



University of California – San Diego, January 31, 2015 Part 1 Page 1 of 22

Sandy Kurtin, RN, MS, AOCN, ANP-C
Rafael Bejar, MD, PhD

Dr. Rafael Bejar: Some of the questions you have will be questions that other people have and we're recording this. So if you just stare, I will be running from each other, a few others on YouTube.

So, this is my first (inaudible 0:13) talking about what (inaudible 0:14) are and I always think that (inaudible 0:17). So the (inaudible 0:17) that these aren't one disease. They're really a bunch of different diseases. So I mentioned that this is a plural term that there's more than one Myelodysplastic Syndrome. There's many. They all share some common features and you guys are familiar with many of those, I'm sure. They're low blood counts are predominate feature that gets people diagnosed, but what's actually happening in the marrow is that there's one cell that has grown and grown and grown and essentially taken over. We call that clonal growth of the marrow and in fact the marrow sometimes have too many cells and I'll show you a picture of that and the thing that we are often concerned about is the risk as this disorder progresses to become acute myeloid leukemia or AML. It's actually not that rare of a disorder. It may seem like it because if you're diagnosed and you may not know anybody else who's ever had it, but it's fairly common and it affects up to 45,000 people annually in this country. It's probably highly underdiagnosed because one of the reasons is that it becomes more and more common as people get older and we used to assume low blood counts were just a part of normal aging. Now, we recognize that's not the case. We're making this diagnosis more and more often.

Just to show you how relevant age is. These are different age groups along the bottom and the incidence of MDS is shown in the red bar. It goes up and up and up with each decade and then you can also see the (inaudible 1:41). It seems to be a little bit more prevalent. So, that isn't going to... that's shown in the green bar there compared to the purple. So, very age dependent diagnosis even though it can happen in folks in their teens, 20s and 30s.

So, why do people get MDS? It turns out that a very small minority of MDS patients get it because they have a familial predisposition. It's hereditary. They inherited this risk for MDS at birth. Usually, these folks tend to get MDS very early in life and for the most part it has nothing to do with most people with MDS are given. There's no family risk with MDS for most people and there's about 10 or 15 percent of patients who have had exposure to a prior DNA damaging therapy. Usually, folks who have had a prior cancer and received chemotherapy and we know that can damage the bone marrow and it can lead to MDS in some people. It's, again, not the most common... Most people who get chemotherapy don't get MDS unless people who have MDS didn't have any prior exposures, but we do know there is a link between these things. So by far, the most common is what we call (inaudible 2:46) or it's brand new and that's about 85 percent of folks. We really don't know why most people get MDS. We know that there's a few things that put people at risk, but the risk factors don't seem very large. So, we're beginning to understand a little bit better about how this happens and we know that age is probably the single greatest factor that contributes to this.

So, I want to talk a little bit about what MDS actually is at the cellular level just for a second because I think it explains how our therapies work. So in your bone marrow, right now you have cells whose

job it is to divide and make all the blood cells that are floating around in your circulation. So, this is a stem cell and the stem cells are really unique property. It has the ability to divide and make a perfect copy of itself and this is a good thing because we want our stem cells to be around for our entire lives or it can divide and make a daughter cell and that daughter cell will go on to create all of the blood elements that we need and there's a balance between these two things under normal circumstances. Sometimes you divide and make a perfect copy of yourself if you're a stem cell and sometimes you divide and you make a daughter cell that produces all the blood. If you get that balance wrong then you can have problems. Now, I'll give you an example of that. So in MDS what happens is as these stem cells acquire mutation that changes that balance. Now, the favor dividing and making perfect copies of themselves and they do that at the expense of making daughter cells that can make blood. So, their daughter cells don't work as well as they should. So, what do we see in patients when we look? We see that there are too many cells in the bone marrow and there are too few cells in the blood. The cells that the bone marrow is trying to make are suffering from the effects of this mutation and they're ineffective. They're not really making blood cells the way they should and unfortunately this process evolves over time and in some patients can lead to even more cells in the bone marrow, more primitive cells, what we call blasts. You may have heard that term talking with your doctor. These are leukemia like cells and a small number of them can be normal, but as they grow to be more and more we know that that puts people at increased risk of leukemia and the more of these abnormal cells are the less likely the blood is making... the bone marrow is doing a good job of making blood and like I mentioned in some patients there's a risk of AML. So from my research practice, I'm very interested in how these mutations actually do this, how they drive the disease and can we intervene, but in my clinical practice, I'm actually much more concerned about what these mutations are doing out here in the first where we see people's blood counts because this is what people feel. This is when they feel tired or they have risk of bleeding or they have a risk of infection because the blood counts are low. They're not so concerned about this happening in the bone marrow. So with therapies that are designed to kill these cells on the left and we have therapies that are designed to coax more mature blood cells out of the abnormal bone marrow and I'll talk about those two different kind of therapies when we get to the therapeutic part of it, but some therapies are really aimed at knocking out the disease and other therapies are really aimed at supporting the blood counts.

So, how do we make the diagnosis? For many disorders, this isn't an issue. It's pretty to diagnose things like colon cancer. You get a biopsy and send it to the lab and they can tell you what it is. It turns out to be much more difficult to make a diagnosis in MDS and I don't know how many of you have struggled with knowing you had low blood counts, but taking quite a while before you're actually get to a diagnosis. Pretty common. In fact, many patients that I see on two or three bone marrow biopsies before a diagnosis has actually been made. The problem is that MDS looks like a lot of other things and it overlaps with a lot of other things. So, here's a list of other diseases that look like MDS in some cases and what they might be confused with. On paper it looks pretty straightforward. You need to have low blood counts that were described there and you have a bone marrow biopsy and you need to have evidence of dysplasia. Dysplasia just means abnormal looking cells. You need to have blasts or you could have blasts or you could have abnormal chromosomes. So, it looks like it's pretty straightforward and it turns out there's a lot of things that have nothing to do with MDS that can give this picture. It's a long list of these things here. Vitamin deficiencies, viral infections like hepatitis or HIV, heavy alcohol use, (inaudible 7:00) efficiency, a lot of

medications especially medications that are used to treat autoimmune conditions and things like that, autoimmune conditions themselves. So, we go through a long list of things of what else could this be before we actually get to the diagnosis. They can take quite a while, but ultimately we do have some good (inaudible 7:18) to help us do this. This is what the pathologist sees. So here at UCSD, we have a MDS Center of Excellence and that doesn't mean that we just have one physician that's really good at treating patients with MDS. We have an entire team and that team is comprised of hematopathologists whose job it is to look at these things through the microscope and be sure that we're dealing with what we think we're dealing with. So often when patients come to see me for a second opinion, I'll have them bring their slides or ship their slides to us so our pathologist can give a second opinion. Often that's more valuable than talking to me. He's actually making sure they have what they think they do and on the right there is actually a bone marrow piece and it looks almost entirely purple. In most folks it should be about 50 percent white. That means that there's too many cells. This is an example of what we look at under the microscope.

