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https://reachmd.com/programs/cme/keeping-pace-with-hematologic-malignancies-understanding-classifying-and-stratifying-mds/13282/

Released: 03/31/2022
Valid until: 03/31/2023
Time needed to complete: 15 minutes

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Keeping Pace with Hematologic Malignancies: Understanding, Classifying, and Stratifying MDS

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Keeping Pace with Hematologic Malignancies: Understanding, Classifying, and Stratifying MDS” is provided by Prova Education.

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Dr. Sallman:
Myelodysplastic syndromes, or MDS, is considered to be a culmination of different hematologic malignancies associated with myeloid cells. It’s a clinically heterogeneous disease and the prognosis can range from months to years based on a patient’s age, mutational status, and concurrent comorbidities. In order to effectively treat the patient in front of us, we first need to classify their disease and to understand its risk stratification category, really personalizing it for each patient. We have a lot to discuss today.

This is CME on ReachMD, and I’m Dr. David Sallman. I’m from the Moffitt Cancer Center in Tampa, Florida. I’m an assistant member and currently the myeloid section head overseeing clinical trial research in the myeloid group.

Dr. Garcia:
Hi, and I’m Dr. Jacqueline Garcia. I’m one of the adult clinical investigators at Dana-Farber Cancer Institute in Boston, Massachusetts.

Dr. Sallman:
Let’s get started. So, upon identification of a patient with MDS, we need to categorize their disease based on a multitude of different factors. Dr. Garcia, can you walk us through this process and explain how different risk stratification levels affect outcomes and prognosis?

Dr. Garcia:
Absolutely. It’s such a great question. When we first meet patients at clinic, we really are leaning on our prognostic scoring systems to give us an idea of who’s going to do well, how is their disease going to behave, and what is the treatment recommendation that’s going to come out of this meeting? And so, the International Prognostic Scoring System, or IPSS, and the revised IPSS [IPSS-R] are the 2 most common accepted and validated scoring systems for estimating prognosis. There is yet to be a strong consensus for superiority of prognostic scoring models, and each has its own advantages and limitations.

So, let’s first look at the IPSS. It’s found easily online. There’s a great calculator, as well, and this focuses on scoring bone marrow blast percentage, karyotype, cytopenias, and divides patients into low, intermediate 1 – these are both lower-risk MDS diseases – and then intermediate 2 and high – these are higher-risk diseases. So, it divides patients into 4 types of categories. Historically, most of the phase 2 and 3 trials that have been published have used the IPSS to stratify patients as higher risk. And that was their gateway into entering into a higher-risk protocol. This does not incorporate any molecular mutations.

IPSS-R was subsequently developed and intended for use at diagnosis. And this involves more detailed cytogenetic abnormalities, more detailed severe cytopenias, and adds more weight to cytogenetics rather than blasts, and hence, with this more weight on

biological factors of disease, we see that it has provided more detail than potentially more prognostic scoring that is useful to clinicians, as well. The IPSS-R includes 5 categories that fall into very low risk, low risk, intermediate risk, high risk, and very high risk. Essentially, what it's done is it's allowed us to explore the intermediate risk group and really separate patients that behave more like a lower-risk type of disease versus the intermediate risk patients that really behave more like a higher-risk MDS disease. And so, we were really able to take that gray area and separate patients.

Patients with lower-risk disease, on average, can live for years or even, you know, even a decade, and their treatments are mostly based on palliation, focusing on red blood cell production, and really monitoring patients for signs of progression. The higher-risk group, on the other hand, tend to have excess blasts and have risk or higher risk of developing acute leukemia transformation, and those are the patients we want to be more aggressive with. And so having a clearer understanding of those with MDS where their prognosis is not going to be as robust as the lower risk, where we're talking of months and years before aggressive progression. We really need a handle on who these different groups of patients are and who we should be more aggressive with and what therapies they're eligible for.

