

MDS–Diagnosis and Treatment Update

Gail J. Roboz, MD
March 12, 2013 • 1:00 PM

Slide 1 - Welcome & Introductions

OPERATOR:

Hello, everyone, and welcome to *MDS–Diagnosis and Treatment Update*, a free telephone/web education program. It is my pleasure to introduce your moderator, Lauren Berger, of The Leukemia & Lymphoma Society.

Slide 2 - Gail J. Roboz, MD

LAUREN BERGER:

Thank you. Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Gail Roboz for sharing her time and expertise with us today.

Following Dr. Roboz’s presentation we’ll take questions from the telephone and web audiences.

I am now privileged to introduce Dr. Gail Roboz, Director, Leukemia Program, and Associate Professor of Medicine at Weill Medical College of Cornell, Cornell University, New York Presbyterian Hospital in New York.

Thank you so much, Dr. Roboz. Please go ahead.

Slide 3 - MDS: Diagnosis and Treatment Update

DR. GAIL ROBOZ:

Hi, everyone.

Slide 4 - Myelodysplastic Syndrome - Definition

So let’s move right into the topic at hand, which is MDS, myelodysplastic syndrome. I think most people have a lot of difficulty even pronouncing this term, let alone defining it. So let’s first start out by building a definition.

Slide 5 - What is bone marrow?

Myelo means bone marrow. And other than occasionally ordering bone marrow as a delicacy in a restaurant, a lot of people really have no idea what is bone marrow. And in fact, it’s the spongy central part of long bones. And you can see here a photograph or a schematic of a long bone in which a syringe has been inserted, to try to get into the central bone marrow cavity.

Slide 6 - What does bone marrow do?

And the reason for the procedure, to get in there, and the reason that this entire discussion is centered around bone marrow, is because bone marrow is the factory that produces blood cells. It makes white blood cells that fight infection. It makes red blood cells that carry around oxygen. And it makes little tiny cells, called platelets, which are important if you get a cut or are bleeding, in order to control clotting.

The bone marrow is a very, very important organ, and it’s very tightly regulated. The body knows how many cells it’s supposed to have, of white cells, of red cells, and of platelets. And there’s very much a Goldilocks approach here, that too many is not okay and too few is not okay. The body really wants the right number of all of these different cells. And there is a tremendously complicated signaling pathway or pathways that operate within the bone marrow in order to regulate the production of these different cells, both so that they function normally, and so that they’re produced in normal quantities.

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Slide 7 - Dysplastic

The term dysplastic, myelodysplastic syndrome, dysplasia refers to the abnormal appearance of cells when viewed under the microscope. And dysplasia is actually not necessarily obvious, even to an experienced pathologist. There are subtle differences in the shape, sizes, intracellular particles or little tiny things that are actually viewable inside cells, that define dysplastic appearance. But it's actually quite a subtle art to become good at recognizing dysplasia in cells. And there are quite important diagnostic criteria that pathologists know to make a diagnosis of myelodysplastic syndrome. Clearly seeing one funny looking cell under the microscope is not enough to make this diagnosis.

And it's quite well known to hematologists and to pathologists that dysplasia can actually be caused by many medical conditions, not only MDS. And we'll talk a little bit later about some of the other confusing diagnoses that can, for all the world, look like myelodysplastic syndrome.

Slide 8 - Syndrome

Now the third term in our definition, syndrome, is important, because this is a collection of signs and symptoms that are associated together. And one of the most important points to know right away about myelodysplastic syndrome is that it's quite complicated in terms of what a patient may look like or feel like. You may have two people sitting in the waiting room, both of whom have MDS, and they may complain of totally different problems and they may have totally different medical issues ongoing. So it's very important, especially as you talk to colleagues or friends or other people in chat rooms who might be having what you think is the same thing as you do, to recognize that within myelodysplastic syndrome there is a very wide range of clinical features that is associated with the syndrome. And this we're going to talk about a little bit later as we try to define what the clinical problem is that a particular patient is having and what might be the treatment options for that particular problem.

Slide 9 - Myelodysplastic Syndrome

Now all of this, I hope, has been relatively simple so far. So how do we get from that nice simple definition to a heterogeneous group of clonal hematopoietic stem cell disorders? Which I've learned to say quickly and easily, but immediately gives everybody a headache and is quite confusing.

I want to spend a second, though, on the technical and scientific definition of the term because I think it is quite important for everybody to realize what we are dealing with.

Heterogeneous means, again, not the same. Characterized by significant differences, both in the pathologic appearance and in the way that patients seem. Clonal. Clonal hematopoietic stem cell disorder. This is an important term because this actually has to do with the fact that myelodysplastic syndrome is a malignancy. It is a neoplasm. It is a cancer. It is not bone cancer. It is not bone cancer. And this is something that's very confusing to people because well, bone, bone marrow, that sounds like the same thing. It absolutely isn't.

But unfortunately, for myelodysplastic syndrome, there is in fact a clonality to the disorder, which means that hematopoietic stem cells or very, very early stem cells in the bone marrow that haven't decided what they want to be when they grow up yet, whether they're going to be a red cell or a white cell or a platelet, are involved in a clonal or malignant way in this disorder.

