Treatment Options for Low- and High-Risk Patients Based on the Prognostic Information Obtained

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Previously, we discussed your approach to diagnosis and risk assessment in patients with MDS. How do those prognostic findings translate into treatment decisions for patients with low-risk disease?

If they are asymptomatic, patients diagnosed with lower-risk myelodysplastic syndrome (MDS), as defined by the International Prognostic Scoring System (IPSS)[1] or the Revised International Prognostic Scoring System (IPSS-R),[2] can be observed until they have symptoms or disease progression. For symptomatic patients, the management approach depends on the underlying cytopenia.

Most patients present with an isolated anemia. If the hemoglobin is low enough (and/or the symptoms are significant enough), we would offer supportive transfusions as an option for patients. If the MDS harbors a deletion of del(5q), then one can offer them lenalidomide, which is an oral agent that is Food and Drug Administration (FDA) approved. If the serum erythropoietin (EPO) level is low, we can start erythropoietin-stimulating agent (ESA)-based therapy; however, if the serum EPO level is high, exogenous EPO will not likely be of benefit, and so in that setting then we can consider lenalidomide. We also have learned that patients with *SF3B1* mutations may not be as responsive to ESA-based therapy.

We have specific predictive algorithms that help us to predict whether or not a patient will respond to erythropoietin; the EPO level in the serum is one part of that equation, and the other part of that equation is how heavy their transfusion for PRBC (packed red blood cell) requirements are.[3]

Ultimately, patients can have progression despite getting erythropoietin, as erythropoietin does not modify the disease. About 30% of patients diagnosed with MDS have the presence of ring sideroblasts in the bone marrow aspirate, and for these cases where ESA therapy is no longer effective, then we recommend luspatercept (also can consider this if there is the presence of a *SF3B1* mutation and ring sideroblasts).[4] For other patients with MDS that do not have the presence of ring sideroblasts and for whom ESA-based therapy is no longer helping, one can consider the addition of lenalidomide for those patients. If the MDS is not responsive to these approaches, then initiation of hypomethylating agent (HMA) therapy to decrease transfusion dependence is often the next step.

There are other special cases/entities to consider. If a patient is diagnosed with a single-lineage dysplasia and an isolated thrombocytopenia, we would offer supportive transfusions for active bleeding and/or procedures. For those patients who are really struggling with blood blisters, bruising, or bleeding, aminocaproic acid may be an important agent to consider. For some of these patients, we can start another agent, such as eltrombopag or romiplostim, that works to boost the platelet count. It's not a disease-modifying treatment, but as long as the blast percentage is not elevated (less than 5%) in such patients, that would be a reasonable approach.[5]

Isolated neutropenia may occur in certain patients. In these cases, we need to rule out other etiologies such as cyclical neutropenia, large granular lymphocyte (LGL), paroxysmal nocturnal hemoglobinuria (PNH), and rheumatologic disorders such as lupus. There are no data to support the use of granulocyte colony stimulating factor (G-CSF) to boost white blood cell production, unless patients are truly struggling with repeated infections or ongoing problems related to infections. I try to remind our patients to make sure their vaccinations are up to date; that sometimes can be a struggle, but I think many patients recognize the importance of vaccines, particularly those who are at risk for pneumonias, shingles, and pertussis. For others with neutropenia, we typically will recommend patients to be on acyclovir and occasionally antibacterial prophylaxis if there have been prior bacterial infections. There's less data with regard to antifungal prophylaxis.

Ultimately, as the patient progresses beyond lower-risk disease, or in patients that have lower-risk MDS but really are very symptomatic, the initiation of HMA therapy can often help. There are no data at this point to substantiate that starting HMA therapy in earlier stages of low-risk disease improves overall survival. Again, what really drives those decisions are symptoms or other considerations such as transfusion dependence and/or concern of transition to high-risk MDS (mutations and/or blasts or progressive change in cytopenias).

All of these considerations are available in a treatment algorithm for low-risk disease that is available in the most recent American Society of Hematology (ASH) educational program.[6] I also think it's important to mention that clinical trials really should be part and parcel to any algorithm for patients with lower-risk MDS. With luspatercept, for example, we are trying to better understand whether we can use this agent in patients that have lower-risk MDS who are transfusion dependent, and even before ESA-based therapies.[7] There's a whole host of novel therapies that are emerging, even in lower-risk MDS patients, that are important to consider, and knowing what is available in the clinical trial space is essential.

How has the approach to HMA therapy selection changed with the introduction of an oral treatment option?

When we think about treatment of patients with higher-risk MDS, we are typically going to be pursuing an HMA-based therapy. We look to the studies such as the Cancer and Leukemia Group B (CALGB) from years ago that led to the FDA approval of azacitidine. The randomized, controlled trial demonstrated that compared to supportive therapy, HMA treatment reduced leukemic transformation risk, improved survival, and improved the quality of life for patients with the diagnosis of MDS.[8] Subsequently, the randomized, open-label phase 3 study by Fenaux and

colleagues demonstrated an overall survival in those higher-risk MDS patients who received azacitidine over those MDS patients who received conventional care regimen.[9]

Azacitidine is administered once a day for 7 days, and decitabine is administered once a day for 5 days. Both of these agents are (in general) thought to work similarly and are hypomethylating agents (chemotherapy). Our institution favors the use of azacitidine because the Fenaux study showed that azacitidine did improve overall survival for patients with MDS, whereas the other studies using decitabine were not able to replicate similar outcomes using similar clinical trial design. That being said, there is a lot of use of decitabine in our patient population with MDS, and now there is an oral version of decitabine. This oral tablet is a combination of both decitabine and cedazuridine and it is now approved by the FDA.[10] It is exciting for the MDS population to have an option of a pill rather than having to go to the clinic for IV or SC administration.