One of the limitations of the assays, as I mentioned, is they were developed to be used at diagnosis, not necessarily at any time. So, they're not "dynamic," but many of us apply them in clinical practice at various times in patients' presentation just to get a sense of how a disease may be tracking. We also use, in clinical practice, genetic mutations, and in more recent data presented by Cleveland Clinic and Elsa Bernard using molecular risk stratification, there has been additional discrimination of prognosis compared to the historical IPSS and IPSS-R wherein the mutations were really able to really stratify patients that were higher risk and pull out some mutations like those in SF3B1 that might be able to predict a more favorable prognosis. So, using mutations has been incredibly helpful.

Dr. Sallman, is there anything else you take into consideration when diagnosing and stratifying your patients?

Dr. Sallman:
So, just to reiterate, it's absolutely critical, not only at baseline, but I would say dynamically over time to evaluate with a comprehensive next-gen sequencing panel. Those can range, again, anywhere typically now 40 to 50 genes, although some, for example, can be over 600 genes; we're going to continue to refine that. So, it's just really a key instrument that is required not only for prognosis but ideally really in treatment selection over time.

Dr. Garcia:
The diagnostic and treatment landscape in MDS is changing rapidly. In response, we must rely on the most up-to-date resources we have.

Dr. Sallman, can you give us a brief overview of the current prognostic scoring systems and updated evidence surrounding the new stratification tools?

Dr. Sallman:
I think one thing that we've had a challenge from is a lack of new therapies. But that has given us quite an extensive amount of time to further characterize prognosis in our patients, and really the major scope of this right now is trying to define, quote/unquote, who is higher risk. Higher-risk MDS patients that require therapies have a standard of hypomethylating agent therapy, that could be azacitidine or decitabine, and again to get approvals, you have to have specific cutoffs for patients. And so, we've heard from Dr. Garcia, the historical IPSS.

The first, it was actually some clinical changes. If you look at the IPSS-R group, several studies have looked at can you further refine that intermediate group, which again, 5 different classifications, and intermediate's kind of a red-headed stepchild. It sometimes gets lumped into lower risk; it sometimes gets lumped into higher risk. There are 2 ways to potentially clinically-stratify that. So, if a patient has a score of 3.4 or higher, and then we were a part of a publication with MD Anderson group where if patients were older, over the age of 66, packed red blood cell transfusion dependent or high circulating blasts, there's a score that could risk stratify into intermediate high versus intermediate low. But again, I think the real key is that numerous publications have looked at the impact of individual mutations. We really know SF3B1 is good; we really know that TP53 is bad. But then with a lot of the other genes it's a little bit controversial.

There have been several large initiatives to look at this. The first to describe would be actually a JCO publication by Drs. Nazha and colleagues from the Cleveland Clinic group; we were a part of this, as well. And it was around 1,500 MDS patients where there was comprehensive clinical and molecular data. There was a training cohort included with the MLL [Munich Leukemia Laboratory] group and then we were actually a validation cohort. And what was nice is that, not surprisingly, on top of clinical prognostic scoring systems, the addition of molecular variables did improve the c-index, or the overall concordance or better risk stratification of these patient groups. It was validated both in the setting of a prospective clinical trial, patients that went to transplant, patients on treatment.

And then really a multi-international group known as the IWG Molecular Committee, this was led by Dr. Bernard and colleagues and

was just presented in abstract form at ASH of 2021. This looked at almost 3,000 patients that had MDS. Very well put together cohort, extremely comprehensive, probably the most well done as far as the genetic variables that could be included. They were able to show that, again, the addition of molecular factors could either up- or down-stage patients. Now there will be 6 categories ranging from very low to very high. Again, the c-index did perform well across all of these. And I expect that we should see an online calculator as soon as this publication, and it should be similar to the MIPSS [mutation combined with revised international prognostic scoring system], where you would enter all your variables and ultimately get a prognosis readout for your patient.

There will still be some big questions. There will be a level of missingness, so not all centers will assess for all of the molecular factors. What was reported, again, in the presentation was that even with missingness, the prognostic tool was still variable. The one big question in my mind, though, is how are we going to use this? We already have 3 ongoing randomized phase 3 trials that are utilizing the IPSS-R. How will this help us? Is this just going to be a prognostic refinement or is this going to be our standard tool when we go for both lower-risk and higher-risk trials, I think, is a big question in my mind.

Dr. Garcia, what are your thoughts particularly around molecular prognostication in patients with MDS in your clinic?