Once we do a diagnosis, the next thing that I do in the clinic is to try to figure out which one of the many different Myelodysplastic Syndromes does a patient have and we have some guidelines for that because I want to take a look at that, which I won't go through the details of, but it just gives you an idea that some people may have what's called Del 5Q. It's deletion of part of chromosome five. Others might have ring sideroblasts. These are all terms that really weren't designed for patients, but help us distinguish which type of MDS people have that inform us about what is likely to happen with MDS in the future and how it is that we should treat this individual patient and roughly speaking as you go down this list that the disease gets more and more aggressive. There also are some people who don't just have MDS which means low blood counts. They have MDS and a myeloproliferative disorder which means they might have too many of one kind of blood cell. So, I have a few patients, for example, that they're anemic and have really high platelet counts or have very few neutrophils but have a lot of other kind of white cell called a monocyte and you might fall into one of these other categories. So the take home message for this isn't to know what all the categories are. It's to know that there are many and that a lot of what we spend our time doing initially is trying to figure out exactly within best describes an individual and sometimes they don't, so we have these (inaudible 9:21) bins at the bottom that say unclassified. You're undef. We really don't know exactly what bin you fall into.

Any questions about that so far? If you do, feel free to jump in.

So the next thing that I do after I know which bin to put people in and how to think about their disease is to try to figure out what is likely to happen to their disease going forward because one of the major decisions I have is not only how to treat, but whether I should treat at all. There are many people who don't need treatment and the best way to know what to do is to have an understanding of what the disease is likely to do if I were to do nothing. So, we have some great tools that help us do that. The one that most people are familiar with is called the IPSS, the International Prognostic Scoring System. This was published way back in 1997. So, it's approaching 20 years old now and the nice thing about it is its pretty easy to use. It's really straightforward. There's only three categories – chromosomes, there's leukemia like cells in the bone marrow called blasts and the number of blood lines that are down. A few people just have anemia or who have anemia and low platelet counts and

we can use that information to get a score, put that score on the table and put people under one of these four risk groups – low, Intermediate 1, Intermediate 2 or high and when we look patients who are in this different risk groups have important differences in overall survival and they have important differences in risk of getting acute leukemia and the people who are in the low group almost never get leukemia, less than 20 percent of the time and there are people, of course, in the high risk group have a much higher rate of this. As a clinician, we tend to draw a line right between these two for people who have low or Intermediate 1 in a low risk group. We put people at Intermediate 2 and high in a higher risk group and I'll go back when I get to that point we'll talk a little bit more about why this distinction matters. Now, you may have heard that the IPSS as I was saying almost 20 years old, has recently been revised. So, we have a new version of it called the IPSS-R for revised and it gets a little bit more complicated, but it does a better job of helping us predict prognosis. So, I really switched to using this, but it may be a little bit less accessible to patients. It still looks at the same categories, but it does it with greater detail. Now instead of just saying you get a point if you have anemia, you don't get a point if you don't. Degree of anemia matters. Severe anemia gets more points than mild anemia. The same is true for platelet count and instead of being in the four groups, it puts patients into five. So, your physician, your doctor, may have done something like this with you when you were originally diagnosed and we actually will do this sometimes continually. Again, it's really helpful because it helps understand what would happen if we didn't treat patients. So, one of the things that I often get questioned is, "You know, I'm in the high risk group. I really don't like that number that's associated with that high risk group, that survival number," and I have to remind folks that that survival number refers to patients who were never treated. So that's important because we have treatment options for patients and that survival number may not apply to you. So, don't get discouraged when you see that. It really just is a tool to help know what would happen if we did not treat.

Any questions about that?

You can look this up online at ipss-r.com or go to the MDS Foundation website. They have a link to this (inaudible 12:58). You can plug in your own values or ask your doctor to do that and you can see where you fall. It's even adjusted for age. This tool is really designed for folks who are 70 years old. You get a few more points if you're older, you get a few less points if you're younger.

I spent a lot of time on that because this is actually one of the fundamental things that drives our decisions to treat and how to treat. We do what's called risk adaptive therapy. You've heard a lot about the personalizing therapy. Well, need a personalizing therapy for a long time. You really try to tailor it to the person who's sitting in front of us by going through all those exercises that I just mentioned and we have a lot of options for MDS. Here is a partial list of some of the things we have to think about. The top is observation. At the bottom is stem cell transplantation or I guess really at the bottom is clinical trials, which I think are always the best option. There's a lot of stuff in between that we have to pick from and we have to decide which one is appropriate for which patient. So, I'll spend a little bit of time going through what the treatment options for MDS are right now that I consider a standard of care. I will say clinical trials are always the best option because in almost every clinical trial, I would say every clinical trial we get here, for example, if patients are getting a drug or a getting a treatment and they're getting the standard of care plus something else. No one is

ever randomized to something worse than they would have gotten off the trial. So in the worst case scenario, you may be randomized to the standard of care and in the best case scenario you may get something that can help you do better than you would have otherwise. The other thing that I noticed is that folks who are on the clinical trials get a little extra attention because not only do they see me, they see the clinical trial nurse, they see the clinical trial coordinator. They have a lot more opportunities than (inaudible 14:46) really to catch things early if things come up. So it's actually (inaudible 14:50) clinical trials tend to do better than folks not on clinical trials. I think that attention has to do a little bit with that as well.

So, there are guidelines out there. The National Comprehensive Cancer Network is an organization of over 40 cancer centers that sends experts to think about what the best way to treat patients are and not just for MDS but for every type of cancer and I'm on that committee who (inaudible 15:17) one of the institutions that's represented there and we divided MDS really into two major bins – the lower risk patients and the high risk patients and we treat them a fairly different way. You can see that this upper algorithm focuses on observation whereas this lower high risk algorithm really focuses on active treatment and I'll go into some of the details of these in a moment.

So, let's start with the lower risk MDS patients. These are patients who tend to have very few leukemia-like cells in the bone marrow. If they have low blood counts, they tend to be mild. They are often transfusion dependent, but not always and their risk of developing leukemia is lower. So, my goal in treating a patient like this is to improve their quality of life. The first question I ask is do I need to treat them at all? Anything I can offer you is going to have some side effect. There's going to be some risk even if it's small. If you were recently diagnosed with MDS because of some abnormal blood count or something like that you may not even be symptomatic. You may not know it and it may not necessary to do anything about it now. We'll just follow over time being careful to note when things change if they change and consider treatment at that time. So, that's my first decision that I have to make. There's no advantage treating early or aggressively and observation is often the best approach. So another question that I get is are transfusions treatment? So if a person has low risk MDS and they're getting red blood cells, for example, are we treating the disease? My thinking no. That's an example of supportive care and it should be done if necessary, but to me that's something that needs to be treated. That means that treatment should be considered for that person because getting a blood transfusion, I think, does impact quality of life because you have to come to the clinic, you have to get your blood drawn on a regular basis and there are risks to blood transfusions even if they're relatively small. So if a patient of mine requires transfusions then I will look for ways to reverse that transfusion dependence. I'll look for ways to boost their blood counts, so they no longer need transfusions. So, my first consideration is does a patient have... it follows the guideline here we say do they have clinically significant low blood counts, consider supportive care and if they're symptomatic then I'll consider treatment and we'll talk about some of the different options and how I go through that list.