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And it's characterized, the next part of the definition, by ineffective hematopoiesis. What that means is that the marrow is trying and trying and trying to create more blood cells, but they're not coming out correctly. They're not maturing and growing up in a normal marrow. Some of you, who are dealing with this disease, may know that the doctor has said the bone marrow is full of tons of cells trying to form, and yet every time you go into the office you may have low platelets or a low blood count. Well, why is that happening? How come the bone marrow is producing so many cells, but they're not getting out into the blood where you need them? That is what ineffective hematopoiesis means. Blood forming that is not working. It's not resulting in mature normal blood cells that help you by populating your blood.

Progressive pancytopenia is what most patients with MDS have, which means low blood counts. There are some who have normal cell lines, one or the other may remain normal, and there are occasional patients who actually have an elevation, for example, in the white count or in the platelets. But for the majority, it's actually low blood counts that turns out to be the biggest clinical problem.

Morphologic abnormalities means that under the microscope the cells look funny, they are not forming and maturing normally, and a propensity to transform to AML means in this case about a third of patients with myelodysplastic syndrome, unfortunately, do progress to a more severe bone marrow failure problem, called acute myeloid leukemia.

So this complicated definition basically means that there is a malignancy, there is a malignant stem cell disorder in the bone marrow in which the bone marrow is unable to effectively make the important blood-forming cells that we need for daily life. The cells look funny under the microscope. And in about a third of patients it can turn over into acute leukemia.

If you look down at the rest of the slide, I think that we've now covered all of the elements of the rest of the slide. I would just like those points to be available to you for reference in case they come up in some of your pathology reports. For example, some of you may have seen dysplastic hematopoiesis or impaired differentiation as terms in pathology reports. What these mean are that the cells, again, look abnormal under the microscope and they're not growing up and maturing normally.

The other attention-grabbing words here are blasts. Those are early leukemia cells. And in myelodysplastic syndrome, the numbers of those early leukemia cells are important.

Hypercellular bone marrow in about 90% of patients means, again, the marrow itself very frequently has tons of cells, but they're just not getting out and doing their job.

Peripheral cytopenias means low blood counts. A risk of progression to leukemia, as we discussed, in about a third of patients.

And then this is an important point, that in about 50% of patients there will be abnormal cytogenetics or abnormal chromosomes. This doesn't mean that it's a genetic disease that is transmitted to children or grandchildren. It is, in the vast majority of cases, not. There are very, very rare familial MDS syndromes, but they are exceptionally rare. But what it does mean is that the clone of stem cells involved in the patient's particular disorder may have characteristic chromosome abnormalities. And this may be important in defining which treatment is the best. And it also may be important in following the disease after treatment. Because if

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you know which chromosomes are abnormal to start out with, you can follow that through the treatment and see whether or not they go away.

Slide 10 - Risk Factors

Why do people get myelodysplastic syndrome? Most of the time we have no idea. More than 80% of patients we really have no idea why they develop the disorder. We do know that prior exposure to chemotherapy, with or without radiation therapy, for example, for another type of cancer, is a risk factor for MDS. It doesn't mean you shouldn't get treated for whatever cancer is diagnosed. Of course, one should. But there is a risk afterwards in the years after treatment that that could turn into myelodysplastic syndrome in a rare percentage of patients.

Advancing age is a risk. We don't know exactly what about the aging bone marrow puts it at risk. That will be a Nobel prize-winning discovery. There are certain congenital diseases that are associated with MDS. And there are actually reports of association with environmental toxins, but the data aren't really great. And this is the source of much anxiety for patients because the data really don't guide us very well.

Slide 11 - MDS Risk Factors

We know that things like increasing age, male gender, chemotherapy, these have strong association. When it gets down lower in the chart to things like benzene, organic solvents, smoking, pesticides, we don't really know that much here because there are many, many millions of more exposures than there are cases of MDS, so it's often very difficult to even guess at a causal relationship between an exposure and the development of the disorder.

Furthermore, even in the situations where we think we might know what the exposure was, currently that doesn't influence the treatment that is selected for a particular patient.

Slide 12 - Bone Marrow Failure: Signs and Symptoms

So what are the signs and symptoms that we deal with for bone marrow failure? And in this discussion, of course, specifically MDS as a manifestation of bone marrow failure. Anemia, fatigue, you can be pale, short of breath, decreased exercise tolerance. A lot of times this isn't dramatic at all. Patients might say, you know, I always used to jog two miles a day and now I just can't even get up to half a mile. Things that you notice about your own exercise tolerance or your own capability to do what you usually do in a day, are often what gets you to medical attention.

Sometimes it can be quite a bit more dramatic. And shortness of breath, really being unable to get out of bed. But more often than not, it's more subtle than that.

Neutropenia, or a low number of neutrophils, infection-fighting white blood cells, may be noticed also in a routine laboratory evaluation, but may be noticed because you go into the doctor having had bronchitis, followed by sinusitis, followed by pneumonia, followed by a urinary tract infection, and you've never been sick a day in your life and can't understand why all these infections are happening, sometimes that's what leads to the discovery of having low infection-fighting white blood cells.

