendee), Accepting
- Q75: (Attendee), Peaceful
- Q76: (Attendee), Hopeful
- Q77: (Attendee), Thoughtful
- Q78: (Attendee), Sleepy
- Q79: (Attendee), Calm
- Q80: (Attendee), Peaceful
- Q81: (Attendee), Thankful
- Q82: (Attendee), Relaxed
- Q83: (Attendee), Mindful
- Q84: (Attendee), Calm
- Q85: (Attendee), Thoughtful
- Q86: (Attendee), Centered
- Q87: (Attendee), Harmonious
- Q88: (Attendee), Peaceful

**Q89:** (Attendee), Determined

**Q90:** (Attendee), Fortunate

**Q91:** (Attendee), Soft

**Donna Cetroni:** (Attendee), Soft and accepting.

**Q93:** (Attendee), Peaceful

**Q94:** (Attendee), Ernest

**Q95:** (Attendee), Quiet

**Q96:** (Attendee), Peaceful

**Q97:** (Attendee), Calm

**Q98:** (Attendee), Relaxed

**Q99:** (Attendee), Happy

**Donna Cetroni:** There is no drug that can do that in three minutes. What I usually do is go around the room, but in the interest of time I knew we didn't have time to do that, and you're not getting away with that in the back row.

**Q100:** (Attendee), Relaxed

**Q101:** (Attendee).

**Donna Cetroni:** (Attendee), playing with his phone.

**Q102:** (Attendee), Observant

**Donna Cetroni:** Observe and don't decide, that's what I was taught. The first time I went from true Western medicine into a class with a physiatrist who's teaching me about energy medicine that I can't see and she taught me that it's physics, sweetheart, you know it in a sonogram, but you don't know it in the healing world because we lost something over time.

"Love someone and let someone love you. I would like my life to be a statement of love and compassion and where it isn't, that is where my work lies." That's Ram Dass. He was like a

hippie, guitar player who turned into a wonderful, spiritual, song man and teacher. So that's where your work lies while you're getting your treatments, while you're supporting your loved one. Love more than any other time in your life.

On patience, have patience of all things, but first of all with yourself. How many times do you wake up, I did this Thursday night as I'm driving to the City, I'm going to a concert with Deva Premal & Miten, I know I'm going to be home really late. I actually just started a post-Master's in Patient Safety and Quality at the University of Chicago Medical School. I mean I'm like I'm going to Baltimore on Saturday morning? I had papers to do, I wanted to get a PowerPoint done and I'm telling you as I was driving I was saying, "You're a no good daughter, she's home with a caregiver, you haven't seen her in three days, you have a son who's affected with Down's syndrome, and you need to spend more time with him, you blow him off because he does so well," and on the other hand I said, alright inner critic, go out to Starbucks, leave me alone I have important work to do, I'm going to Baltimore. Then I called my husband and the people that would support me and said, "Can you do me a favor and deliver my mother's pills and give Galina her money and could you make sure that Jonathan gets to Barnes and Noble and the library because he's affected with Down's syndrome," but he's the next Pope, Buddha, I don't know what. He just studies and studies and studies everything. He's learning Italian now.

Patience is the ability to live while waiting. So, I used to tell my dad, who ended up having five strokes before he died and he lost his voice, but he didn't lose his mind and he did know next up Heaven. That's what he said, he didn't say that, but I would say do you want to go to the hospital anymore, and he'd be like no. I go, "Do you want hospice to come and help you and mommy?" and he would say yes, but I was like, dad, live everyday. That's what we're supposed to do till we die, live everyday till you die because we're all aging every single day. We don't know how many days we have left and if we waste one day, we're wasting a gift and he used to say to me all the time, "Every day you get up is a miracle, every day you wake up and get out of bed." I remember one time I had a trimolleolar fracture and I was in the middle of raising my kids, and school, and ... I went to their house for three or four days to take care of me when I got out of the hospital and I remember him, on his knees and he had to be 85 because it wasn't too long ago, praying while I was sleeping. He thought I was sleeping, but I opened my eyes and he was praying at my bedside that I would be able to get back in order to be able to do the work that I was supposed to be doing for my family and for myself. So, have patience with yourself. Forgive yourself first, then other people.