So if treatment is needed, where do I go to first? I look for my most effective therapy. Right now, our most effective therapy for MDS, unfortunately, only works in a small minority of patients. So this Lenalidomide or Revlimid and you guys may have heard of this drug. It works extremely well in patients who have a particular chromosomal abnormality. It's deletion of chromosome 5Q. About 80

percent of patients who have this will respond and often their responses are very dramatic. They'll go from having hemoglobins that are about 50 percent a normal range to having hemoglobins that are normal. That's a huge difference and the response duration can be very long. In patients who have been taking for four or five years before they even need to consider taking anything else. So, this is (inaudible 18:34) and we recently learned that this medication does work in patients who do not have Del 5Q but it's much less effective. Instead of working in 80 percent of patients, it works in about 20 percent of patients and instead of having treatment responses that last a couple of years, treatment responses last anywhere of eight to 12 months, but it's still an option and I think it's going to be increasingly an option for patients who are good candidates.

Q1: What is the longest patient that's been on Revlimid?

Dr. Rafael Bejar: What's the absolute record longest that a patient's been on Revlimid?

Q1: (inaudible 19:11).

Dr. Rafael Bejar: The drug was approved in 2005. So, there are some patients that have been on it essentially since then who have been on trials. They're a very small number. Most patients, about 50 percent of the patients, will need to try another option within about two years.

Q1: (inaudible 19:27) not working anymore and what are the side effects?

Dr. Rafael Bejar: Well typically, because their response that isn't sustained longer than that. The disease will come back. This is not a cure unfortunately. There are some people who have difficulty with Lenalidomide. Not everybody tolerates, so there are a lot of side effects that can happen, but for the most part I'd say that most patients that I give this drug to we can find a dose that works for them.

So, if Lenalidomide is not the best option for a patient, they don't have that Del 5Q, for example, then I go for my second best option? My second best option are red blood cell growth factors. These are sometimes called EPO or ESAs or Procrit or Aranesp, they have different names. They're erythropoiesis stimulating agent, the ESAs, Aranesp, Procrit (inaudible 20:16). Lance Armstrong juice, this is what we use to the top of the Alps seven years in a row faster than anybody. They won't make you a better bike rider. I tried this.

So let me talk about how they work. So I mentioned before that the stem cells can divide and give rise to daughter cells. They become all of the mature elements that we see in our blood. Well, there are (inaudible 20:41) that help to do that and EPO is one of those things that your body normally makes EPO. Now for whatever reason in MDS, that EPO signal isn't heard by the bone marrow as loudly as it should be. Many patients have low EPO levels, lower than we would predict when they're diagnosed. So if we give more EPO, we can sometimes squeeze out a few extra red blood cells from that abnormal bone marrow and by doing that avoid have the need for having transfusions. So, one of the tools that we use is a little predictor and if your serum EPO level is less than 100 you get two points; if it's less than 500, you get one point. If it's over 500 meaning if your body is already making a ton EPO, it's very unlikely that my giving you more is going to be helpful. So, you

lose points for having high EPO levels. You also get some points for how many blood units you need. If you start really low, it's less likely they're going to be able to get you above the threshold needed to stop the transfusions. Using these tools, you can usually figure out how likely people are to respond. If you have a very low EPO level and you only need a couple units every once in a while then you can have a very high likelihood of response, 74 percent greater. If you have negative features and you're unlikely to respond then this is not a best option for you.

Q2: If you've had a high EPO level, would there be a reason for it to suddenly drop off that you would need this kind of treatment?

Dr. Rafael Bejar: Yeah. That's a good question. So, EPO is made by the kidneys. So if a person has kidney damage, their EPO level may be lower than it should be. So even a person had very high EPO levels in the beginning of their diagnosis, if their kidneys have for whatever reason declined over time, their EPO level could drop. So, it's something to consider rechecking if that has happened, but usually for most cases, if it's high at the beginning it's probably going to be high for quite some time. Also, I want to point out that there's other growth factors, the ESAs are red blood cell growth factors. There's also white blood cell growth factors at the bottom of GCSF and sometimes we combine the two. It turns out that they're synergistic that if a person didn't respond to an ESA by itself that sometimes they will respond if you've had a white blood cell growth factor as well. We typically don't use the white blood cell growth factors by themselves unless a person is at risk of infection or has an infection and then the newest drugs which I'll talk in greater detail are these middle ones, they're TPO analogs. These help generate platelets and these have been very helpful in patients who have extremely low platelet counts.

So if growth factors aren't a good idea or a good option for my particular patient, what's the next thing I can consider? Well, it turns out that in some people suppressing the immune system actually makes the blood counts better. It seems a little bit weird. Right? Nowhere did I mention anywhere about the immune system being involved in MDS, but it turns out that the immune system is a big player in MDS. The immune system normally goes around and looks for abnormal cells and takes them out. That's one of the things that protects us from getting cancers and other diseases and in MDS we think might be happening is the abnormal cells are stimulating the immune system and the immune system is coming in the bone marrow and kind of wrecking it for everybody. So, it's knocking out the normal cells as well and making it more difficult for blood cells to develop. So if we suppress the immune system, we don't really change the disease in any significant way. We don't hurt it, we don't make it better, we don't make it worse, but we do make it easier for the bone marrow to produce blood cells. That's if the immune system is really playing a big role in the lower blood counts. So if we have some MDS patients that instead of having too many bone marrow cells, have too few suggesting that the immune system is messing things up in there. There are a few other features that we look at and if a patient has some of these features they may be good candidates for immune suppression, again, not the majority but increases the number of people who have this option.

So keeping on the track of the lower risk MDS patient I want to talk about iron for a moment. So, there's a (inaudible 24:40) there. That is about the amount of iron that we all have in our bodies

normally. Most of it, about half, in our red blood cells. That's about three or four grams of iron and every time... every day that you eat something you ingest a very minuscule amount of iron. It's very tightly regulated and under normal circumstances your daily losses are about the same. Really tiny, tiny amounts. If you were to eat a whole bunch more iron, it would just pass through your system. It wouldn't be absorbed. It's really well regulated, but when you get three units of blood, that iron that's in that blood goes directly into your blood system and gets incorporated. So, it's like adding a nail to this pile. Every three units of blood increases the iron stores in a person's body significantly and over time you can imagine that pile of nails is rather big and it can cause problems and now fortunately it takes a while for that to happen. So, I'm talking on the order of 20, 30, 40, 50 transfusions before people will actually get too much iron, but too much iron can be a problem. It can affect how the bone marrow works. It can affect other organs like the liver and heart and many patients who have lower risk disease who are going to live a long time with their disease may get into trouble if they need to have many, many, many transfusions over their lifetime. So, we've looked at ways to get rid of that iron. These are ways to chelate iron and there's a few different solutions. The one that's been around the longest is at the top, Desferal, is a subcutaneous pump that injects a little chelater under the skin. The second one is one of the newer agents. It's an oral suspension. It's (inaudible 26:19) dissolve in orange juice and drink and this allows you to essentially pee out the iron. All these treatments, unfortunately, do have some side effects and need to be done for a long time before they have any beneficial effect. So, most people who get a benefit from these drugs they've been on it for six months or 12 months and about half of my patients don't tolerate them for that long. A lot of GI upset, diarrhea or constipation and in some cases kidney trouble or liver trouble as well. So, these are an option, but again not for everybody.