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Thrombocytopenia or low platelets, bruising, unexpected bleeding, these are some of the signs and symptoms that patients will present with when trying to get a diagnosis made.

Slide 13 - Performing a bone marrow aspiration

And this schematic may be familiar to some of you. Once we see, as hematologists, that there are abnormalities in the blood counts, we do move forward to performing a bone marrow aspiration and biopsy because, until you look in the bone marrow, in the factory, and see what's going on, you're really much of the time only able to take a guess from looking at the blood counts. And although I did put an "ouch" sign here, I can say that really much of the time, although I don't think it'll ever be anybody's favorite procedure, much of the time it can be accomplished quite quickly and without too much discomfort. So it's worth it to get this done somewhere where they do an awful lot of them.

Slide 14 - Other diseases of bone marrow failure

Now this slide is a scary slide that I just wanted to put up for reference, of lots of different complicated disorders that actually are in what we call the differential diagnosis or other possibilities that could be causing bone marrow failure. And I'm certainly not going to give a lecture right now on all of these complicated diagnoses. But the point here is just to, once again, underscore that MDS is not always an easy diagnosis to make. It can be quite challenging. And it can be quite difficult, even for experts, to distinguish between MDS and some of the other diagnoses on this list. For example, aplastic anemia and PNH, which is another rare, but important bone marrow failure syndrome.

Slide 15 - Required Initial Evaluation

So I think that very frequently some of the discussion in the early part of a new diagnosis is, is it really MDS, are we sure that we have met the diagnostic criteria for MDS? And I think that this is really a very critical point. We know that the guidelines, for example, the NCCN guidelines point to quite a bit of diagnostic information, a history and physical, you need a blood evaluation, you need somebody to look at the slide of the peripheral blood, bone marrow tests, and then a bunch of these other lab tests that are listed here, including specifically checking the thyroid function, because that's another area that can frequently lead one in the wrong direction. If the thyroid is abnormal, that can sometimes cause anemia and be another diagnosis that needs to be excluded before you make a diagnosis of MDS.

So these components are very frequently done, even in the first visit, with the hematologist. But it's quite important to very methodically go through and make sure that all of the elements of the story fit together and point to a diagnosis of myelodysplastic syndrome.

Slide 16 - IPSS-R Prognostic Scores Values

And then once you are there, there are a variety of ways to figure out how bad this particular MDS is going to be. This schema over here of the IPSS, or the International Prognostic Scoring System-R, which means revised, is showing a way, it's not the only way, but a way of using the chromosome results, the percentage of blast cells or early leukemia cells, the hemoglobin, the platelets and the neutrophil count, to kind of all fit together in an algorithm that is related eventually to prognosis. And each of these is scored and eventually comes up with a total score for the expected prognosis of the disease.

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DR. GAIL ROBOZ:

I would be very, very careful, I'm urging everybody on the phone, to be very careful about doing this, because it's really hard when somebody flashes a number, not to assume that you're being told how long you're going to live. Doctors are bad at that. And although it is important to try to figure out as much as possible about a person's particular disease, so that we can make good treatment decisions, please don't let anybody tell you how long you're going to live, unless you have a really, really good fortuneteller, because the doctors are not good at it. And I think it's very upsetting sometimes for patients to be given a number that says well, this is how long you're going to live. Because there are many patients who live much longer than expected and, unfortunately, there are those who progress much more quickly than would be predicted by any specific algorithm. So these results are always to be taken with a very big grain or maybe a cup of salt.

Slide 17 - Newer prognostic models

The other thing I can tell you is that there are newer prognostic models coming out, literally on a weekly basis, in MDS, which include other stratification points. For example, 60 range – you know, if you're 60 years old or if you're 90 years old, it's all the same. Clearly it's not all the same. And there are 60-year-old patients who are in wonderful shape, playing golf every day. And there are 60-year-old patients who are having multiple other medical problems. Clearly those two patients are going to have different discussions in terms of treatment options. So we need to be very mindful of age, what other diagnoses a patient has had, how long have they had MDS, what prior treatments might there be, what is their overall performance status or how much activity can they do. All of these clinical factors are very important for treatment.

The other thing is, the area of molecular diagnostics is becoming extremely important. We are able now to recognize the gene sequencing. Many mutations that are increasingly associated with MDS. I have to encourage everybody this is a hazardous area because sometimes we find mutations and we don't know what they mean. Most people find it upsetting when you say, you have a mutation in ABCD. Somehow that doesn't sound good. But a lot of the times we don't actually know what it means. And one of the reasons why clinical trials and having patients register themselves and hopefully their bone marrow eventually to be analyzed in clinical trials, is so that we start learning about how many people really do have certain mutations and what happens to them. Because if we find a mutation, but we don't know anything about what happens to a patient with that particular mutation, then it's useful and it's information which isn't doing anybody any good.

Slide 18 - How is MDS treated?

