

Speakers:

Rafael Bejar, MD, PhD

Peter Curtin, MD

Emily Knight

Rafael Bejar: And again, it doesn't mean that the (inaudible 0:01) drug's not available. Obviously, people can go and buy it if they need to as well. So, I don't fear that anything coming in the ACA is going to prevent me from practicing medicine the way that I would like to. I think that the net affect of the law on people who have Medicare and things like that will be minimal that it really won't affect their choices that much. I think people who don't have insurance will have many more choices than people who opt to participate in the health exchanges and things like that will have... will see some research that impacts the choices many patients... much the same way that your private insurance company now may say that you have to try these generic drugs before you can try these more expensive drugs.

Q1: Yes, how does Revlimid work on the cell and gives it a hemo?

Rafael Bejar: So, you have asked how Revlimid works in the cell and that is a question that befuddled scientists for quite a long time. So as you know, the reason that we even consider this drug in this disease is because its precursor, Thalidomide, seemed to have good efficacy in MDS, but Thalidomide doesn't do just one thing nor does Revlimid. It really does about five or six or seven different things all of which may be important pathos and we don't understand yet at the molecular their level what Revlimid is doing. So, we think it's multifactorial or we think it does affect the cells directly particularly in patents who have chromosome 5 abnormalities, but I think it also changes the environment that these cells live in. It modulates the immune system, so the immune system may now wake up and recognize if there's abnormal cells in its midst. So, it's a multifactorial drug and as we learn more about how it works, I think we're going to be designing better therapies and have fewer side effects.

Q1: Now, why is it also in a warning that more that cancer cells could appear somewhere else because of the drug?

Rafael Bejar: So, in Revlimid there is a black box warning for patients that have multiple myeloma. That's one of the diseases that's treated with Revlimid. They have noticed that they have a higher rate of secondary malignancies, other cancers, and we don't understand why that it is and we don't... as far as I know, see no evidence of that in MDS. So, that it's on there because of an observation that we made in patients who have multiple myeloma. The mechanism with that is not understood.

Q2: I was diagnosed with MDS back in 2005. It kind of morphed into (inaudible 2:35) immune analytic anemia. Is that still considered part of the MDS umbrella disorders or is that a separate (inaudible 2:46)?

Rafael Bejar: He has been saying autoimmune hemolytic anemia considered in MDS. I've seen this a few times and when I've seen it, it isn't because of the MDS. What I've seen and I don't know if this necessarily true in your case that patients who have MDS who need transfusions can

in some cases develop antigens or can develop antibodies, can develop an immune response to the blood transfusions that not only target the blood that they receive, but target their own blood cells. So, I see it as a complication of treatment, not necessarily as part of the disease and it has a variable course. In some patients that I've seen, it has kind of exhausted itself out with a treatment of steroids and in others, it has been more chronic, more difficult to treat, but I don't consider it to be part of the disease itself. I really consider it to be a response to the therapy that we've given, but it's a rare complication.

Q3: I just finished a 10 month course of Vidaza and I was given a choice by the doctor to continue or stop treatment and I asked him what he would do and he said he would stop the treatment. So, my platelet count is now 134, yeah, 134. So, it's normal. In the future, would I just go back on Vidaza to jump it up a little bit if it drops?

Rafael Bejar: I'm going to try to generalize that question a little bit and, Peter, you can jump in. What do we do when Vidaza either no longer works or we stop taking it because of side effects or things like that and that's a difficult question to answer. I don't necessarily know what the answer is. If a person has stopped taking Vidaza because they don't feel well when they're on it or they're tired of having to coming to clinics so often and so on, but they're cancer okay, I would consider re-challenging that patient. That is, again, giving that drug once more should their counts fall. If a person has stopped responding then I consider what this drug might actually be doing for them. If it's not doing much and it's not making them feel well then it may be that the right thing to do is maybe to stop it and try to consider another options. So in some cases, I have restarted Vidaza and in other cases I really try to move on to something else.

Q5: I read an article on the infusion of ozone into the bloodstream that said it that would help individuals that had a blood disorder, but it did not give anything as to any scientific research of any kind. What do you gentlemen know anything about that, the infusion of ozone and does it do (inaudible 5:34)?