So again, just to run through my guidelines. Do I need to treat? Does Lenalidomide work? Can an EPO like drug work? How about immunosuppressive therapy? Do I need to think about iron in this particular patient? In other words, are they getting a lot of transfusions or likely to get a lot of transfusions and there's a couple of other considerations at the bottom which is always consider a clinical trial.

So, what novel treatments are there? That's the standard of care. So, what new things are on the horizon? One of the things that we have in a clinical trial here at UCSD is oral Azacitidine. This is a drug we typically use in higher risk patients and I'll talk more about it later, but it's been formulated into a pill that patients can take and it's been aimed at patients with low risk disease who do require transfusions. Now, the advantage is, obviously, it's more convenient. It works just as well as far as we can tell and that's why we did the clinical trial, but it may have a few extra side effects. The one thing we're hoping is that since this is a pill and it's easier to take that patients can take it longer that actually may be more effective. That's what we pull (inaudible 27:52) into this medication. So right now, low risk patients who are transfusion dependent, oral Azacitidine is a clinical trial that might be right for them. I mentioned before platelet growth factors. So, these are FDA approved, but not for MDS. So, they're being studied still in MDS. However, the studies, I think, are pretty mature in the lower risk patients. These work extremely well even in patients with platelet counts of less than 10 these drugs can boost the platelet count to put people on a much safer range and avoid the need for a transfusion in a good number. So, this is something that since these drugs are already FDA approved that I've actually started to incorporate in my practice for that lower risk patient who has extremely

low platelet counts. Sometimes it's for patients who also may have an ITT like or idiopathic thrombocytopenia type picture. In higher risk patients, we're concerned that these growth factors that stimulate the bone marrow may be stimulating the wrong cells. They may be stimulating the leukemia-like cells. So, we still avoid the use of this drug in high risk patients.

This is something that's an earlier phase clinical trial, but it's so cool that I just needed to mention it. So, bone marrow, again, it's tightly regulated. Right? So, there are growth factors that tell the bone marrow to make blood cells and there are growth factors tell it to put on the brakes. Well unfortunately in MDS, the brakes are on way too hard and this is one of the brakes. There's a little protein floating around called TGF-beta or a whole family of them. They Bind a receptor and they put the brakes on. So, we want to release those brakes. So with these very (inaudible 29:24) folks that Acceleron did is they took the receptor that normally binds that little protein floating around, that signal and they chopped off the top. They took an antibody that normally floats around your bloodstream and they chopped off the bottom then they glued the top of the receptor and the bottom of the antibody together. So now, you have this little protein on the right that floats around the blood stream and it eats up these factors. It binds them and prevents them from actually working on the real receptor. So, this is what ends up happening is that this combination product floats around and grabs these guys and the brakes are off. So now, the bone marrow can make blood. This was initially not designed for MDS. This was designed to help another process, I think, osteoporosis where the same brakes prevent the formation of bone. Well, they gave it to folks and they saw that their normal hemoglobin levels suddenly went up by 25 or 30 percent. It's alarming. Some people even had symptoms from this. So well, can't use it in osteoporosis. Why don't we try it with people who start with a low blood count? Maybe we can get them to normal and that's what we're doing now. We're putting these in a clinical trial to see if we can do that and the early data is very encouraging. So, the drugs are ACE-536 and ACE-011 and I'm going to wait till they have a brand name because the generic names are hard to pronounce. It's Luspatercept and Sotatercept.

Any questions about low risk MDS?

Q3: What is 5Q deletion?

Dr. Rafael Bejar: So, we have 46 chromosomes. Most of them are in pairs. So, 23 unique chromosomes. Chromosome 5 has a top arm and a bottom and a bottom arm and if you lose part of the Q arm which is the bottom arm then you're known to have deletion 5Q or Del 5Q. It's a very specific chromosomal loss where not the whole chromosome is gone, just the 5Q... Just the Q piece is missing.

Q4: Do you can never get them replaced.

Dr. Rafael Bejar: That's right. So in the cell, it has lost 5Q it never gets it back, but you have other stem cells floating around. So, what we hope we can do is get rid of the 5Q cells and let the normal stem cells repopulate.

Q5: How's that coming along?



University of California – San Diego, January 31, 2015 Part 1 Page 10 of 22

Dr. Rafael Bejar: Well, we got some workarounds and the stem cell transplant is essentially that is because we hope to get rid of the 5Q cells or whatever they happen to be, put in new cells to replace them and doing that in a patient without a transplant has not yet been successful both... I went to a symposium yesterday in our division which entered (inaudible 31:59) and it was just opening here. The whole idea there is to apply stem cell therapies and new ways and novel ways and it was amazing to see what things are on the horizon. The work is being done both here and nationally is incredible.

So, let's talk about high risk MDS.

Q6: I had a question. It seems to me (inaudible 32:22) are a hot place for a cost saving. How much does physician (inaudible 32:32) to choose a patient the indication for (inaudible 32:36)

Dr. Rafael Bejar: So, you're saying that many institutions are pressed for cost savings.

Q6: Healthcare institutions.

Dr. Rafael Bejar: Healthcare institutions.

Q6: (inaudible 32:42)

Dr. Rafael Bejar: Yeah.

Q6: Would that affect the physician (inaudible 32:50) or the expensive medication?

Dr. Rafael Bejar: That's a good question. So, how does cost affect physician decisions about treatment? So right now, we live in a very (inaudible 32:58) time. We actually get paid more for doing more. So sometimes we as physicians let's say here at UCSD, we may treat people when they don't need treatment because that's the incentive. We get paid if we do that. We don't get paid if all we say come back in six months. So, I don't see that people are neglecting care under the current system. Many people we're treating, but you're absolutely right. Many of the therapies that I'm talking about are extremely expensive and they're getting more and more expensive in many cases. So, we are cognizant of that particularly when patients have to bear part of the burden. We want to make sure that patients can afford the therapy that you write for them.

Any more...?

Q7: When you speak, can you speak into the microphone?

Dr. Rafael Bejar: Yeah. You may have to push the button. I'll repeat your question if you didn't.

Q7: So everyone can hear. If you have a question.

Dr. Rafael Bejar: Okay. So, let's talk about higher risk MDS. So, these are folks that tend to have more of those leukemia-like cells, those blasts in bone marrow, that you may have more severe anemia or more severe low blood counts of other types and they may have more chromosomal abnormalities. So not just Del 5Q, they may have 1, 2, 3 sometimes 10 abnormal chromosomes when you look at their bone marrow.

So, what treatments do we use for them? The, I think, standard of treatment now is the hypomethylating agent. That's one of these two drugs, either Azacitidine also known as Vidaza or Decitabine also known as Dacogen. These are really the go-to drugs for this condition. They both have been extensively studied in clinical trials. They've been around for over 10... about 10 years and particularly with Azacitidine on the left we've shown that it actually prolongs life and when I'm treating patients with high risk disease, that's my goal. They have a disease that is life threatening whereas lower risk MDS may or may not be. I want to prolong life. So, I want to use a drug that will extend life and Vidaza or Azacitidine has been shown to do that in a clinical trial there's a separation there. I would like to see something better because only about 50 percent of patients respond to Azacitidine. It doesn't work for everybody, but it is the go-to option. Now, Decitabine has been shown to work in patients with MDS, but it hasn't shown the same survival benefit. I don't know if that's simply because of the way the studies were done or if we need more data, but for now I'm given the data that we have most of physicians will reach for Azacitidine first. If they decide to use Decitabine they have a very good reason to do that. It's not an inferior product as far as I know and I will treat some patients with Decitabine for... if I think that's the better growth for them.

