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A New Light in Higher-Risk MDS: Emerging Treatment Options

**Announcer:**
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**Dr. Brunner:**
Patients with higher-risk myelodysplastic syndromes, or MDS, usually have a poorer prognosis due to the limited therapeutic options that are available. Hematopoietic stem cell transplantation is the only current curative approach for this disease, but many higher-risk patients may not be eligible or fit for that procedure. There is an increasingly understood need for both new and novel therapeutic advances in this disease to assist patients in not only living a longer life, but also enjoying an improved overall quality of life.

This is CME on ReachMD, and I’m Dr. Andrew Brunner.

**Dr. DeZern:**
And I’m Dr. Amy DeZern.

**Dr. Brunner:**
Let’s get started! As I just mentioned, for patients who have been classified as having higher-risk MDS, we often try to consider them for an allogeneic stem cell transplant, if that is a possibility for them, because it’s really the only curative therapy at this time for MDS. Dr. DeZern, how do you determine which of your patients are transplant eligible and whether some may not be?

**Dr. DeZern:**
So I think it’s a fantastic question at the bedside, and the first thing I’ll mention is that I don’t make a finite decision, certainly, upon meeting somebody at our initial clinic visit. I think it can be fluid. Certainly, there are patients that are in advance of 80 years, where we would really think that it doesn’t meet the metric you noted earlier of quality and quantity. But there is increasing data that age in and of itself simply is a chronologic number is not enough to concretely rule someone out, and those patients should be referred, even if they’re 75 years old. There’s also the HCT-CI – the Hematopoietic Cell Transplantation Comorbidity Index, and we do need to think about what other medical problems, medications, potential complications the patient could have to know if they’re a transplant candidate. Certainly, if somebody is lower risk when I meet them, this isn’t the main focus of our initial discussion. We may mention it, exactly as you did, about the potential path to cure, but we really spend much more time on it if somebody is high risk at presentation. And that’s part of why I mentioned it’s a fluid assessment, because if someone has excess blasts at the time that I meet them, I would like to take them to transplant, but we do need to reduce those blasts to less than 5% and hopefully improve their molecular genetics and their cytogenetics, where we can, to ensure a more positive transplant outcome.

Is there anything else, Dr. Brunner, that you take into consideration if you’re trying to determine if one of your patients is transplant eligible?

**Dr. Brunner:**
I think you bring up some excellent points, and that's often the same discussion I'm having with my patients.

**Dr. DeZern:**
So if you decide, based on that discussion, in your informed opinion that the patient is ineligible for transplant, what else can we do? Do you mind taking us through some of the novel and emerging therapies that are out there for our patients with MDS?

**Dr. Brunner:**
Absolutely. I think one of the big changes in the last 5-10 years and beyond in MDS is really being able to tailor a therapeutic goal for each patient. So there are a number of trials that are currently looking at ways that we can improve upon the chance of response, as well as once we achieve a response, can we improve upon that duration? Sometimes, these therapies are borrowed from other diseases, and one of the biggest developments in leukemia care in the recent years has been the finding that if you add a pill called venetoclax to azacitidine, you can enhance its activity in acute myeloid leukemia.

Now, MDS is distinct from acute myeloid leukemia in a number of ways but does share some overlapping features. Often, for instance, the mutation profile of patients who have MDS may have many similarities to patients who have so-called secondary acute myeloid leukemia or oligoblastic acute myeloid leukemia. And in that setting, we increasingly are exploring whether the same therapy that we use in AML, venetoclax combined with azacitidine, dosed at a slightly different regimen can also be effective in MDS. So there's currently a study looking at venetoclax combined with azacitidine compared to azacitidine alone in the phase 3 setting to determine whether what we've seen in AML translates to MDS. If you think about AML being 20% or higher blasts and MDS being less than 20% blasts, it makes sense that that's really a continuum. And so for people whose disease is bordering on AML, you wonder if they might get the same benefit of disease reduction using this combination.

So venetoclax is a BCL-2 inhibitor. It interacts with the apoptosis mechanism of cells. Apoptosis is the way that cells undergo programmed cell death. And when we look at the combination of azacitidine and venetoclax, early phase studies show that that response rate was nearly 80%, so the majority of patients who have a high blast count when you start, at least in these smaller studies so far, seem to really have a reduction in blasts and a reduction in disease burden in that regard. So even for patients who might be transplant eligible eventually or for who that conversation is not clear, there is some interest in looking at combinations such as venetoclax and azacitidine that might reduce the blast count.

One of our understandings of transplant is that transplant probably has some cellular effect – a graft versus leukemia effect – that allows people to stay in remission for longer, in addition to replacing their bone marrow with a new marrow. And so a number of therapies have looked at this so-called immunologic targets in MDS and AML and other myeloid cancers to try to identify is there a way that we can target the immune system to help prolong responses and control disease. Sabatolimab is an antibody that targets one of these immune checkpoints, TIM-3, which is expressed on immune cells and also on some of the blast cells in MDS or AML. And it's also being studied in a phase 3 setting, adding that antibody to standard azacitidine, to see, A, does it have increased activity for response rates, but also if we can get the immune system to recognize residual MDS cells. Do people live longer or have a longer duration of response to therapy than they would have with azacitidine alone? And so I think that both of these studies are looking at different aspects of MDS care that we really need to improve upon but which are still lacking.