Enjoy music. Music stimulates peacefulness, creativity and in a holistic sense of balance. There are all kinds of ways to use music. Go to the music you love. So, if it's the Beatles or like I was going to a Billy Joel concert so I just bought four Billy Joel CDs and I went to Sirius and went to the Billy Joel station everyday for three months until when I went to that concert I literally knew every word of every song at 62, and so the 20 year-old that was sitting next to me is like, "Wow!" Have a passion for something. That's not your work, that's sometimes not your family, have it for something that is different, that excites you that wakes you up in the morning and



excites you. On the other hand if it's classical music or if you're a really excitable person you probably don't want to go to electronica. You don't want to because it's going to take you to another place. It's going to take you not balanced. On the other hand, I studied the healing power of sound and there is a resonance and entrainment that happened with music. If you're excitable, if you're stressed but you also have a history of depression, you don't want to go to something so slow. It puts you to sleep because you like leave the music feeling not well. You have to go to something in the middle. So, go to every genre, just listen to what makes you happy. When my mother gets in the car she's usually like, my husband died, he said he was going to take care of me the rest of his life, I'm like mom, "He did, like you're 94, you're still okay, you're paying a full-time caregiver. You're really blessed." So I can't have that conversation anymore because sometimes I want to go like this, so I put the Frank Sinatra station on in the car and all of a sudden she's singing "more is the greatest love," you know that was our wedding song, it was so beautiful. I'm like, oh my God, thank you. The Frank Sinatra station because sometimes you just go I don't have it. I use music. When I don't have it I use music.

Don't let anything dull your sparkle. We all have that little sparkle in our heart. That thing that makes us very happy. If people are telling you that you're not good enough, you're not loveable, you're not deserving, I don't know, just go look in the bathroom and go, I am good enough, I'm deserving and I'm loveable, I am not dumb, fat and ugly, because that's the other end of that. Or you just look in the mirror and you go, you know I know my hair's not going to be good today because it's bad weather. What does that do to your brain? What does that do to your confidence? What does that do to your day as all day looking in the mirror? I'm going to have done it because I've had curly hair at a time when you were supposed to have straight hair. Live passionately and honor the preciousness of who you are. This happens to be in Lavallette, by the way, New Jersey. You are loved, you're enough, you are beautiful, you are worthy, you are irreplaceable. The story of your life. Think of someone you love and respect. How would you treat yourself if you imagine that person lived inside of you? So, just think of someone like your grandmother or someone you just had perfect memories, like I have that now with my grandson. He's just my, sun and the moon and the stars as soon as he comes in my presence. I actually told my daughter a joke the other day, Joan Borysenko said that, I love this joke because my daughter was trying to like, you know a little bit, and she was like mad at her son, her son and her were having a hard time so I just kind of took them up. We were in Kohl's and I'm trying to buy him clothes and she's giving me an attitude. I take him and I go like this and he loses his shoes and she's like, what is she doing? He starts laughing. He starts walking with me and we're all happy and she still like, for whatever reason, that wasn't my fault, really. It never is, and I said to her, you know what Joan Borysenko said this weekend, because it was Monday and Sunday I had left Joan, she said, "You know why grandchildren and grandparents love each other so much?" "And she said why," and he's really smart and insightful, she's living her first lifetime, I go, "Because they have a common enemy." (Laughing) Well either it was going to go well or not so well because I didn't say it, Joan said it. It was alright. So he laughed. He went like this (laughing) and everything changed. We went for yogurt, we had a good time, she didn't want to be the enemy.

So, sometimes you just have to realize that you are worthy and you are loveable and I'm going to say this over and over again, deserving and you are your creative self, you are a creation here to learn lessons and give love to others and follow your purpose whatever that is.