Peter Curtin: I guess what I would say... you know, the Internet is a powerful thing for good and I've been around long enough that patients used to come to see me in clinic and not know anything about their disease and nowadays when people come to see me in clinic they know a lot about their disease and I think a lot of that is the Internet that is information is just out there, but I think the Internet also has some really great information and some misinformation and so when someone says they have an immune therapy that is guaranteed to cure cancer and my patients come to me and I know why they come to me with that information because what I'm doing is not curing them and they're looking hard. They're not going to sit back on their butts. They're going to get out there and look. They're looking for other things, but you always have to look and see what's the data, has it been a good clinical trial, has it been published somewhere, a reasonably good medical journal because otherwise a lot of people have ideas about how to cure cancer and that's great, but ultimately you have to put that idea into a clinical trial and show that it actually works before anyone's going to put much stock in it. So, I've heard ozone things. I've heard PH things. I've heard lower your blood sugar things. All kinds of stuff. Sounds very reasonable, but really haven't been shown to make a difference in most cases.

Q6: How contagious is MRSA and have you heard of it leading to MDS patients?

Comment: That's an interesting question.

Peter Curtin: So, the question is how contagious is MRSA, Methicillin-resistant staph aureus and can it lead to MDS and the answer is MRSA is very contagious. So, staff and strep on our skin, they're in our nose, they're... and many of them are very sensitive organisms but there's a lot of MRSA around and I can tell you as someone who has worked in major medical centers all my career, MRSA is everywhere in all of the big hospitals. It's all over the place. So, it is quite contagious and we currently are isolating patients with MRSA. When patients are admitted to Thorington Hospital, we swab their nose and if their culture is positive then they get isolated for that disorder. Now... So and there are resistant bugs of all sorts in major hospitals as you can imagine which was why hospitals are not necessarily the best place to be all the time especially when your immune system is not so great. In terms of bacteria causing MDS, I'm not aware of any data to say that happens. I mean, one question I always get in every MDS consult is somewhere in the middle or the end where did this come from? Why do I have this? And it's true of any cancer, but I get that every time and Dr. Bejar and other molecular biologists and scientists can often study the end stages of the disease, but it's harder to get back at the beginning or more importantly before we can identify it as a disease what was going on back then and so where these things come from is often very hard to sort out or not understood.

Q7: I was struck in your talk by the sort of disconnect between the mutations that you done a very nice job of showing and the treatments that were almost in a separate section which was kind of like throw the kitchen sink of available cancer treatments in a clinical trial and see what sticks. So, Azacitidine is hypomethylation agent. What is known about the or what have you measured about how Azacitidine and the hypomethylations relates to the mutations that you sort of characterized.

Rafael Bejar: That's a great question. There's an active research project going on in my laboratory right now and one of the things they'll say is that we get drugs and we label them with how they work. So, we call Azacitidine and Decitabine hypomethylating agents. If we look at the DNA, we see that the DNA is hypomethylated after treatment, but it doesn't mean that that's all that those drugs do. They may do other things that we don't yet understand and, in fact, we have applied those therapies to patients with MDS before we even knew that enzymes involved in the demethylation process or the methylation process were mutated in this disease. So, what I looked at is to see if there any mutations that predict response to treatment with Vidaza and other drugs and we have found some signals there, but it's not like we can find a mutation that says zero people with this mutation respond in other mutation where we think 100 percent of people with this mutation respond. It really is just changing the balance. So for example in the data that I mentioned briefly, patients with a mutations in TET2, this is an enzyme that is involved in the DNA methylation pathway, they tend to have a higher rate of response to treatment with Vidaza but it's not like they have a 10 times greater likely to respond. It's more like a factor of 2 or 3. So it doesn't necessarily change (inaudible 10:42) the mediations, but it does change my expectations. So for example if I have a patient who as you may know Vidaza it takes several cycles to see if responds. If a patient hasn't responded after the second cycle, that doesn't mean anything. We continue on, but if a patient has a TET2 mutation and I think they're going to do

well and by cycle 4 they haven't responded, I might push onto cycle 5 or 6. It may change the way that I treat patients, not necessarily who I've decided to treat.

Peter Curtin: And the only other thing I would say is that one of... I think Rafael Bejar's slide said something about personalized care. There's no question that here at UCSD in MDS and other cancers, we're working to try and figure out the mutation profile of individual patients and as much as possible begin to tailor the clinical trials they go onto based on what we find out. It sounds like... reasonable, but as you can imagine it's harder to do because you have to find the mutations and then get a drug and that drug has to be ready, but it is happening here and elsewhere and I think there's no doubt that drugs that target mutations in a given person are going to work better than if you take 100 people and just throw that drug at... and so that's the kind of the current wave of drug development that's happening.

Q8: (inaudible 12:01) that I'm very interested in a genetic analysis side and if someone is interesting in having that kind of testing done, what would the next steps be? A lot of physicians aren't onboard with that.