The pharmacokinetic exposure equivalence of this oral decitabine plus cedazuridine as compared to intravenous decitabine has been demonstrated.[11] I think there are some physicians who are not as enthusiastic to use the oral version as they would like to see more prospective data with this agent, but with more experience and the patient enthusiasm (due to the ease of administration) I suspect this will be embraced . Patients will need to have adequate insurance support so that they can access oral medications without an exorbitant cost. I think that will be a challenge for the future and is a key issue across all health care.

It could become very costly for some patients to pay out-of-pocket for these oral medications and we will be challenged by this for sure in the USA. If those medicines are not well-tolerated, compliance issues with those oral versions may also compromise outcomes. We're going to have to navigate that in an intentional way, and make sure that we're supporting our patients as best as possible, and the infrastructure for this will likely need to be improved. If they are having toxicities, they will need quick access to a touchpoint in clinic (nursing support, clinician support) and potentially have a fast track to come to the clinic for intravenous fluid or other supports.

What promising approaches are under study for the treatment of higher-risk MDS?

There is a tremendous amount of research underway trying to improve the outcomes for patients with higher-risk MDS. I'll mention two or three agents being actively investigated that are potentially going to be very relevant and may change the way that we treat high-risk MDS. Generally speaking, the idea is to use combination therapies with the hope that we can keep the disease under control for longer periods of time. I can't stress enough how important clinical trials are in the upfront (and relapsed setting) for patients with higher-risk MDS.

One of the novel combination therapies that I think is quite exciting is the combination of azacitidine and venetoclax, the oral BCL-2 inhibitor. In a phase 1b study presented at last years' ASH meeting, the combination was fairly well tolerated with manageable adverse events in patients with relapsed/refractory MDS, with a rate of complete remission (CR) plus marrow CR of 40% and an estimated 12-month overall survival (OS) of 65%.[12] The challenge with this combination is presence of cytopenias and toxicities that result from the low counts (ie, infections, febrile neutropenia, sepsis, bleeding, transfusion support), although I think we're

getting a handle on how best to manage this in the MDS patient population (and also there are considerations for dose modifications that need to be ironed out).

Another agent that is equally exciting is eprenetapopt (APR-246) is a novel small molecule therapy that restores wild-type p53 function in *TP53*-mutant cells.[13] Patients with *TP53*-mutant MDS often have a highly refractory disease such that even if the MDS goes into remission, the concern is that ultimately it will relapse within a short period of time. Agents such as eprenetapopt have been very exciting. In general, the overall response rates have been upwards of 80% and the CR rates for some of those patients have been higher than 50%, especially in the phase 2 studies. Recently, a phase 3 study of eprenetapopt and azacitidine versus azacitidine in *TP53*-mutant MDS did not meet its primary endpoint, which was disappointing. That was of course deflating, but I think this agent is still probably going to be very important for us to continue to explore and refine, and may be end up being quite relevant in our patients with a very aggressive type of MDS.

Another agent that's coming to the forefront in MDS is sabatolimab (MBG453), a humanized IgG4 (S228P) antibody that targets the TIM-3 receptor, which regulates adaptive and innate immune responses. The recent phase 1b study of sabatolimab in combination with HMAs had encouraging results with regard to the response rates and patient safety. Out of 35 patients with high-risk MDS, the overall response rate (ORR) was 62.9%, the estimated 6-month duration of response (DOR) was 90%, and sabatolimab was well-tolerated in combination with the HMA backbone.[14] A phase 3 study evaluating the combination of azacitidine and sabatolimab is ongoing.[15] There are a number of other TIM-3 inhibitors under development that may also lend themselves to better outcomes in patients with MDS.

How can prognostic data be used to help counsel patients or caregivers and set expectations for outcomes?

Prognostic data is important to share with patients. Patients often ask, “What will happen to me if I choose to do nothing?” I think some of the reason for that question is because people are fearful about the word “chemotherapy.” They may fear the impact not only on themselves with regard to toxicities, but also the impact on their loved ones. That's what people really care about: How much are you going to impact my quality of life, and how much are you going to make me depend on my loved ones/others? Are my kids going to need to leave work to help me? Am I going to lose my independence? Many patients are fiercely independent, and they want to stay independent for as long as possible.

Many of the MDS treatments that are available are well tolerated, and we've given them to patients that are in their 80s and 90s, but often those are also the people who are independently walking around and have a very good performance status. For others who are not doing as well, if their disease progresses quickly and their performance status is rapidly declining, that's a different story. The disease-modifying impact of chemotherapy can be incredibly meaningful to such patients that have had a decline in their performance status that is directly a result of their disease. It is important to get a good sense of how the patient is doing, and some of that information comes from the patient and from the family.

Ultimately, the prognostic scoring system has its limitations. We wish that those numbers mean that you could predict exactly what would happen to the individual patient in front of you, and that's just not the case. There are times where patients and caregivers can get very hung-up on the numbers and not realize that there's a lot of wiggle room for some patients that are outliers to that standardized data. I think those are the more challenging issues that we need to navigate as we talk about the data that we have, and what our thoughts are for that individual patient.

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