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https://reachmd.com/programs/cme/managing-and-monitoring-mds-mds-related-effects-and-progression-to-aml/13518/

Released: 04/15/2022
Valid until: 04/15/2023
Time needed to complete: 15 minutes

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Managing and Monitoring MDS: MDS-Related Effects and Progression to AML

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Managing and Monitoring MDS: MDS-Related Effects and Progression to AML” is provided by Prova Education.

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Dr. Zeidan:
Did you know that about one-third of all patients with myelodysplastic syndromes, or MDS, progress to acute myeloid leukemia?

This is CME on ReachMD, and I’m Dr. Amer Zeidan.

Dr. DeZern:
And I’m Dr. Amy DeZern.

Dr. Zeidan:
Let’s get started. Many patients with MDS are affected by symptomatic cytopenias, especially anemia. Unfortunately, anemia-related symptoms can have a significantly negative impact on patient survival, as well as their quality of life. Dr. DeZern, how do you assess for and treat MDS-related anemia in your clinic?

Dr. DeZern:
I think it’s a great question, and I’ve learned over time there’s different aspects of it. You know, as you point out, really, this is the predominant cytopenia that most patients present with, and they usually come to presentation due to clinical symptoms that the patient themselves note. Perhaps shortness of breath, heaven forbid chest pain, certainly fatigue is an overarching complaint in MDS in general. And sometimes this is what prompts the checking of the initial CBC [complete blood count] that brings the disease to light. But once a patient carries a diagnosis of MDS, we certainly know that a routine part of really good care for them is monitoring of that complete blood count. There’s a lot of different ways to treat the anemia, though the mainstay has long been and probably always will be red blood cell transfusions. But certainly, in the era of limited supply with the Red Cross in the US and then across the world, we have to really think about additional therapies that can mitigate that transfusion independence and hopefully decrease how many red cell transfusions a patient needs.

One thing I have really come to emphasize, both to patients and my nurses and reinforce with myself, is that it’s not just about the number. It’s about how the patient feels at a certain gram of hemoglobin, and I have a lot of conversations with my patients about whether or not they sincerely feel better after we augment the hemoglobin above 8 grams, or in some patients above 9 grams, and we set our transfusion threshold together where we can. If the patient has low-risk disease at presentation, I often use erythropoiesis-stimulating agents [ESA] to try and augment the hemoglobin. I use darbepoetin as well as erythropoietin, depending – like epoetin alfa – and I always use higher dosing regimens to hopefully get a higher erythroid response for these patients. Some patients have added to their regimen a G-CSF (granulocyte colony stimulating factors). This is something I do less than I used to, as I think patients, especially those with ring sideroblasts have another set of alternative treatments that may be helpful.

The other thing I do when somebody is receiving an erythropoiesis-stimulating agent regularly, is monitor ferritin levels in case I'm depleting their internal iron stores, and in that context, I might be making them iron deficient, and so they need to have supplemental iron to allow a continued response to that ESA.

Dr. Zeidan, are there any other agents that you use in your clinic, beyond these traditional methods of treating anemia for your MDS patients?

Dr. Zeidan:
Yes, indeed. You made fantastic points. I generally follow the same paradigm that you mentioned. Unfortunately, many patients will not respond to erythropoiesis-stimulating agents. If you look at different studies, around 40% in total of patients with lower-risk MDS will respond to the ESAs. However, even those who respond generally will lose their response within 2 years. So that leaves us, most of the time, either with what we call primary or secondary resistance or failure of erythropoiesis-stimulating agents.

So what we do at that point usually depends on the specifics of the situation. For example, for patients who have ring sideroblasts, which is an abnormality that's seen on the bone marrow pathology, those patients could use a drug called luspatercept. So this is a new drug that was approved in the US in the year 2020. It's given by subcutaneous injection every 3 weeks, and this drug basically works on the erythropoiesis pathway within the bone marrow so that it reduces the inflammation and the separation and allows more production of red blood cells – what we call maturation of those red blood cells so that the patient will have improvement in their anemia. And indeed, in a large randomized trial called the MEDALIST trial, which was a phase 3 trial that was conducted in many countries, use of luspatercept has resulted in transfusion independence of 8 weeks or more in around one-third of patients who have received the drug, compared to only 13% of patients who have received the placebo, and the median duration of that response was close to 8-9 months. So it's one option I use in my clinic.

Another option I use, as well, is a drug called lenalidomide. This drug works in patients who have a particular chromosomal abnormality called deletion 5q. This deletion is actually seen in patients with MDS in around 15% of the time, and in the lower-risk setting, you could use that even before the ESAs, as I tend to use it, but some people will use it after ESA treatment.

Other options could include also hypomethylating agents, which are drugs generally used in the setting of higher-risk MDS, but sometimes as we – especially as we start to run out of options in those patients, we can use them. Usually, I tend to use a lower dose than what is used in the higher-risk setting.

Of course, most importantly, I think enrollment in clinical trials, because we do need to find new agents. Many of those agents I just discussed, they will work for some patients and not everybody, and even when they work, they stop working after some time. So some of the ongoing trials, I think, that are important are looking at luspatercept in the frontline setting. So that's randomization against erythropoiesis-stimulating agents in patients with lower-risk MDS and anemia.