Rafael Bejar: Right. So, this idea of actually doing genetic testing in a clinical context is relatively new. For MDS it's only been available for about 6 or 7 months. So right now, there's only 1 company that does it specifically for MDS. That's the company that I mentioned before, Genetics (sp? 12:29) here in San Diego and that's something that a physician can order a test and send a blood or bone marrow sample to the company to get back. It only looks at those 5 genes. There are other companies that will do additional gene mutations. There's one called Foundation Medicine that will... is really designed for patients with solid tumors, lung cancer, colon cancer, breast cancer and that things. It doesn't really include a lot of the genes that we think about in MDS, but it does have some of them. So, that's another way to get the genetic profile. The question is how do you interpret that information and how do you decide to act on it and that's one of the things that makes me excited to do a trial like the one that I mentioned where we look at 45 genes. So, we have some experience doing that. We'll see what are the patterns that actually come up and the mutations, how do we communicate that to our physicians and one of the things we hope to do with that information is have what we call a molecular tumor board. You may know that when patients are diagnosed with cancer, we get together, review the case as a group and collectively share our knowledge to help decide what the best way to treat them, but we like to do that with mutation profiles as well so that we can really get the benefit of everyone's experience in the room to try to tailor the best area for that individual, personalize it, based on their genetic profile. So right now, there is that 1 test that's available. There will be more coming and hopefully on a research basis we'll have one up and running here at UCSD relatively soon.

Q9: In your clinical trials, you obviously have a protocol. How much interaction do you have you being a clinician and to say the pharmaceutical company in developing the product accept the protocol?

Peter Curtin: I would say... The question is when a pharmaceutical company is developing a protocol for MDS, how do that clinicians and academic clinicians, how are they involved in that and I think most of those protocols the companies will get sort of thought leaders in the field

involved early on to make sure they don't do something that is going to shoot themselves in the foot. In other words, do a trial that clearly is not going to answer the question that needs to be answered. So, I think that typically at the trial design stage especially when you start to get into phase 3 trials which are big and very expensive and are leading to FDA approval, they definitely will gather together around the roundtable, they'll get 12 or 15 people and talk about it and to try and optimize it. So, I will say academic physicians do get involved in the planning of those clinical trials or in the planning of what's the next trial to do. So, you'll see people get give a talk and they say they consulted this company or that company and that's exactly often what they're doing that kind of consulting.

Q9: I don't know if this question is appropriate, but I've been on (inaudible 15:34) for 8 years and now they suggested when I go on Vidaza and it's kind of scary because if I'm doing one thing all these years and now going to chemotherapy. Could you tell me a little bit about that?

Rafael Bejar: About what Vidaza?

Q9: Yeah.

Rafael Bejar: Yeah. Sure. You're asking a question about... you want to learn a little bit more about Vidaza itself and what it's like to be on Vidaza. So right now the way that we give Vidaza typically is through an IV. It's an infusion that doesn't take very long to give. It does involve coming to the clinic, sometimes having blood test done, getting the infusion. It can take a few hours each day and we do that 7 days in a row and we repeat that process every 4 weeks. So, 7 out of every 28 days are spent coming to the clinic to get this IV infusion. Now, you'll probably have folks in the audience here that have experience with it and you should ask them about their personal experience with the drug, but from my perspective what I've seen is that it is not a very difficult drug to tolerate for most patients. It's not like what we consider standard chemotherapy, the types of treatments that we would use for lung cancer or colon cancer and so on. It doesn't cause hair loss. It typically doesn't cause severe nausea and vomiting. It can cause some fatigue, some GI upset. Those are the more typical symptoms and then there are some rarer, more serious side effects that happen in a very small number of people but in general, I would say that it is a very well tolerated drug.

Peter Curtin: The only other thing I would say is that it's some paradoxically after you get that seven days of therapy, often your blood counts will go down, your white counts, your platelet count may go down and sometimes go down very, very low. It sort of depends on what your bone marrow reserve in the white cell line and the platelet line and so even though you don't have chemotherapy like side effects, nausea, vomiting, hair loss, etc., for some patients their blood counts will really go into the basement and when your white count is low, of course, you're at increased risk of infection. So, those are the things can certainly occur. Because of that, because your bone marrow actually gets turned down a bit after Azacitidine, we typically will have you come in for labs twice a week. So, you have one week where you're there everyday and then you have three weeks where you see us twice a week. So, you end up spending a lot of quality time in your... the infusion center or oncologist's office. So, I always tell people when they think about Azacitidine, it's like going on chemotherapy in some ways. It's not... It's different from chemotherapy, but in terms of time commitment, it's a lot.