So this is actually Atrapalo last weekend and someone was meditating and I did ask if I could take a picture of her. She's not identifiable. Relaxation comes with regular mindful breathing. It's not hard. Every time you think that it's just not working, connect with your breath. Start to breathe for three minutes mindfully, breathing in through your nose all the way down, really feeling the air without modulating, don't work too hard and then exhaling. Do that for three minutes, everything will change in your brain and you'll be like, oh wow, and if you start, I tell nurses all the time because I'm working with nurses and physicians who still in the clinical world and it's exhausting to work in a hospital now. It just is. It's exhausting to work in healthcare. Healthcare workers are definitely giving more than they're receiving unless it's a vocation for them, like Dr. Baer and Dr. Goldberg, taking this time to be with you here today, but people who are in healthcare for other reasons definitely don't find that joy so I just say if you start having a headache, drink water you're probably dehydrated. You probably didn't go to the bathroom for six hours. I was an ER nurse, I knew. Listen if the more blood I had, I was in a trauma area, the more blood I had on my body and on my scrubs and the more I didn't eat and didn't go to the bathroom, the better ER nurse I was. Do you remember those days where you just, there was no taking care of yourself, if you said I have to go to the bathroom or I can't come to work because my kid is sick, they'd be looking at you like, oh no, this is your priority and that's the way I lived most of my clinical days. Now, I say different to people who are devoted to other people to taking care of them. You have to take care of yourself first. If you don't take care of yourself first, you can not take care of anybody else. You just can't. You'll be resentful at the end of the day. Relaxation comes with regular mindful breathing.

So Dr. Andrew Weil has a four-seven-eight relaxation breath. If you do this four times a day and once in the morning and once at night, it doesn't matter how fast you do it or how slow you do it, just not more than four breaths and not more than twice a day. Those are the only rules. So I want you to just sit back, scan from the top of your head to the tips of your toes for any areas that are not relaxed. Shoulders usually, jaws and hips hold tension and just slowly and quietly breathe in through your nose for the count of four and I'll count for you, then you're going to hold it for the count of seven and breath out for the count of eight. I don't want you to work too hard. You may feel even a little lightheaded at the end, but it's going to change things inside and if you do this every single day for a month, you're going to feel a difference. You'll feel a difference in your energy and your ability to balance and your ability to think.

So breath, two, three, four – hold, two, three, four, five, six, seven – exhale, two, three, four, five, six, seven, eight. I'm only going to do one cycle. You'll get this PowerPoint. It helps with sleep, relaxation, reduces anxiety, cravings – if you come home and you're ravenous, sit quietly and do this. It takes just a couple of minutes, four breaths, and then you don't go to the refrigerator first.

That's my rule. Sometimes I break it, because you're like oh please, feed me, I'm so tired. Well what's going to happen is going to make the wrong choices. You're going to eat foods that don't help you and you're not even going to realize you ate the food. It causes positive physiologic and psychological changes and all of what I'm saying, I didn't give you the science because I knew you were going to get a plethora of science, but everything I'm saying is based in science and I have a paper somewhere that can support it, but I don't think you needed that, but if you do just go online.

Make small changes. Tiny baby steps towards your goal. You can't eat the whole elephant. I remember when I started quality and it was so many years ago when the Institute for Healthcare Improvement wasn't even alive yet and John Berwick who is the found of the Institute for Healthcare Improvement did a seminar in Boston and it was a week-long seminar and I was really still a baby. I still was in clinical and I was like, oh you have to evaluate care to see if it works? I didn't even think of that. I was just trained to assess, evaluate the patient, but not overall does this work for a bunch of people. I remember going back to work going oh we have to do this and we have to do this and we have to do that and my vice president, who was a yogi at the time, I think she kind of turned me on to all of this when I was my 20s because she was always looked so balanced and beautiful and energetic, and she said, "You can't eat the whole elephant." I go, "I can eat the refrigerator though." You can't eat the whole elephant. One little bit at a time and then you'll get there.