So, this is a description of what happened in a clinical trial. The overall survival benefit was about 10 months. So, these are folks that had a predictive life expectancy of about a year and a half and people who got the drug versus the best supported care lived about 10 months longer. So, their survival was extended significantly and the response rate was about 45 percent and that's not great. That means more than half the patients did not benefit from this drug. So, we're still look at the better alternatives than Azacitidine, but for right now it is the standard of care in high risk patients.

The other thing to know about Azacitidine is that it doesn't work right away. Azacitidine is given at least the way we give it here is we give it seven days in a row. You come to the clinic, you go to the fusion center, you get an IV infusion on day one, we'll repeat the process in day two, three, four, five, six, seven and then you get 21 days off and then we repeat that whole process again, cycle two, seven days in a row getting the drug, 21 days off. Cycle three, cycle four. It often takes four cycles for patients or six cycles for patients just to see the response and in fact many patients will see their blood counts actually go in the wrong direction initially. So, remember when I showed you that picture of the stem cells that were becoming more and more abnormal and giving rise to daughter cells and were becoming less and less effective. Well, this treatment is really designed to kill those stem cells. It's really designed to knock them out, but the reality is that in most patients MDS those abnormal cells are actually supporting the blood counts for most of the time. So when we knock them down, the blood counts will initially fall. The normal cells (inaudible 37:21) suppress have to grow back before we start to see the blood counts rise and that can take a long time. So, I tell people not to get discouraged. If they didn't need platelet transfusions initially they might after cycle one or cycle two of this treatment, but the hope is that by the time they get to cycle four, five or six that their

University of California – San Diego, January 31, 2015 Part 1 Page 12 of 22

counts are actually getting better and they no longer need transfusions. That's what we're shooting for and about, again, 45 to 50 percent of people will see a benefit from this drug.

The other therapy that we always consider in patients with high risk MDS is a stem cell transplant and this is what we call an allogeneic stem cell transplant or a donor... an unrelated or related donor transplant where a healthy donor has stem cells collected, stem cells are processed, isolated, in some cases, frozen and then the patient receives some sort of chemotherapy and this is really for two reasons. One is to try to kill as much of their abnormal bone marrow disease as possible, but the other reason is really to suppress their immune system so that the new cells that they get are not rejected. Everybody with MDS is considered immunosuppressed to some degree, but it's actually not a very significant immune suppression when we're talking about a transplant. Those donor cells will be rejected if we don't do that treatment up front. We call that conditioning, getting the patient ready for receiving the donor cells and the donor cells will go into the patient and they'll begin to engraft. Now, the real way that we cure patients with MDS using the transplant is not by wiping out their disease before they get the donor cells. It's because the donor cells themselves bring with them their own immune system and that immune system recognizes the disease cells in the patient and kills them. So, that's how we get through (inaudible 39:08) stem cell transplant. Now, the reason we don't use this in everybody is because that an immune system that comes from the donor doesn't just attack the bone marrow cells that are abnormal. It can attack other things in the patient that it shouldn't like the skin or the liver or the gut and cause what we call graft versus host disease and that can be very severe and it can be fatal. So, the morbidity and mortality of stem cells transplant is still higher than we would like and higher than would allow us to treat everybody with this disease with. There are other considerations. Do you have a good match doesn't matter, but in part the biggest consideration you have is age. I think that as folks get older and older they're less and less likely to get through a transplant successfully. So, we've been pushing that age limit quite significantly. I'd say about 15 to 20 years ago we would never transplant anybody over 50. That essentially ruled out 90 percent of people with MDS. We had pushed that bar up substantially down. It's closer to 75. So, we have new ways of doing conditioning that allow patients who are elderly or even usually it's patients who are elderly who don't like me to use that term to describe them. It's patients who may be 75 but look 65. For the most part they have healthy hearts, healthy kidneys, healthy livers and that allows us to get through the transplant successfully despite being older than historically we been able to. Any questions about that?

Q8: What would trigger you to go away from the drug therapy and want to try this option?

Dr. Rafael Bejar: So usually patients with higher risk disease, I'll do the things... and those things in parallel. So, I'll immediately start thinking about transplant for that individual and then consider a drug treatment while we get to... Transplant does take some time. You have to find a donor. You have to go through a long list of things that have to be in order in order to get to go on with the transplant. So, I'll usually look at those two things in parallel. Often it's pretty obvious whether or not a person is not a candidate, but if a person seems like a candidate, we'll push forward.

Q9: Similar to that question what if you have a donor and you're ready to go. Why would you go to a drug treatment? Why wouldn't you just go to stem cell?

Dr. Rafael Bejar: So, that's a good question. For lower risk patients, you will sometimes look at stem cell transplant as an option, but we think that the risks outweigh the benefits that people are likely to live a long time with lower risk disease often dying of something else. So, we typically don't transplant lower risk patients. For higher risk patients who have gotten a really nice response from Azacitidine, we may wait a little bit because for right now they're feeling good. The quality of life always matters, but usually for a higher risk patient if a donor is available, we won't wait too long. We usually will go to transplant for those folks.

Q10: How do they check the stem cells from the patient to see if they're healthy?

Dr. Rafael Bejar: From the donor you're saying?

Q10: How do they check them to see that they're healthy?

Dr. Rafael Bejar: If you're asking about the donor, the person...

Q10: The donor.

Dr. Rafael Bejar: ... the person who donates the cells, they go through a large battery of tests as well. They not only need to be a genetic match, but they need to have no risk of cancer of themselves, no evidence of cancer themselves. They need to have no infectious diseases that might be complicating – hepatitis, HIV, those kinds of things. So, and they're scrutinized and they're also are asked about family history and things like that and one of the things that we concerned of for younger patients who may need a transplant, they may have a sibling ready to donate, but we just have to make absolutely sure that in that individual this isn't a familial case of MDS where the sibling might also be affected. So, we're careful about that. Usually in older patients that's not really a consideration, but we do go through a large battery of tests to make sure that the donor is healthy and a safe donor.

So, just to recap my considerations for higher risk MDS, my goal is to improve duration of life. I don't always... I do this at the expense of quality. Quality of life is still very important and I will have patients who have been on Azacitidine for 12 – 14 months who are getting a response. I've seen a break and they need not to come to the infusion center one week out of every month and that's fine. That's quality of life. We respect that and we work with them. So special considerations. I always prefer for transplant early. So even if a patient doesn't look like they need a transplant at this moment, they should speak to a transplant. They should get a good idea of what that procedure is like and what one might need to go through in order to even to be considered a candidate. I mentioned the two hypomethylating agents. I prefer Azacitidine over Decitabine based on the data that we have. That may change in the future. I don't forget quality of life and I always look for clinical trials. I think Azacitidine while it's a standard of care is not as good as we need it to be. If there's a clinical trial option out there I prefer to put a patient on that.