Dr. Garcia:
You hit it right on the point. In the clinic, we're both incredibly fortunate to be at large leukemia centers, and we have the internal tools available to do our own NGS panel when patients arrive with a new diagnosis. And in clinical practice, we obtain these mutational profiles because we also see that the data and what we clinically see strongly suggests that the mutations matter. In clinical practice, we use this to help us stratify who we should refer to transplantation. And I look forward to seeing some more long-term data because I think we really recognize that even among the higher-risk patients, some of those high-risk patients are not as poorly prognostic as others; they behave more like an MDS and they less so transform to an AML, and we might be able to treat those patients slightly differently. So, I do look forward to more maturation of that data and applying these molecular tools.

Dr. Sallman:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. David Sallman, and here with me today is Dr. Jacqueline Garcia. We're just about to discuss the different MDS risk stratification tools and how they relate to a patient's prognosis.

Yeah, thank you for that really expert commentary. Really completely agree, and I think moving on to a related but slightly different topic, you know, challenges in higher-risk MDS related to age and comorbidities. So, of course, MDS is primarily diagnosed in older patients, you know, median age approaching 70 years of age, and they can present with many other chronic comorbidities. So, Dr. Garcia, how do these clinical variables impact treatment recommendation, especially for your higher-risk patients?

Dr. Garcia:
Yeah, I think you bring up a lot of good points. I guess I would say a few things. For any young patient that does present, you know, we're a little biased. We see patients after they're diagnosed or those that have suspicion for it. So I see many young patients that present with MDS, but you're absolutely right; the median age is in the 70s. So I would recommend that anyone that presents at a younger age, because they'll be living with the disease longer, have more complications, they should be referred to a tertiary care center. So that way, the role of transplantation could be considered and a potential genetic referral to look for any potential inherited leukemias.

For the standard older patient, for those that are higher risk, the recent BMT CTN [Blood and Marrow Transplant Clinical Trials Network] data that was initially presented at ASH 2020 and then later published in JCO in 2021 really demonstrated that for patients that have higher-risk MDS that are indeed eligible for transplantation, they should move to transplantation as soon as it becomes an option, as opposed to supportive care alone or treatment alone. And I think what is really important to drive home is that for those that see patients in clinical practice, most of those patients will be older, but transplantation still remains the only curative modality available. And many of the patients can be considered, especially if they meet higher-risk criteria.

And so in terms of the rest of the patients, while they're waiting for transplant or while they're being considered, the higher-risk treatment portfolio's really slim right now; it's primarily HMA [hypomethylating agent]-based, and we are really looking forward to the results from ongoing phase 3 studies, including azacitidine plus venetoclax, azacitidine plus sabatolimab, which is a TIM-3 inhibitor, and of course azacitidine plus magrolimab, a CD47 antibody. And so we're looking forward to seeing whether or not our frontline therapy will change and please look forward and keep your eyes peeled for that data over the next year or 2.

Dr. Sallman:
I do hope that we are going to improve the quality and depth of remission and actually really excited to see, with all of the novel combinations that Dr. Garcia mentioned, like, what are the data in patients that ultimately get to transplant? Are we truly finally improving long-term outcomes? How should we think about HMA, HMA-combinations for patients that are going there?

Well, this has certainly been a fascinating conversation, but maybe before we wrap up, Dr. Garcia, would you mind sharing one take-home message with our audience?

Dr. Garcia:
I would say one possible – please send mutational profile at baseline for patients to get a better sense yourself of how diseases may evolve over time and who you might need to refer on the sooner side for transplant care or clinical trials at a tertiary care center when it's appropriate. Stay tuned for ongoing phase 3 studies for high-risk MDS. And, you know, continue to see what we might be able to develop in terms of easy-to-use calculators or scoring systems that could be easily implemented into your clinical practice.

Dr. Sallman:
Well, that's great. But unfortunately, that's all the time we have today. So, I want to thank our audience for listening and thank you, Dr. Jacqueline Garcia, for joining me and for sharing your valuable insights. It was great speaking with you today.

Dr. Garcia:
Yeah. Thank you so much. This has been a really fun talk.

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