If you look at the next slide on treatment, this is obviously a very, very individual area. And one of the things that's very important is to make sure, even in the question and answers, that we're not trying to make any type of a general discussion for treatment that you want to apply to yourself. Everybody is an individual, everybody should have a very individualized care plan.

In general there is a wide range of options, going all the way from supportive care, which is just some transfusions, antibiotics, possibly growth factors, and possibly removal of extra iron, although for many patients this does not appear to be of benefit. So that's one option. And then all the way on the other edge of the spectrum is a hematopoietic or bone marrow transplantation. So it's very disconcerting sometimes for patients to realize that it might be reasonable to do everything from just some antibiotics and transfusions, all the way

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to a stem cell transplant. That doesn't make sense to most patients. How could both of those options be for me? And yet that might be the case. So you have to have a very detailed discussion about your own clinical situation.

There are approved agents. Azacitidine, which is marketed as Vidaza®, and decitabine, which is marketed as Dacogen®, are the hypomethylating agents. These don't work like regular chemotherapy drugs, although they are forms of chemotherapy, and they are both associated with improved bone marrow function and possibly with improved survival for some patients as well.

There are immunomodulatory drugs like lenalidomide, which is marketed as Revlimid®, that is also an approved drug which is of benefit for some patients with MDS.

And then in the realm of stem cell transplant, the comments there are that stem cell transplant is increasingly available for more patients. We're able to get more patients donors. And we are able to get older patients, well into their 70s, through transplant at this point. We still don't know, for most of those older patients, whether going through a stem cell transplant is actually better than going through some of the less intensive therapies. That is an area of intensive clinical investigation.

And of course, the last on the list, the novel agents in clinical trials, is truly by far the most important area. Because I can tell you that, unfortunately, although treatments that are currently available are considered standard in MDS, just because they're standard doesn't mean they're any good. And actually we have a lot of room for improvement in the current therapy of MDS to make it both better and more tolerable. So for clinical trials, it's although a wonderful, wonderful thought to be helping future generations, it's actually very relevant to the current generation. And for patients with MDS going on to clinical trials, they can be hoping to help themselves as much as they would be hoping to help somebody down the road.

Slide 19 - Before we decide "how" to treat

In the next slide I just wanted to mention that before we decide how to treat, we need to know why we are treating. And I think that this is an important point because when you come up with a new diagnosis, most of us will say, well, what do I have? I have what? I don't know what that is, but get rid of it. And that is a normal and natural instinct, to say, well, let's get this better.

Slide 20 - Goals of Treatment

But we have to manage expectations here and try to figure out what are reasonable goals of treatment. So I made a slightly snarky slide here, but I'm trying to make the point that, if possible, cure me. Cure is very, very difficult in MDS and there are selected patients who are cured with stem cell transplant, but currently the majority of patients with MDS are not cured.

If you can't cure me, here's my second point, at least make me live longer and feel better. And there are options in that category. Similarly, if you can't make me live longer, at least make me feel better. There, too, I think it's quite important to recognize that in MDS, especially with the approved agents, azacitidine and decitabine, part of the reason why they were approved is because patients actually felt better on treatment

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than off treatment. So there are several situations that I can think of in which a patient may say, well, you know, I'm feeling so terrible, is it worth it for me to go through this treatment? To keep in mind the possibility that you might actually feel better on treatment than off.

And then finally I said, if you can't even make me feel better, then get me another doctor and go back to school. But that's just me being me. And usually, usually we can at least try very hard to do something to get people to feel better.

Slide 21 - Proposed treatment algorithm

This algorithm on the next slide is taken actually from a publication several years ago and, alarmingly, it's quite relevant still today, which is not good. You don't like things to stay the same over a period of years. But basically just in a quick way, to try to have you have a little bit of a graph to look back, to divide loosely into patients who are called lower risk patients and patients who are termed higher risk patients, depending on, again, the chromosomes, the number of blast cells in the bone marrow, and the other features that I showed you on the prognostic scoring system slide.

Couple of important points. Low risk doesn't mean live forever. Unfortunately, there are plenty of patients who are called low risk, who still have many clinical problems associated with MDS and do need treatment. Similarly, high risk patients, high risk doesn't tell you exactly anything. What it means is that, in general, survival is predicted to be significantly shorter than what it would be normally, A. And B, it often means that there's a risk of transformation to leukemia. So for those patients, survival is imminently threatened. And what we're looking for is trying to modify the disease as quickly as possible. For the lower risk patients, we are looking for ones who are truly not having any symptoms, to try to see if there's anything that we could learn about how to make the marrow stay well for as long as possible and not get worse. And for patients with so-called low risk disease, who are having symptoms, might we be able to use growth factors or azacitidine or immunomodulators. What type of medication might we be able to use to improve the bone marrow function and have the patient's symptoms be improved overall, even if we're not sure that any of these drugs will overall prevent progression to worsening MDS or to leukemia in the future.

And that's one of the hardest things for patients to understand, that, well, if you know that this could go on to leukemia, why can't we stop it? We don't know how to do that yet. And that is one of the hopes for many of the novel agents, that maybe they would be able to restore normal blood production in the marrow, so that progression to acute leukemia would never happen.