Q11: So speaking about the clinical trials, how do you normally have for high risk patients going on the same time that you normally find a fit for someone?



University of California – San Diego, January 31, 2015 Part 1 Page 14 of 22

Dr. Rafael Bejar: Yeah. We can find a fit for about half the patients. At UCSD, we have about two or three MDS clinical trials going on at any one time and some of them are for people who have never been treated. Some of them allow people who have been previously treated. So, we have to find one that's a right fit for that individual. Many of these are not for lower risk patients like they've been a distinction between low or high risk. Even though we have two or three trials, not every one is obvious fit for everyone.

So, what are some things that are on the horizon that are coming forward for high risk MDS? We talked about some of those for lower risk MDS. So, one of the things that I was hoping would be near the good news of this meeting would be this drug that was described at our American Society of Hematology meeting in December started (inaudible 45:04) it was the first drug to go through all the way through a phase three trial for patients with MDS who have tried Azacitidine but had it stop working for them or have it never worked for them and we are hoping that this would show a big signal. It showed a very, very tiny signal. In other words the benefit of this drug was very, very small. So, I'm not sure that this actually going to make it all the way to the clinic. The company that made it is trying to find exactly the patient that's most likely to respond. So, we may have some sort of test or genetic study or something that allows us to predict who is the most likely to benefit and maybe in that small population of patients this drug may be a good choice, but right now we're sort of... is a little disappointing unfortunately. There is an oral form of this drug that's being tried in low risk MDS that's a little further in (inaudible 45:52) development, but that may also be another place where you see this drug in the future.

So one of the things... I mentioned that for Azacitidine, people need to come to the clinic seven days in a row to get this drug, but one of the reasons for that is that Azacitidine has an incredibly short half-life. We give it to somebody and within a couple of hours their body has metabolized it. It's gone. So, whenever to make sure that it has an effect to give it over and over and over again. That's why I really like the oral version of the drug because people can take it at home 21 days in a row and their bone marrow actually sees more of the drug over time, but they're trying to address that problem for higher risk MDS. This company took Decitabine which has the same problem and glued it to another molecule Guanfacine and made it a slightly bigger molecule and this molecule works much like Decitabine. In fact, it gets turned into Decitabine inside the cell, but it lasts much longer. It has a much longer half-life. So maybe we can give this drug once every three days instead of every day and maybe once a week. We're not sure. We're still figuring this out but maybe having this drug present for longer will also be more likely to give a good effect. So, this is in trial now in phase two clinical trials and earlier phase trial as I mentioned before and it was tried in a mix of patients who have previously been treated with Decitabine or Azacitidine and it makes the patients who were never treated and the response rates don't look great. They're on the order of 26 to 31 percent, but that's actually really good for MDS especially people who previously seen a drug very similar to this. So, this is very encouraging. I think the first place that we'll use this is in patients who have no longer responded to Azacitidine. We'll try a drug like this that may get a quarter of the patients back into a response.

So, this is an area that is actually very, very exciting. I talked about a new suppressive therapy before for MDS. This is a little bit different. This is actually a new boosting therapy. One of the things that we know is that tumor cells of any kind in order to survive need to invade the immune system. If the immune system picks them up, they're goners. So, the tumor cells are very savvy and have come up with a lot of ways to shut the immune system down and this is one of the ways that they're doing it. T cells are one of the immune cells that we have in our body and they have a receptor that goes out sniffing for anything abnormal, an infection or tumor, and if they detect a tumor cell they're going to try to kill it unless the tumor cell signals 'I'm friendly. Don't kill me.' This is one of the ways that we prevent autoimmunity. So, tumor cells take advantage of the fact that we have a friend flag. This is a receptor called PD-1 and PD-L1 that they stimulate and instead of killing that tumor cell that this T cell recognized and says, 'Oh, this must be a normal cell. I'm going to ignore it.' The tumor cell will actually... the T cell will actually shut down. So it gets a positive signal because it connected to the tumor cell, but it gets a very strong negative signal from the tumor cell saying 'ignore me.' So, we developed antibodies – drugs – that block this interaction. They actually... it was anti PD-1 or anti PDL-1 that actually prevent that friendly signal direction from happening in the first place and now when a T cell recognizes a tumor cell, it knows what to do. It kills it. This drug has now been approved in malignant melanoma. It's being studied in a lot of other solid cancers, lung cancer, breast cancer, prostate cancer, you name it, and it's shown some really amazing things. We're about to try this in MDS. We have the clinical trial that we'll be opening here hopefully in a couple of months where we can use this in patients who may have tried other treatments to see if it's effective on them. We're still working at the safety level. This is a relatively new compound for MDS patients but hopefully we'll get to a point where we can increase the dose and try and see if it works. So, I think really exciting areas totally compared to what we done before.

This is a hedgehog and I show this picture not because I like hedgehogs, I do, but there was a guy studying flies and noticed a mutation and his flies kind of look like hedgehogs. So, he called the mutation, the genus, mutated a hedgehog gene. Well, it turns out that that gene is a really important part of this complicated cascade of molecules that actually drives the survival of stem cells. So, this hedgehog protein is created by one cell. Stem cells use this signal to stay in a stem cell like state. It's also what drives that imbalance when I talked about where the primitive cells stay primitive longer than they should and we show that if we can block that signal that those blast like cells may no longer get that growth signal and they may actually start to die. So, the hedgehog inhibitors are new classes of drugs that were developed in part here at UCSD. One of my colleagues, Catriona Jameson, is in our hematology group has a laboratory where she studies this contents and other (inaudible 50:50) with the HD scientist that has helped developed these contents and we've actually been able to bring them clinical trials here at UCSD and I want to show you, I think I have time, a brief video about one patient that's been on it and she's given us permission to do that. Let's see if this works. Bear with me. I have to switch computers for this. Do you guys have any audio in the back or not yet?

?: I'm not seeing it.

Dr. Rafael Bejar: Let me try again. It's a big file, so it may just take a moment. One more time.



University of California – San Diego, January 31, 2015 Part 1 Page 16 of 22

This is a story about a little patient who was treated with one of the early kind of (inaudible 52:14) with this drug. She happened to be a great responder and they've featured her on the news and I wanted to see if I could show you that minute long interview. I'll try one more time. Okay. It looks like it's not going to work. If I get it to work by the end, I'll let you know. Let me switch back. So, while I'm doing that, anybody have any questions about the treatments that I talked about so far?

Q12: Can I ask something personal? I've got MDS 5Q deletion for four years now and I've gone through the Revlimid. I've gone through Vidaza twice. It worked well the first time. Then I went back on it and it didn't work as well the second time and I'm now transfusion dependent and I'm taking Exjade. What's on the horizon because I've gone through every protocol that they listed? I'll be 74 in June and I just went to the City of Hope and he said that I'm low risk because that under two percent (inaudible 53:43) or less. So even though I had 10 for 10 matches, by the way, which is pretty cool, but that they said that I'm not a candidate for a transplant. So, what are the next steps on the horizon?