For those just tuning in, you are listening to CME on ReachMD. I'm Dr. Amer Zeidan, and here with me today is Dr. Amy DeZern. We are just about to discuss current and emerging therapies in MDS-related anemia, as well as monitoring our patients for progression to acute myeloid leukemia.

Dr. DeZern:
You know, I really do think there's increasing options, and how we sequence these drugs for our anemia patients will be very important going forward. I'll just mention that occasionally some people also use androgens, or danazol, to augment the hemoglobin. This is something I pull out rarely but in select patients could be a consideration if a clinical trial was not available.

But I think all of this just speaks to the fact that MDS is a very heterogenous clonal bone marrow disorder that has high risk for transformation into acute myeloid leukemia, or AML.

Dr. Zeidan, how do you monitor your patients with higher-risk MDS who have the potential to progress to AML?

Dr. Zeidan:
Yeah, and I think this is an important subject. For higher-risk MDS versus lower-risk MDS, certainly some patients will progress to acute myeloid leukemia. The risk tends to be higher, of course, in patients who have higher-risk disease. However, overall, around 35% of patients – one-third of patients with MDS will progress to acute myeloid leukemia. Why is that important to know? Because most patients with MDS unfortunately end up dying from MDS and not with MDS. So even if MDS does not progress to acute leukemia, we should treat it aggressively, because most patients unfortunately have complications from the cytopenia, such as infections, bleeding, complications of anemia.

In terms of the monitoring for progression to acute myeloid leukemia, there isn't a standard setup where you do that like what you do, for example, in solid tumors. Here, generally, we would monitor the patient based on the blood counts, so if the patient had responded to

an agent and then they started to drop their blood counts and they had worsening anemia, worsening thrombocytopenia, or worsening neutropenia, or if they start developing some peripheral blood blasts, I get concerned that the disease is accelerating. Other things I watch for, clearly, are changes in the symptoms of the patient, where the patient might be more fatigued or started to have constitutional symptoms such as night sweats or weight loss or other symptoms of worsening cytopenia, such as bleeding. But commonly, we pick up progression to acute myeloid leukemia on doing bone marrow biopsy. In a patient who's responding to treatment and doing well, I generally will not do bone marrows on a routine basis just to monitor, for example, as they do in solid tumors where they do CAT scans regularly. I will do the bone marrow usually when there's a change in the clinical status of the patient or if there is a worsening of their blood counts.

Dr. DeZern:
I do this very similarly, and, you know, something that you emphasized nicely is that a clinical change in the hemogram and the patient is what prompts the marrow. And I tend to do this as well, and as I'm watching for these clinical signs and symptoms, I'm trying to determine who's transplant eligible versus ineligible. It's a question we have to continuously ask ourselves, and, you know, some of the signs and symptoms of progression that you noted, like increased depth of cytopenias and transfusion burden or peripheral blasts, probably actually do not herald a patient transplant eligible at that time. We really want to ask ourself that question early on and make sure that the MDS patient with disease that has high-risk features sees a bone marrow transplant physician early on in their course to have a discussion. It doesn't mean that we've made the concrete decision to proceed with transplant, but we're asking ourselves if we should do HLA typing or if we should make sure that the patient and their family recognizes that transplant is the only potential path to cure in MDS. And the sooner the conversation is had at an expert transplant center, I think, the better all parties can view the lay of the clinical landscape for that individual patient.

So unfortunately, I feel like sometimes these patients don't meet a transplant physician until they have progressed to overt higher-risk disease, and then it's not necessarily possible. And so I like to consider the vast majority of patients potentially transplant eligible if they have high-risk disease that would warrant it from the beginning, and then we talk about patient-related factors, donor-related factors, conditioning-related factors, and then certainly disease-related factors. This includes some of the next-generation sequencing mutations, which might suggest that transplant could be a very favorable outcome, or an increased number of mutations might suggest we really must have very, very robust disease control to make the potential toxicities of transplant warranted in that setting. And I think there's a lot of things that go into this determination, but asking the question is a really important part of it.

Dr. Zeidan:
So this certainly has been a fascinating conversation, but before we wrap up, Dr. DeZern, can you share your take-home message with our audience?

Dr. DeZern:
There's so many good take-home points that you've made today, but I think the overarching theme in MDS in general is it's a very heterogenous disease. We must treat the patient and their symptoms that's in front of us, and we must constantly reassess to ensure that we address what issue is most pressing clinically for the individual MDS patient, be that anemia, be that unfortunate progression of their disease, or the need for a potentially curative transplant.

Dr. Zeidan:
And I would add to that is referrals for clinical trials is very, very important. We have a large number of very exciting drugs, both for higher-risk and lower-risk MDS, and I think the field is looking similar to how acute myeloid leukemia field looked a few years ago, when we had 9 drugs get approved within a span of 3 years. So I think the field is very exciting right now for patients with MDS, and despite having some reasonably active drugs right now, we clearly need to do more, so referring patients for clinical trials is very, very important.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Amy DeZern, for joining me and for sharing all your valuable insights. It was great speaking with you today.

Dr. DeZern:
I had a great time, too, Dr. Zeidan. Thanks for the opportunity.

Announcer:
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