Slide 22 - Essentials for an MDS patient

And then just to wrap up a couple of points. Know your risk group. At least know and understand where your doctor thinks you are in the scheme of MDS diagnosis. Nobody is perfect at predicting this, but for sure you should know if you're considered in one of the high risk categories, so that you can assess your options quickly.

Know your treatment options and know whether you should be considering a stem cell transplant and a clinical trial. Clinical trials in this area are absolutely critical and for many patients they are the only way to get

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access to novel drugs. And I can tell you for sure that there are plenty of patients, especially those for whom the conventional therapies have not been helpful, where it is critical to try to get on something, anything that is new, because what we have on the shelf doesn't work very well.

Similarly, transplant is something that is available for many more patients than what used to be the case. So it's at least worth the discussion with your doctor or with a consultant, that might this be an option for me.

Also, know what the results are that are reasonable to expect from treatment. Cure with this disease is extremely unusual at the moment, but know what to be looking for. Are you at least thinking that your blood counts are going to get better or that you're going to feel better or that you're going to put on weight? Try to know what the specific clinical problems are that you have and what is the likelihood that they're going to get better.

Definitely know the potential side effects of therapy, but recognize that if you read the package insert on a Tylenol®, you're never going to take that either. Most drugs have a million possible side effects and we have to figure out patient by patient which ones are the most likely for you.

The most important thing to know actually is, what are the likely effects after receiving any particular drug, how quickly is the drug expected to work, and how quickly might the side effects go away.

Know about your resources. Clearly the LLS is a phenomenal one with many, many resources, both online and via the telephone, to help you navigate the world of MDS and figure out whether you're on the right track.

And also, very importantly, this needs help. You need family, you need caregivers, involve them in the treatment planning, try to figure out who's going to be responsible for remembering what during a conversation in the doctor's office, since these can be quite overwhelming. And even reaching out to some of the resources via the LLS or via outside groups, to try to figure out how you can get more help in managing the information and guiding your own therapy.

I hope this has been helpful. I will turn the presentation back over to Lauren and would be happy to take a crack at some questions.

Slide 23 - Question and Answer Session

LAUREN BERGER:

Thank you. We'll take the first question from the web and Marie asks, "What is the status of research on platelet-stimulating agents?"

DR. GAIL ROBOZ:

So that's an excellent question. Clearly, one of the biggest clinical problems in MDS is having a low platelet count. And for a long time there really wasn't much that we could do to successfully stimulate platelet production other than transfusion of platelets.

There are platelet-stimulatory agents that are commercially available, primarily for the treatment of ITP or – this is idiopathic thrombocytopenic purpura, which is an autoimmune disorder that results in low platelets, that

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is not the same as MDS. So these drugs are approved for a different purpose, but they have also been looked at in MDS and do seem to be of some benefit in certain patients, both alone and possibly in combination with drugs like azacitidine or decitabine, to improve platelet counts.

The problem is, number one, this is still in research only, so this is not something that is generally available to patients outside of a clinical trial. And one of the important considerations is that when you're stimulating the bone marrow, you're not only necessarily stimulating good cells. And the question is that, in the long term are these types of agents going to be safe or might there be a possibility of stimulating any bad or leukemic cells in the marrow.

And I would say that the jury is still out on that topic. There are more trials ongoing. It seems that the drugs are effective in raising the platelet count, but the question is, does that make you live longer or better if your platelet count is higher, and that's not necessarily the case. And also will they be safe over the long term for patients with lower risk disease, is there any possibility that they could actually make the disease worse over time. And I would say that that is not a fully answered question yet.

LAUREN BERGER:

Thank you, and thank you for the question, Marie. We'll take the next question from the telephone audience, please.

OPERATOR:

The next question comes from Paul from Ohio. Your line is now open.

PAUL:

After developing AML and being treated for it, can you later develop MDS or be diagnosed with MDS?

DR. GAIL ROBOZ:

Unfortunately, the answer to that question is yes. And you can in fact even undergo a stem cell transplant for either AML or MDS and subsequently have either a return of the same or potentially the development of a new MDS.

Mercifully, that situation is not common, but unfortunately, because of the use of bone marrow-damaging agents in the treatment of both MDS and AML and actually in the setting of a transplant, it is not impossible to have that develop as a secondary complication, I wish it would be.

LAUREN BERGER:

Thank you for your question, Paul. We'll take the next question from the web audience and this one is from Marnie and she asks, "What has been your experience with hypomethylating agents in low risk patients? And in which low risk patients have you used this?"

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DR. GAIL ROBOZ:

That’s an excellent question. One of the things that I wanted to make clear in my presentation was again the terms low risk, high risk. They don’t really tell you a lot about what’s going on with a patient. And there can be a patient who has technically a low risk disease, but who might be quite compromised in daily life due to transfusion requirements, for example, either of red cells or of platelets.