This picture, all the other pictures are mine and you can use them freely. This one is not mine. Accentuating the negative and the power of whining, awfulizing, obsessive worry. So you wake up in the morning, everything's awful, like you really feel it, like it's so awful. I feel awful, my joints hurt, my head hurts, I don't know how I'm going to do this, how am I going to do Thanksgiving, I don't want to do Thanksgiving anymore, why are my kids not doing Thanksgiving, I was supposed to pass the baton, and this one's living in Asbury and that one's like I'm too tired because I'm a teacher and I have one child. Well, I had three children and I worked in the ER, so you get up and everything's awful. Just do it. Do that, say that. Look in the mirror until you start laughing at yourself because that will also come in and you know you always had, you get bored and then you have to go do something else and why do you have to keep on going to school and why couldn't just be happy making meatballs on Sunday like your father told you you should, and you shouldn't have read all those books because now your thinking has changed. All those things that have been put in your mind and in your heart and in your soul from your past will affect you if you're not conscious of them and if you repress them, they just get bigger and bigger and bigger. Almost like a cartoon, you know when there's negative energy it gets bigger and bigger and bigger, and then until Batman or Wonder Woman comes and stamps it out, things don't change. Well be that for yourself, but look in the mirror and don't try to repress the feelings or the thoughts. Just let them out. Say I'm awfulizing today. Everything's awful about everything. Look there's weeds in the garden, you said if we bought this house you were going to pick the weeds and I never would have to, now I'm trying to set the

table and I'm looking at the weeds. This stuff goes on in our heads and it can drive us crazy, but you know what it does, it takes us away from a peaceful heart. It takes us away from being kind to each other. It takes us into a place where nothing matters except for the thing that's awful. Right? So just go right with the awful. Laugh at yourself in the mirror and get on with it. Be kind and gentle.

When you open your heart your peaceful self will shine and your body and mind will relax. Compassion will help you find balance and inner peace. When you're empathetic to another person you will find compassion to help them. So my mother is a pain at times, but you know what, she went to eight different grammar schools, she worked really hard to help my dad buy the house of his dreams, she told me after my son who is affected with Down's Syndrome because I was always an academician, but I didn't know it, and I was like now I can't go to school, she goes why not, you're not mentally challenged. I swear to God I didn't think about that. I thought I have a son whose needs me and she said to me it's the best thing you could do to go to school, because it's going to be a good distraction and it's going to help you be a better mother to your son and really what it's done for him is he's a lifelong learner. I told him we'll take him to Italy next year if he learns Italian, so what is he doing? Oh yeah, he's learning Italian. He texts me in Italian. They tell me he has an IQ of 56. There is no way. He could speak a very basic Italian language fluently. I just always gave him a goal. You want to, now we're on the point system because I need some help at home. I'm like, "Hey, if you bring in the garbage and do this and that, you get a point for everything you do." He's like, "Really." So the first week it was \$7. I go, "How much do you want to make next week?" He goes, "I don't know, \$13." I go, "Really? How about \$15?" So, this week it was \$15 and really I don't care if I pay him \$50 a week because my house was cleaned, the bathroom, I couldn't believe it! He shaved, he did everything, he put the stuff on his feet, he did his wash, he's 34, so he's kind of like 17 in some ways and 94 in others.

Meditate, who me? Oh my God, you don't have take a transcendental meditation course to meditate. You really don't. Just wash the dishes. I'm washing the dishes now. That's all you have to do is be perfectly present with your inner world and really attentive of your thoughts and then letting those thoughts go when they start to, it's kind of like there's a really good meditation where think of yourself as a wheel, a bicycle wheel, and the hub is where your peaceful heart and your intelligence, your amazing genius mind lives and on the outside where the tire would be is all that other stuff. I got to go shopping, how am I going to get that paper done by Monday, all the stuff that takes you away from getting the job done. So when you're meditating just think of this wheel and then those thoughts are the spokes of the wheel going to the outside. So every time a spoke, you're in the line of the spoke, you go alright, let me right back to the hub and you go back to your breath. I am peaceful. I am calm. If you put positive affirmations in your head within three minutes you'll produce enough neurotransmitters to change what's happening in your body and your mind and your spirit.