Q10: I took Vidaza a lot. What is the difference between Azacitidine (inaudible 18:33)?

Rafael Bejar: Your question is what is the difference between Vidaza and or Azacitidine and Decitabine. Chemically, they are very, very similar drugs. They're different at one position and in fact one is the pro drug for the other. It means inside the body, one is turned into the same compound as the other one. Now, they have presumably the same targets, but I think the reason that we mention Vidaza more often is really just based on clinical trial experience. So as you may know, there was a clinical trial looking at outcomes with Azacitidine and in that clinical trial identified that patients, particularly patients who had higher risk disease, lived longer if they were treated with Azacitidine compared to placebo. So, it was the first drug in MDS in this patient population to show a prolongation of survival which is a big milestone. Now, there hasn't been a similar trial with Azacitidine. There have been trials that tried to look at that but didn't quite show that same effect and then you have (inaudible 19:35) Azacitidine is a worse drug. I don't think it necessarily is. It just may be because the trial was... either it didn't include sufficient patients or wasn't designed in a way that would really demonstrate that affect. So, that's still an open question, but Azacitidine has the advantage of being the only drug to be shown in a clinical trial to prolong survival. So, we tend... If you look at the NCC and violence treatment for MDS, they say that Azacitidine is what they call a category 1 recommendation. The top evidence is support its use and Decitabine is 2A which is just beneath that. So, there is a slight difference between those two drugs in terms of preference based on data.

Q11: I was just going to ask, some hospitals can't do 7 day consecutive treatment and so they do a 5-2-2 regiment, so you don't take another weekend. Is there any new data to say that's equivalent or not?

Rafael Bejar: My understanding is that two regiments whether you're given seven days in a row or five and two days off and then two days again, don't show any significant difference.

Q12: This is a specific question, but my doctor said to ask you guys. Is there something between Procrit and Vidaza? Is there some new thing that hasn't been... you're working on that in that step...? It seems to me a step down if you have to go to Vidaza and do you continue the other, Procrit, while you're doing Vidaza or no?

Rafael Bejar: As I mentioned there is one study that looked at the combination of both Procrit or erythropoiesis stimulating agents and Azacitidine together and it's suggested that you could get responses out of patients that didn't respond to one or the other. So, it isn't necessarily that we decide to combine them because we think that that will give to a better response. It's really an option for patients that don't respond to the Procrit shots first. Adding Azacitidine may make a responder out of someone who was a nonresponder. I want to ask how we are on time? I'm going to stick around a little bit later to answer more questions as well.

Emily Knight: I can do the Building Blocks (inaudible 21:42) now and then we can break for lunch and (inaudible 21:45) questions.

Rafael Bejar: So, why don't I do that? We'll stick around. We can go around individually and be available for questions.

(Applause)

(General inaudible chat 21:59 – 31:02)

Emily Knight: I'm just going to get started here to introduce the *Building Blocks of Hope*. Everyone should have gotten a *Building Block of Hope* binder when they came in. I know we did run out. So, I did take names and addresses down. If you didn't get one, they'll be mailing it out to you, but it's our new educational tool that we're pleased to introduce and offer to patients and family. So, the meaning of the *Building Blocks of Hope*. The *Building Blocks of Hope* is a global print and online patient advocacy initiative providing a personalized education program for patients and caregivers to prepare, participate and live with MDS. The colors of the *Building Block of Hope* include Tucson teal, Navajo red and desert sand. They're reminiscent of the Southwest landscape with the beauty of the night sky over the sand swept desert and stunning mountain ranges. The colors represent welcoming, warmth, stability, (inaudible 32:16), passion and protection. These colors form the base for the *Building Blocks of Hope* logo constructed in a wavelike pattern indicating the fluidity of life, health and fitness. The single red band which continues up into the plant symbolizes strength and improvement in bone marrow function. The idea of hope for the future and extension of life is emulated in the sprouting plant. These are all the nurses who are part of the MDS Foundation and helped work on and put together the binders. So, what the *Building Blocks of Hope* does is it answers common questions you or family members may have about MDS. We hope that this is a tool that will help you understand the diagnosis of MDS, how MDS is diagnosed, what your treatment options are, any side effects from treatment and what can be done to control them, what new treatments are on the horizon to treat MDS, consequences of blood transfusions and should you receive iron chelation therapy, how to select a bone marrow transplant center and importantly how to keep yourself healthy. So while you're looking through your binders, you can explore the *Building Blocks of Hope*. You'll be able to understand the disease, know your IPSS and IPSSR risk category, ask questions about your treatment options, the treatment schedule, possible side effects, how you're going to manage those side effects, which treatment, you're going to have to consider different lifestyle changes, transportation, know that you can ask for help. The MDS Foundation is available and has support groups. Hopefully, you have support groups locally. Become a partner in your MDS journey and build your MDS plan. In your binder, there's a tab where you can track your progress. So, I'll kind of... We already talked about a lot of these slides. So, I'll just skim through them on what MDS is and get to the *Building Blocks of Hope*. We already reviewed most of these and then we can break for lunch and then come back and go over any other questions that you have. So, I'm just going to get to the tabs.