I think in general most of us in the field are hoping to treat patients on a clinical trial, who are in the low risk category, so that we can actually follow them over time carefully and compare with other patients, to test not only whether the clinical problem, for example, transfusion dependence or whatever else is going on with the patient, to see if that gets better, but also to see if over time it is effective in reducing the rate of transformation of that low risk disease to a more high risk situation.

That said, because the drugs are commercially available and because not everybody can always get onto a trial, there definitely are symptomatic so-called lower risk patients who are really not doing well with transfusion support or with other supportive care, that we do treat with hypomethylating agents. And there are definitely responses among those patients in reductions in transfusion requirements.

I cannot say whether those patients have a quote-unquote healthier marrow for the long term, but certainly in dealing with the complications that they might have in the short term, the drugs can be helpful.

There are also ongoing clinical trials, for example, now in low risk patients. There is an ongoing clinical trial involving an oral hypomethylating agent. So the question is that, over time might there be modifications in the current therapy, making it a little bit better for the lower risk group. And that’s something that is being studied in clinical trials.

LAUREN BERGER:

Thank you. We’ll take the next question from the telephone audience, please.

OPERATOR:

Our next question comes from Rachel in New York. Your line is now open.

RACHEL:

Thank you. I was wondering what the relationship is between dietary intake of iron and the Procrit® that I get to improve my hemoglobin and hematocrit. Eating iron-rich foods does not seem to have any effect on my hematocrit and hemoglobin.

DR. GAIL ROBOZ:

This is a very important question and I’m glad that you brought it up because it’s actually not a simple issue at all, so you’re not missing something by being a little bit confused, what’s going on.

In myelodysplastic syndrome it is uncommon for patients to be iron deficient. And actually what is more common is that for patients with MDS who are requiring even intermittent transfusions, usually the iron levels in the blood and in the bone marrow are running high rather than low. That said, patients with lower risk MDS

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DR. GAIL ROBOZ:

who are being treated with Procrit, sometimes do run the risk as the Procrit or Aranesp® or whatever red cell stimulator you're taking, as that drug is trying to work to stimulate red cell production, it is possible to deplete iron stores and it is likely that the doctor will check along the way whether or not that's happening with you. Because if you're not requiring transfusions and you are on a red cell growth factor drug, it's possible that you would become iron deficient, and then they would probably put you on iron pills.

In general, eating iron-rich foods is a pretty ineffective way to solve this problem because you have to eat an awful, awful lot of it. And even with perfect absorption, if you really had become iron deficient, using the red cell growth stimulatory drugs, probably you would need to actually be supplemented.

I have to emphasize, though, that it is a mistake to just randomly take iron or B12 or any supplement that's generally associated with improvement in red cells, if you've been diagnosed with MDS, because you probably aren't deficient in any of those. And if you're not deficient in them, then taking extra is not helpful and in the case of iron, especially for patients who are receiving transfusions and probably have plenty of iron, the last thing you want to do is try to get even more in through dietary intake.

LAUREN BERGER:

Thank you, Rachel. And we'll take the next question from the web and this one's from Colin. "Does CMML fall into MDS, since WHO, the World Health Organization does not classify it under MDS?"

DR. GAIL ROBOZ:

So CMML, and I just want to distinguish this for the rest of the audience, CMML is chronic myelomonocytic leukemia. This is not, underlined, not the same thing as CML, which is chronic myeloid leukemia, which is only one letter away, but a very, very different diagnosis.

The person with this question is asking an important and subtle question because CMML has been a disease that sounded a little bit difficult to find a home in a specific pathologic classification. It has both features of MDS and features of the myeloproliferative disorders, which are bone marrow disorders or actually bone marrow neoplasms, because these are also malignant disorders, that are generally characterized by hyperproduction of blood cells.

So for example, in CMML patients, it's very common to have an extremely elevated white blood cell count, 30,000, 40,000, 50,000. Many of the circulating cells are monocytes. And those patients may have very high white blood cells, but then might have low hemoglobin and platelets. So again, the bone marrow can't make up its mind. It's making too much of one thing and not enough of the other.

It does not either technically or clinically fall clearly into the MDS or MPD category and most of us think of this as a really separate disorder, which is a hybrid with features of MDS and of MPD. It is frequently excluded from clinical trials because the patients' clinical features are so different than others with MDS. It depends on the trial, whether it is or is not included.

LAUREN BERGER:

Thank you. We'll take the next question from the telephone audience, please.

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OPERATOR:

The next question comes from Lorraine in Ohio. Your line is now open.

LORRAINE:

Yes, I have a question about damage to the organs from Revlimid. I am on Revlimid. I have 5q. And I wondered if there is any information out there, what it would do to kidneys and to the heart and that sort of thing. Is there any information on that?

DR. GAIL ROBOZ:

There definitely is quite a lot of information actually available about Revlimid and its clinical consequences to patients. And I would encourage you to both check out with your doctor's help, there is a lot of information on their website, as well as there are brochures, patient information brochures that are available. There are, in fact, patients who have had kidney, stomach and other complications, but these again are in individual cases and usually with close monitoring with your doctor's office, both of your kidney function and of your blood counts and checking you out in general and seeing how you're doing, both via dose modifications and sometimes occasionally even dose interruptions, the drug can usually be administered safely. But there certainly are many potential complications. And again, these are very carefully outlined in the patient brochures that you can get. And then you can discuss with your doctor how your monitoring is going forward, to make sure that your risk of these complications is minimized.