Healing is a process and not an event. It doesn't happen and it feels like something. It may feel like bliss. It may feel like blisters. Just know that on the other end of healing is peace and joy. Eat chocolate and buy shoes. I have a piece of chocolate, dark chocolate every day, usually 70percent cacao, but if I can't find it, I don't care what kind of chocolate it is. It could even be Nestlé's. Make sure it has an almond in it. Just one little piece. Not the whole bar, not the whole shoe. And shoes. I love shoes because they always fit. I don't have to worry about weight I am, so I almost thought and I was telling Tracy I have like, I was just kind of feeling like a little guilty about my shoe buying and felt like a hoarder because I actually at one point had a beautiful credenza filled with my amazing shoes. I thought this is really sick. So, I decided that for every pair of shoes I bring in, I'm going to give two away, a pair of shoes. So, somebody will come to my house and I know maybe they're a little less fortunate financially than I am at this point and I'll be like, you know I have this great pair of shoes and usually they're in a box and I probably wore them once, but I have to give away one if I brought another one in, and they go, "Wow really? You're going to give me these shoes. I go yeah, I did wear them once, so it's not really a gift, it's not even regifting."

**Q102:** What size are you?

**Donna Cetroni:** Nine (laughing)

Take care of yourself and have gratitude for those that you love and make yourself one of those people. Love yourself. It's really hard to be healthy and come back to a place of gratitude and trust and joy if you're so critical of yourself and critical of your life, and you know what, forgive those people in your life that have given you a hard time. Nobody has had perfect parents and I certainly am not one. No one has had perfect parents. We're not perfect. We're imperfectly perfect. Just be that. My clients someone will say, "I want to be just like you." I go, "Don't be just like me, it's too hard, it really is. If you're trying to be like me, it's hard for me to be like me. I can't imagine you trying to be like, be like you! Be whoever it is you are." That's all I do is be like who it is that I am. Knowing my gifts, knowing my weaknesses, and accepting that I am not perfect and I'm going to say things that aren't perfect and I may hurt somebody's feelings without intention, but just do me a favor, instead of talking about me in the cafeteria, just say to me, you know what you said at that meeting today was quite offensive because my intention is never to be offensive. So, if I have a chance to say, I didn't really mean it that way, then our relationship is built on trust and we can be more productive at work and at our home.

Alright, so, do we have time or am I like way over? Any questions? I know this has been a long four hours for you, probably time to go outside and get some sunshine.

**Q103:** I have a question.

**Donna Cetroni:** Sure.

**Q103:** I heard you say you studied health and music or sound, are you aware of the 432 MHz and all of that stuff?

**Donna Cetroni:** Yes.

**Q103:** I discovered all of that this past summer.

**Donna Cetroni:** You did? That's wonderful.

**Q103:** I'm a geologist, so it was funny when you started saying geology.

**Donna Cetroni:** Well you know we are organisms that are vibrating. We happen to be human but we will respond, ourselves will respond and entrain to sound just like we have proven over time. So Steven Halpern is a wonderful, look him up Steven Halpern, look up Steven Halpern. I love Jonathan Goldman (inaudible 3:11:06) it could block some of the responses. There's this whole system in your liver that can be affected.

**Q103:** The other thing I was going to bring up because you brought up physics, I don't know if you've ever seen what the bleep do you know, because that's a really awesome way to character the science of what you're talking about. It's a good story.

**Donna Cetroni:** Anyone else?

What the Bleep Do You Know? That's a really good documentary.

**Q103:** Down the Rabbit Hole too.

**Donna Cetroni:** Oh there's a million of them.

(Inaudible – applause)