Dr. Rafael Bejar: So some of the things that I mentioned earlier in the lower risk segment, I think are good options for people who have been through some of the standard treatments like you described. I'm particularly excited about those ACE compounds, the ACE compounds, the Sotatercept and Luspatercept that essentially you would be a perfect candidate for a clinical trial of one of those agents. I think those are things we think the side effects are small. So, they're not like very aggressive treatments like a stem cell transplant, but we think they can actually improve blood counts even after people have been through those other treatments.

Q12: Are they available up in the LA area?

Dr. Rafael Bejar: They might be. So one of the researchers that I'll talk about is called clinicaltrials.gov. This is a website that anybody can go to. You can put in some key words, so look for clinical trials around the country, but I'd like to do is actually... you can actually limit it by region. So, you can say I live in Southern California. What are the clinical trials that relates to MDS in my area that are open right now and you can get a list of those and I'll show you not only which sites they're available at, but who the contact person is at each of those sites so that you could do your own search. The website is getting friendlier and friendlier over time. I would encourage you to try it. It's like doing a Google search with clinical trials. It's really... or maybe you ought to find something that way.

So, the last couple of minutes I just want to talk about some of the things that we're doing on the research side to help us understand more about MDS. When I started in this field about over 10 years ago now we knew about a few genes that were mutated in MDS, but most patients didn't have these mutations and we didn't really know what they meant, but now the number of genes that are mutated in MDS turn out to be a huge number, well over 40. I haven't been able to put them all on here and some of them are really frequent. Many patients will have mutations of the same gene. We're starting to learn what these mutations mean. So, we're starting to figure out whether they can tell us something about the likelihood of developing leukemia or the likelihood of responding to a therapy. So, that's the type of research that I do here at UCSD is looking at how these mutations effect

outcomes and we studied a large panel of patients, well over 460 in this particular study and the reason that we've been able to do that is because we ask all of our patients if they'd be willing to participate in our research here and all that means is that if they're already going to have a blood drawn or a bone marrow biopsy that they allow us to take a little bit of that sample and take it back to the lab where we remove everything and everything else and we are able to study it and by doing that we've learned a few really impressive things. So, one of the things that we've learned is that there are some genes that predict a worse outcome than we might have otherwise thought of. So even a lower risk patient that has one of these mutations may not be lower risk. So often, we'll check to see if they carry one of these mutations because it could affect my decision to treat. It could affect how I treated. So, that's one of the things we learned early on. About 30 percent of the patients will have a mutation in one of these genes and these mutations do indicate more severe disease. So, you may see your physicians looking more and more into different (inaudible 56:49) genetic testing to try to figure out what your true risk might be. I'll skip this example. I'm just showing you the patients who have mutations don't do quite as well. The other thing we began to learn is that there are certain genes that predict better outcomes of treatment. Patients with a TET2 mutation are more likely to respond to Azacitidine. So if I was on the fence about treating somebody or if I had treated someone for a couple of cycles and they haven't responded yet, but they had one of these favorable mutations, I might be more likely to continue with treatment. The other thing we look at is how about stem cell transplant. You know not everybody does well with stem cell transplant. Are there any mutations that might help us predict that? We have found that a couple of mutations do help with that. So, I'll give you an example of that. This is a survival curve. I don't know if you guys are used to looking at these, but essentially you just go out a certain amount of time and go up and you see how many people in this group are still alive at that time. So for people who have mutations in that top gene, P53, if you go up 12, 24, 36 months, not very many people are left alive if they have that mutation and got a stem cell transplant. The same is true for some of these other genes, but if people had none of these three mutations, their survival rate was 60 percent. Substantially better. Again, not exactly where we'd like it to be, but there's a huge difference between these two groups. So now, we screen patients. Do they have one of these really bad news mutations? If they do, they shouldn't go through the transplant, at least in my opinion. We're still working on how to fine tune that, but this is just an example of something that we were able to learn from genetics. Actually, this is just a figure that shows that it... We used to look at chromosomes and it turns out that if the chromosomes are bad that's a bad news feature, but it really matters whether or not they have a P53 mutation because if they don't then those patients do just as well as everybody else. So, we're actually learning how to make some patients fall into a better than predicted bin as well.

So, I'll end what we do here. Patients come in and we ask them to donate samples to our research studies. We sequence them for genes. We put that information into a repository and we share that information and the samples with other researchers who are interested in learning more about MDS and we're applying a lot of things that we know now in the clinic.

Q13: Is it to our benefit to do a genetic testing (inaudible 59:06)?

Dr. Rafael Bejar: I think people who have very low risk disease, the lowest of the low, it probably won't change what we do for you. People who are more intermediate, it might change what we do

University of California – San Diego, January 31, 2015 Part 1 Page 18 of 22

and people who are high risk and considering transplant it might change what we do. So, there's a certain population of patients where I think that's important. I know that testing should happen for everybody just yet, but there are certain scenarios where I think it's useful and your physician should have a handle on that.

So, I'm going to end. Yup?

Q14: My question is would you talk about hydroxyurea and Gleevec?

Dr. Rafael Bejar: Hydroxyurea.

Q14: Yeah because I'm (inaudible 59:49) whereas Vidaza and hydroxyurea has been working fine for me.

Dr. Rafael Bejar: So hydroxyurea is a drug that we typically don't use in MDS. It's a drug that is normally used in patients who have too many blood cells. So, a disease called polycythemia for example. There are some people with MDS who have a combination of low blood counts and high blood counts. So, some of those folks will get a drug like Hydrea to lower the platelet count, for example. So, we do use that sometimes. The other drug you mentioned was Gleevec. Gleevec is a drug that is used, again, not in MDS, but in a related of chronic myeloid leukemia or chronic myelogenous leukemia and that's one of these drugs that is totally transformed that disease. My understanding is that it's really not effective in MDS. There may something some very...

Q14: (inaudible 1:00:37).

Dr. Rafael Bejar: Yeah. So, very unique scenarios in which that's the case and genetic testing may help identify if someone has a mutation likely to benefit from that drug, but for the most part that's not a drug that I use in MDS.

Q15: Yes, a question about the genetic markers that you were talking about. Is that a standard of care before a stem cell transplant?

Dr. Rafael Bejar: That is not. So, that was published about four months ago. That is really just beginning to be at the cutting edge now. We're planning a very large trial that looked at about 87 patients. We're looking at about 1,000 patients now. So really verify that's real. If that is a real scenario then I think a standard transplant isn't sufficient for those patients. When you do a transplant plus with some other treatment that really focuses on trying to get at that mutation. I think that would be what happens in the next few years, but I think in a few years that will be a standard of care.

Q16: I had a question about after you go through a transplant and let's say (inaudible 1:01:35) and it's successful, (inaudible 1:01:39)

Dr. Rafael Bejar: So people who go through a transplant and make it out, let's say, to a year or... 100 days is a good mark. It's about 50 percent of people who will see the disease come back despite the

transplant. So even if you make it through the transplant stage, relapse is still a possibility. It's about 50 percent of people.

Q16: Well, what happens after that then?

Dr. Rafael Bejar: No, not at all. There still are other treatment options or clinical (inaudible 1:02:09) exactly like that, but we will go back to one of the drugs that we tried before, for example, or we'll try combinations of drugs. There's still many options for people even after relapse.

Q17: Is that genetic testing in a blood test or is that done through a bone marrow biopsy?