LAUREN BERGER:

Thank you for your question, Lorraine. We'll take the next question from the web audience and this one's from Elkie, and the question is, "You mentioned there really isn't a cure. With an allogeneic stem cell transplant, do you find that these people relapse and progress to AML or just relapse with MDS alone?"

DR. GAIL ROBOZ:

So there are patients, unfortunately, who do undergo allogeneic stem cell transplant for MDS and then relapse. I would say that both scenarios happen. Sometimes the relapse is of MDS and sometimes the relapse eventually progresses toward AML. So both can happen. It is the case, you know, many people are assuming that if you can go through a stem cell transplant, that that means you're cured for sure. Unfortunately, it doesn't guarantee that, and sometimes there are regimens or clinical trials that are implemented for patients, even after stem cell transplant, in an effort to prevent the disease from either reverting back to MDS or from progressing.

We don't really know for sure, it depends on the individual patient, but we don't know for sure whether any of these post-transplant modifications are going to improve the overall cure rate. But for patients who are at very high risk of relapsing after the transplant, either because of features of their disease or because of features of the transplant, it's definitely a point worth considering, whether or not to do treatment after the transplant.

LAUREN BERGER:

Thank you for the question. We'll take the next question from the telephone audience, please.

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OPERATOR:

The next question comes from Phyllis in Florida. Your line is now open.

PHYLLIS:

Yes, I'm calling for Phyllis. The question is, she's being treated with Vidaza right now, and if her hemoglobin levels are not rising sufficiently, they're only going up to – into the 10s, occasionally up to 11 – is it now time to look towards different type of treatment?

DR. GAIL ROBOZ:

Hemoglobins in the 10 or 11 range are actually very good. So the last thing you ever want is a doctor to take care of you by telephone without meeting you, so I certainly don't want to do that. But in general, depending on where a patient starts out, hemoglobins of 10 or 11 are – if that represents a response or an improvement from where Phyllis was when the treatment was initiated, I would consider that to be potentially going in the right direction.

You should keep in mind that with treatment like, for example, Vidaza, it doesn't have to go to completely normal in order for the therapy to be considered working. Even if you improve to the point that the patient is feeling better or requiring fewer transfusions, that could still be considered a success. And when you discuss it with your doctor, again, you should try to figure out what level you guys are looking for to define a success. But certainly by the specific number that you're giving, I would have that conversation and make sure that you're not doing better than you think you are.

LAUREN BERGER:

Thank you for the question. We'll take the next question from the web audience. "What is the criteria for determining that MDS has converted to AML?"

DR. GAIL ROBOZ:

So the technical definition of AML is greater than or equal to 20% blasts, myeloblasts, in a bone marrow biopsy. And that is what defines this transition. That said, the author of the question may have a more subtle point in mind, which is that, is it really different if there are 19% blasts versus 21? Does something incredible happen to distinguish between those?

And the answer to that is no. This is, in fact, a disease, when it progresses to MDS to AML that is on a spectrum, and you can have a patient who is behaving clinically for all the world like AML, with 14 or 15 or 16% blasts, and then there are other patients who are kind of hanging out, looking just the same at 25% blasts as they were at 14 or 15. So getting stuck on the numbers is never a good idea here because they don't tell a lot about what's going on with the patient.

That said, the numerical assessment is important for clinical trials because there are trials that are open for patients who have greater than or equal to 20% blasts that are not the same necessarily as those for patients with fewer numbers of blasts. So that's when things tend to get a little bit more numbers-focused, is when there's a trial at play.

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DR. GAIL ROBOZ:

Otherwise, the thing to consider most is the total picture. So for example, in the setting of rising blasts in the marrow, falling platelets, patient is feeling worse than before, that is a disease that could be evolving. And even if the number is 14 or 15 or 16% versus 20, I wouldn't be terribly reassured that it doesn't meet the specific pathologic criteria for leukemia, if all of those other things are happening – platelets are falling, patient is feeling worse – all of that matters, too.

But the technical answer to your question is greater than or equal to 20% in the bone marrow.

LAUREN BERGER:

Thank you, and that question was from Janet, so thank you for your question. We'll take the next question from the telephone audience, please.

OPERATOR:

The next question comes from Joan in New Jersey. Your line is now open.

JOAN:

Hello. Seven years ago when I was diagnosed with MDS I had the trisomy of number 8, which put me in the intermediate group. And basically I really never get an answer that I understand, what this trisomy of number 8 is doing to me.

DR. GAIL ROBOZ:

I'm not surprised to hear that because, unfortunately, the state of the art doesn't know exactly how to answer your question. There are patients with trisomy 8 or three copies of the 8 chromosome, who actually hang out in a very stable situation for many years at a time. And there are others who progress and have worsening signs and symptoms of bone marrow failure. And we don't know at the moment, among patients with trisomy 8, to distinguish between those who will hang out and stay stable for a while and those who will need treatment. So the reason you're not getting a clear answer is because there isn't a clear answer.