You know, one of the other things that we are trying to do with MDS care is tailor it more effectively to each patient. And some of the targets that we see in AML can also be identified in MDS. So as AML has become a disease where we utilize increasingly targeted therapies, some of those do have a relevance in MDS. Perhaps the most commonly encountered, although still seen in a minority of patients, are mutations in IDH1 or IDH2. Whenever I see a patient, I make sure that they've had kind of complete mutation testing, because if they do happen to have a mutation in IDH1 or IDH2, that can be a treatment used at some point during their course. When to use it, we don't always know, but there is data of patients who've been treated with IDH inhibitors which are oral therapies that you can take daily, both in the up-front and in the relapsed refractory setting.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Andrew Brunner, and here with me today is Dr. Amy DeZern. We're just about to discuss the different novel and emerging therapeutic treatment options for patients with higher-risk MDS.

Dr. DeZern, are there any other emerging therapies that you would consider in the treatment of your patients with high-risk MDS?

**Dr. DeZern:**
Yes, it's a good question. I tell patients about the other 2 that are out in the world as well. The first is the ENHANCE trial, which is magrolimab in combination with azacitidine compared to azacitidine monotherapy for untreated patients. And it's an incredibly interesting drug, magrolimab. It's a first-in-class antibody that targets the macrophage checkpoint inhibitor CD47. And so the drug magrolimab selectively binds to CD47 that's expressed on the tumor cells, and it blocks that interaction with the signal protein, and some

people call this the “don’t eat me” signal, which is kind of a funny situation. But by blocking CD47 with magrolimab, macrophages, which do the eating in this situation, can go to the cancer cells and the MDS cells and be attacked. And so that’s how it can eliminate the disease burden in MDS.

Magrolimab actually has been shown to have utility across a lot of tumor types, but preclinical data show that the combination of magrolimab with a hypomethylating agent like azacitidine could really have rapid response and prolong survival. And what’s interesting is the combination is very well tolerated in early phase studies of myeloid malignancies, both MDS high risk as well as AML, and some people might say, “Oh, it’s, you know, this immune checkpoint issue,” but there have not been any significant immune-related adverse events that have been shown in the trial so far. These patients can have an early anemia that responds to transfusion, because CD47 is expressed on more mature erythroid cells as well, but aside from that, we’re still going to learn about some of the other things as more patients are treated with it.

The other phase 3 that’s currently going on would be called the SELECT-MDS study, which looks at a different compound altogether, tamibarotene, in combination with azacitidine compared to azacitidine monotherapy. It’s a pill like venetoclax is. And tamibarotene is a specific agonist for the retinoic acid receptor alpha [RARα] that binds to these retinoid receptors and can be given in combination with azacitidine, again with the goal of reducing blasts with limited toxicity. It’s the selective RARα agonist, as I’ve alluded to, and it’s shown to bind and then activate differentiation genes and enhance apoptosis in the malignant cells. So I’m really excited in the higher-risk MDS space for all the potential therapies and emerging treatments for these patients.

With all of these emerging treatment options, there’s still definitely room for improvement, Dr. Brunner. Can you explain why we need even more options for our higher-risk patients who are ineligible for stem cell transplant?

**Dr. Brunner:**
Absolutely. There are a number of things that, even if we have new options in MDS, will still come into play as we try to tailor our treatment plan. I might see a patient who’s older, with a number of comorbidities, and I worry about a side effect profile, even if that regimen is more active. I might also need to consider whether a patient has a specific plan B if this first option doesn’t work as well as we would like. You know, a great area of need is in relapsed and refractory MDS, where once a patient’s disease stops responding to that first line of therapy, we often are faced with very few options to try to get them new response and improve their disease.

And so one of the hopes is that after we see a number of these agents move through these frontline trials, is that we’ll actually have drugs that are active in the second or third line, that we’ll be able to move from an initial therapy strategy on to an active second-line strategy with our patients. I think that that’s where targeted therapies may play a role, and it’s also where tailoring a treatment to how a patient’s disease is behaving at that time, whether it might start out with excess blasts so we use an agent that more active at blast reduction, but later on blood counts may be a bigger problem, and perhaps we pivot our therapeutic strategy at that time. I hope that we have that kind of flexibility in the treatment in the future, and that’s really where we’ll need a number of trials to address those questions.

Dr. DeZern, is there anything that you’d like to add?

**Dr. DeZern:**
Well, I think you make some fantastic points, and I’ll just emphasize that as in much of medicine, but I think especially in MDS, expectation management from the beginning is really key, and it’s that initial planning with diagnosis, but then this is the trial we’re going to try first, or this is the therapy we’re going to attempt in the beginning, and to constantly re-evaluate how the individual patient is handling it, be it drug-drug interactions or performance status issues, and then also managing the expectation that these are not curative options outside of transplant, and we have to decide about those referrals and then what might be the second treatment or even the third.

**Dr. Brunner:**
I agree wholeheartedly. This has been a fantastic conversation, but before we wrap up, Dr. DeZern, can you share one take-home message with our audience?

**Dr. DeZern:**
Mainly just refer to clinical trials for our patients that are able.

**Dr. Brunner:**
Absolutely. And I do think we underutilize transplant referrals. I always encourage people to at least talk with somebody about transplant.

Unfortunately, that’s all the time we have today. I’d like 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:**

Thanks. It was great speaking to you, too. Goodbye, everyone.

**Announcer:**
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