So becoming a partner in your care, building your MDS plan. Tab one in the book is understand MDS. It's a complete description of the disease process and answers common questions and you can see that in the binder. Tab two is seeking treatment. The treatment of MDS can vary based on the type of MDS you have and how severe it is. This section will provide details about various approaches to treatment. The tab three, quick tips. The quick tips offered in this section include guidelines for monitoring and managing your symptoms. Tab four is the iron overload

tab. It's a possible outcome of receiving repeated red cell transfusions. This section answers common questions including how iron overload can be treated and then the tab five is My MDS Plan. Understanding the diagnosis of MDS will help you and your caregiver take an active part in your individualized treatment plan. The My MDS Plan provides several tools to allow you to track and manage your journey. So, what might be helpful before you write on the papers is to just make copies so that you can continue to track your progress and then tab six, the MDS Foundation. It's an internationally publicly supported organization dedicated to serving MDS patients, their caregivers and professionals that are working to improve the lives of patients living with MDS, provides a number of resources which support the Building Blocks of Hope program. We have online and live patient and caregiver support, coordination of support of the patient and caregiver forums like this one and then the print and digital global education resources, Coalition of Centers of Excellence, planning and facilitating biannual international scientific meetings and then a lot of supporters to thank that made the *Building Blocks of Hope* possible. Without their support and contributions, we would have this tool. So, we just want to acknowledge them for their help. That's the end of the slideshow and what the *Building Blocks of Hope* is. Does anyone have questions specifically about the *Building Blocks of Hope* and as I mentioned earlier if you didn't get the binder, Audrey has your name and information and we'll be mailing them out to you. If you have friends or other people who are interested, you can go to the MDS Foundation website and request one and it's also online.

Q13: Where's it's in... headquarters?

Emily Knight: New Jersey. Any other questions?

Q14: Is your slide deck available online?

Emily Knight: Both the slide decks from today will be available online and in audio.

Q15: What role does nutrition play in the whole...?

Emily: Nutrition is very important. You need to eat well balanced meals. Nutrition, diet, exercise, all of that is important in staying healthy. We don't specifically promote one diet over another. Just well balanced.

Q16: At some point in the MDS progression of the (inaudible 39:12) do you change your diet to one that's not going to be fresh fruit?

Emily Knight: Some people when they have a low white count, low neutrophils, that your doctor may tell you to avoid fresh fruits and vegetables. Some may tell you if you wash them well, you're okay. Important that you cook your food thoroughly. Maybe don't eat out at restaurants that you're not sure of when your blood counts are low.

Q17: Meaning low blood counts meaning how low? When you're in the...

Emily Knight: Like your neutrophil count less than 1,000.



Q17: Or you absolute grams. How low?

Emily Knight: Yeah. AMC less than 1.

Q17: Less than 1. Okay. That's just watching out for bacteria?

Emily: Correct. Yup. Yes.

Q18: Do you want to mention that there is a local support group if people are interested in attending.

Emily: Absolutely. Yes. Here at this hospital?

Q16: No, it's in Oceanside.

Emily Knight: Oceanside. When does it meet?

Q18: It meets the third Saturday of each month and it's open to anybody with MDS, they can (inaudible 40:28) family, friends.

Emily Knight: So, the third Saturday of every month, there is a support group in Oceanside open to anyone.

Q18: If anyone wants more information, they can see me about it.

Emily Knight: Great. Anybody else have any questions, comments? Well, I think they're probably getting set up for lunch. You can break. We'll have lunch and you can come back and if you think of more questions, we can go over them.

Q19: Is this a safe restaurant?

Emily Knight: Yeah.

Q20: Is there... upfront is a private and government funding (inaudible 41:10).

Emily Knight: For the Foundation. I'll have to ask Audrey. She'll know more about the funding. I know we get... I mean, lots of contributions from (inaudible general conversation 41:18 – 42:03).