What I can tell you is that there are definitely patients in both categories. So if your doctors are feeling that you're doing pretty well and that your blood counts are stable and they are taking a watch-and-wait type of approach, that's not unreasonable because there are patients with trisomy 8 who, in fact, do hang out in that type of a stable situation.

There are also, though, patients with the same chromosome abnormality who have a more aggressive type of disease. So generally speaking, I favor close follow-up, monitoring blood counts closely, checking the bone marrow more repeatedly if there are changes in the blood counts, and also looking at how you're doing as a whole to guide the rest of your therapy.

LAUREN BERGER:

Thank you for your question. We'll take the next question from the web and this one's from Demaris. "I was diagnosed with ITP thrombocytopenia. Last week I was diagnosed with MDS. Is this just a progression of the ITP? I got my first shot of Vidaza this afternoon."

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DR. GAIL ROBOZ:

So it's not totally unusual that patients would have initially been told that they have ITP. The problem is that I can't tell without reviewing the slides and the reports and the entire medical information, whether in your particular situation, the initial diagnosis was incorrect, or whether in fact there were differences in the pathology between what was seen before and what is seen now. It's not unusual that people would initially have what looks for all the world like ITP and then subsequently it looks more dysplastic on the marrow. But sometimes also we end up going backwards and saying, well, maybe there were some features of early MDS.

The good news is that very frequently that distinction actually doesn't matter much in terms of dictating your treatment, but from a curiosity point of view, the only way to know would be to go backwards and compare and review the original bone marrow slides from the first diagnosis.

LAUREN BERGER:

Thank you. We'll take the next question from the telephone audience, please.

OPERATOR:

The next question comes from Marilyn from Ohio. Your line is now open.

MARILYN:

Hello. I have a question about, if you could give me an explanation, short of God's healing, if after two years of treatment for MDS, it disappeared. I no longer have it. And I'm thankful.

DR. GAIL ROBOZ:

That is great news. So I guess the definition of a disease going away is usually a pathologic one, with resolution of all the abnormalities that might have been noted initially. There are patients where treatment is successful and the disease goes away. I can't, of course, give you an explanation of what happened to you because I don't have any of the details of what exactly happened to you, but I certainly would like to congratulate you on doing so well. And it's always wonderful to hear people are doing well. We love to try to figure out why people are doing well, so that we can then help others enjoy that wonderful success.

LAUREN BERGER:

Thank you for your question, Marilyn. The next question comes from the web and this one's from Judy. "Does the need for transfusion increase with the duration of the disease?"

DR. GAIL ROBOZ:

Typically yes. So worsening bone marrow failure is often a feature for patients over time. The amount of time that it takes for worsening bone marrow failure is variable from patient to patient, but typically when there is a transfusion requirement, especially right from the beginning, that does get worse over time. If you're started on treatment, the hope is that whatever treatment you're started on, would be able to slow the frequency of the transfusion requirements, at least for a period of time.

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LAUREN BERGER:

Thank you. We'll take the next question from the telephone audience, please.

OPERATOR:

The next question comes from Kathleen in New Jersey. Your line is now open.

KATHLEEN:

I have pancytopenia. And I'm in my tenth year of MDS. Currently on Revlimid. And with pancytopenia, it frightens me sometimes that all counts are down, almost all the time. But as you said before about the 9 on the hemoglobin, I guess that's still good.

DR. GAIL ROBOZ:

Well, I certainly appreciate your concern about having pancytopenia and that is something where we always are concerned with low red cells, low white cells, low platelets, we're always concerned about potential complications. The good news is, it sounds like you've been doing well for a long time and it is true that sometimes on treatment the counts can actually get lower before they get better again. There are levels of pancytopenia, though, that some are safer than others. And with hemoglobins of 9s and 10s and with infection-fighting cells that are running around or over 1,000, even with numbers like that that are technically low, they're actually not associated for some patients with big risks and walking around. So it is possible to have pancytopenia with low blood counts, but to still be doing pretty well overall, which I'm hoping might be your situation.

Slide 24 - Resources

LAUREN BERGER:

Thank you for your question, Kathleen. And thanks to all of you for your questions. We hope this information will assist you and your family in your next steps.

If we were not able to get to your questions, please call The Leukemia & Lymphoma Society's Information Specialists toll-free at 800-955-4572. Or you can reach us by email at infocenter@LLS.org. Our specialists can provide you with information about MDS research and clinical trials and other questions you may have about treatment and about financial assistance for treatment. You can also access a video on MDS on the LLS website at www.LLS.org/webcast. There are additional programs and other information in your participant packet.

Please help me thank Dr. Roboz. We are so grateful you have volunteered your time with us today.

On behalf of The Leukemia & Lymphoma Society, Dr. Roboz and I would like to thank you for sharing your time with us today. Good-bye and we wish you well.

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