Dr. Rafael Bejar: So, it can be done through blood. It turns out that a lot of the cells... most of the cells in the blood are derived from the lateral bone marrow cells. So, it's perfectly fine to do a peripheral blood test.

Q18: (inaudible 1:02:38)?

Dr. Rafael Bejar: What has happened now is that more companies are offering it in a way where they bill insurance and if the insurance decides not to pay because they consider it experimental or whatever, the companies will drop it. So, they haven't been going after patients for reimbursement. So, I've done genetic testing at company labs for dozens of patients and no one has ever gotten billed. So, I think it's something that at least for the... I'm not sure how the company makes money. That's their problem. So in the meantime, I take advantage of that. If a patient I think would benefit from genetic testing, I'll order it knowing that the patient isn't going to be harmed financially by it.

Q19: Is MDS a public health concern?

Dr. Rafael Bejar: Is a public health concern. I don't know exactly what you mean by that, but MDS is a public health concern in my opinion. It's the patient population that I treat, obviously. It's not so common as to be one of the top things on the list of the CDC's priorities, but it is becoming more and more common as our population gets older and I think that the lack of really good treatments for MDS means that it is an area that deserves more focus.

Q20: Do we know the relation of what creates of MDS?

Dr. Rafael Bejar: I mentioned at the beginning that there are some scenarios that we do know why it happens. I think what we're starting to learn now is that as all of us get older the likelihood of having one bone marrow cell dominate the bone marrow gets larger and larger. There's a recent study that's a little bit unnerving that said if you looked at people in their 80s who are fine, no blood problems whatsoever, about 10 or 15 percent of them had some of the same mutations that you identify in MDS patients. They did not have MDS, but they had some of the same mutations and we know that those patients are at slightly higher risk. So, we think that MDS is actually a disease that probably takes years or decades to evolve and only at the later stages does that actually cause problems and that's when we notice it.

Q21: But we still don't know (inaudible 1:04:46).

Dr. Rafael Bejar: We don't know why. I think the answer really does come down to bad luck for most cases and if mutations just happen at the right place then the cells can get an advantage and grow and grow and grow and I think that's true for most other cancers that we see (inaudible 1:04:59) smoking induced or the same thing.

Q22: Have you ever seen the (inaudible 1:05:03) in this film? Have you ever seen anybody that's ever had MDS that (inaudible 1:05:08)?

Dr. Rafael Bejar: So, I have seen people who have been misdiagnosed and I have seen people who were told they had MDS for years and years and years and then one day they're better. I think if they truly have genetic abnormalities there are things we can do to make them better, but I wouldn't see the disease go away on its own.

You had a question.

Q23: I hear Vidaza and Dacogen treatment you say it only extends lifespan by 10 months?

Dr. Rafael Bejar: So, that was the average extension. So, you got to remember that there are half the patients there who didn't respond at all. They got no benefit. So of the people who responded, the people who did benefit, their extension in life would be predicted to be much longer probably closer to two years or something like that and some people more than that, some people less than that, but that was the way the clinical trial was described is everybody who got the drug gets lumped into the same group and that group lived an average of 9 ½ months longer.

Q24: Where are these genetic testing companies?

Dr. Rafael Bejar: So, there's a bunch of them now. For a full disclosure I actually consult for one of them and it's local here in San Diego called Genoptix. I have consulted for others including the one that I use most often is called Foundation Medicine based in Boston. They actually do one test for all blood cancers and they look at hundreds of different gene studies. I think it's the most comprehensive test and that's the one that I was referring to when I was talking balance billing the patient. It's something that's not just available here. Really any physician can order that test.

Q25: I gave a specimen from saliva. Is that also...?

Dr. Rafael Bejar: No. So, saliva specimens will not contain the right kinds of cells to look at. We're looking for mutations that are in the bone marrow or blood. Saliva may be contaminated by a little bit of blood but...

Q25: (inaudible 1:06:55) volunteer.



University of California – San Diego, January 31, 2015 Part 1 Page 21 of 22

Dr. Rafael Bejar: That may be a different type of study. I want to make sure that we move on, so I'll be around to answer other questions. Just wait for acknowledgement of the people in hematology are MDS Center of Excellence team. The folks who actually put together the meeting, (inaudible 1:07:12) in particular who took time out of her day yesterday and started to set it up and the folks in from the A/V group who put it together, our amazing clinics and infusion center nurses and staff who many of you are patients here and know that they really are the caretakers of our patients here. It's not the physicians. It's the nurses and staff and the incredible patients and families who are helping us do more with this disease.

(Applause)

?: Dr. Behar, if you have time and there are more questions (inaudible 1:07:43), it's time for us to continue with that.

Dr. Rafael Bejar: I'm happy to take some more questions. I didn't want to cut your time.

?: That's okay. We'll adjust.

Q26: Excuse me. I had a question about the foundation. How do you use that so my mother-in-law can have that test? What would be the next steps to use it?

Dr. Rafael Bejar: So, that test is incredibly broad. It covers hundreds of genes. That's probably only 15 or 20 that I'm most interested in. So many times, I'll get that test done and we'll find mutations of genes that I think are irrelevant for MDS or at the very least I don't know what to do with that information, but in some patients we'll find mutations in these genes that I think I do understand better and they help us tell us something about the risk. That's the way that I use them most often. If someone's intermediate risk and I'm debating whether or they should be treated and they have one of these bad mutations, I may decide to treat in hopes of really extending their life. So, that's the way that I use it most often. It's really looking for that core set of genes that are important.

Q26: But in terms of maybe a new therapy or something different.

Dr. Rafael Bejar: So occasionally that can happen as well. That's actually the way the Foundation of Medicine test was designed was to look for mutations that totally would be a great candidate for drug.

Q26: (inaudible 1:08:56).

Dr. Rafael Bejar: Exactly. In MDS, it turns out that those sensitizing mutations are just not very common. So if we were to find one then I would be very excited about trying a therapy that's tailored to that mutation. The fact is I have yet to find that after looking at dozens of patients. I haven't found any that are very tightly linked to a particular drug that I didn't already know about.



University of California – San Diego, January 31, 2015 Part 1 Page 22 of 22

Q27: I'm a possible candidate for immunosuppression. Are there any advances or changes in that area?

Dr. Rafael Bejar: The immunosuppression field has been pretty flat for the last few years. The way we do it are pretty standard. The most interesting study we've had recently is they compared are what are one of the immunosuppressive agents called ATG. ATG is an antibody that can come either from a rabbit or horse. Take a rabbit versus horse. So, that doesn't sound very exciting, but that's the most exciting study we have. It turns out that the original ATG was made in one horse. His name was Cesar and people were very concerned when Cesar got old and died because they didn't know if they were going to be able to replicate that immunosuppressive drug. Fortunately, they were able to do it in rabbits and horses and we now have a better understanding that the horse match would be better. It's lower side effects and might be more effective than rabbit even though we thought rabbit was going to win out the horse/rabbit battle. What we have gotten better at when someone is immune suppressed with MDS, they're at risk at getting infections. A lot of the anti-infected drugs have gotten much better. We have better antifungal drugs. We have better antibiotic drugs. So, we are much better at controlling the infections associated with immune suppression.

Okay. Thanks.

(Applause)