Chronic Anemia in MDS: Focus on Newer Strategies for ESA-refractory or Relapsed Patients

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For patients with MDS today, how significant is the burden of anemia?

Out of all the cytopenias, anemia is by far the most common in myelodysplastic syndromes (MDS), and particularly so for patients that have lower-risk disease. Anemia is also the cytopenia that most commonly drives the morbidities of the disease, which are typically fatigue, shortness of breath, dyspnea on exertion, and inability to perform daily normal activities, all of which impacts the patient's functional status over time.

Patients with MDS may experience a downward spiral that is often concordant with the degree of anemia. Patients with anemia also require frequent follow-up, with patients requiring blood as often as weekly or sometimes twice-weekly. Each transfusion typically takes 2 hours, so these patients may be spending a considerable amount of time in cancer centers just related to blood transfusion. These patients may require platelet transfusions, or have issues with infectious complications as well, but in general, anemia often may be the main or sometimes only issue in patients with lower-risk MDS. In patients with higher-risk MDS, addressing anemia is an important part of therapy; however, we have to think of other disease-modifying therapies as well.

What is typically your initial approach to the treatment of anemia related to MDS?

I think the first step is always asking the question: Is this patient symptomatic from their anemia? There's significant heterogeneity in that—some patients are quite sensitive at different hemoglobin (Hb) cut-offs, and other patients can be quite asymptomatic at very low Hb levels. So I think the first step is to dive in deeply in with the patient, and family members should also try to figure out whether or not they are symptomatic from their anemia.

When Hb levels are above 10 g/dl, we typically aren't as concerned, though I have had patients experience symptoms above that level. In general, when we're thinking about treatment, it is in patients that are less than 10 g/dl. Patients absolutely require blood if the Hb is less than 7 g/dl, and then there is a gray range of Hb levels between 7 g/dl and 9 g/dl in which therapy could be indicated depending on factors such as age, comorbidities, or clinical factors. In such cases, erythropoiesis stimulating agents (ESAs) are typically the first line of therapy, most commonly darbepoetin alfa, which is typically given every 3 weeks, or epoetin alfa, which is given weekly.

Response to ESAs is fairly predictable—if a patient has an erythropoietin (EPO) level greater than 500, that predicts a very low chance of response, so a lot of people say there's no reason to use it in that scenario. In patients that have an EPO level less than 100, response rates can be quite high, even in the 60% to 70% realm, and they can be durable for months to years. And then there's a gray range between 100 and 400 that is a little bit is dependent on the patient's transfusion burden. When the initial treatment is ESA therapy, we typically give it for at least 12 weeks to determine whether there is a response, and if no response is seen, then we are in the refractory setting and we need to think about other therapies.

However, all patients will eventually lose response to an ESA. There may be the very rare patient on ESA therapy for many years, say 5 years or more, but 95% of patients or more will be off treatment in less than 2 years, and the average time on therapy with a good response is probably around 1 year. Essentially, all patients are going to need other lines of treatment because ESA therapy does not change the natural history of the disease. The ESAs do not treat the underlying mutations of the disease—it's really a supportive care measure that eventually runs its course over time.

What is the current approach to treatment of anemia for patients who have failed ESAs?

If we look at the specific population of patients who have MDS with ring sideroblasts (MDS-RS)—which means that they either have greater than 15% ring sideroblasts on bone marrow biopsies, or they have at least higher than 5% ring sideroblasts and have a gene mutation known as splicing factor 3b subunit 1 (*SF3B1*)—once these patients are ESA-refractory or relapsed, then luspatercept would be indicated with the goal of improving anemia.[1,2]

Luspatercept, an erythroid maturation agent, leads to an improvement of Hb in 50% of patients, and about 40% of patients will achieve transfusion independence (TI).[2] These responses can be durable, on the order of a year or more, although some patients have been on luspatercept therapy for over 2 years.

The added side effect burden of luspatercept versus placebo in the randomized phase 3 trial is very minimal. There are a limited number of side effects, such as fatigue on the day of injection, so for most patients, it is quite well tolerated. Thus, it's very reasonable to use luspatercept in that setting—it is not a disease-modifying therapy, but patients can have durable responses, and biomarkers that may help predict which patients may have a response to treatment are being sought.

It's unclear whether or not luspatercept has any specificity to ring sideroblasts. The MDS-RS patient population was chosen for the phase 3 trial because they're almost always lower-risk MDS and have issues with anemia. So although the main indication of the drug is in patients with MDS with ring sideroblasts, there have been responses to luspatercept in phase 2 studies in lower-risk MDS patients without the finding of ring sideroblasts.[3] This has culminated with the randomized phase 3 COMMANDS trial,[1] which is comparing luspatercept versus ESAs as a frontline treatment for all patients that have lower-risk MDS and anemia. This trial is accruing internationally and may change the frontline standard of care for lower-risk MDS patients.

Lenalidomide is the standard of care for MDS patients with deletion 5q [del(5q)].[4] We would consider lenalidomide ahead of luspatercept in the rare del(5q) patient that also has ring sideroblasts because it is disease-modifying. Separately, lenalidomide, particularly if used in combination with ESA therapy, does lead to TI at levels in the upper 30-percentile range. This is based in part on phase 3 data from the randomized phase 3 ECOG-ACRIN trial[5] showing that the combination of lenalidomide and epoetin alfa had a higher response rate compared to epoetin alfa alone in a lower-risk MDS population who were refractory to recombinant human erythropoietin (rHu-EPO). These responses are probably at least as durable as those responses for luspatercept. Although lenalidomide is on-label only for MDS patients with del(5q), this therapy, with or without ESAs, is utilized frequently in the US given lack of alternative therapies.

Lastly, a majority of US patients with transfusion-dependent MDS will ultimately receive the hypomethylating agents (HMAs) azacitidine or decitabine.[6] There is clear activity—about half of all patients can achieve a response, and levels of true TI are again in the 30- to 40-percentile range. However, HMAs haven't been shown to be disease-modifying, and if patients treated with HMAs lose response or fail to respond, the disease behaves much more like higher-risk disease. So I would say that, as a field, we're trying to delay HMA monotherapy longer and longer, and to use other therapies before that for our patients.[7] Potentially, novel HMA combination therapies which have shown promise in higher-risk MDS will also have more disease modifying activity in lower-risk MDS patients, although safety will be even more paramount in the lower-risk cohort.

How do you apply these findings and observations in clinical practice?

Practically speaking, if anemia is the main issue we're trying to mitigate, then of course supportive care is important, and we think about ESAs upfront. For patients with MDS and ring sideroblasts, we use luspatercept after ESA therapy. We do consider lenalidomide with ESA for non-ring sideroblast MDS patients, and of course for patients with del(5q) MDS. Beyond that, I highly favor clinical investigational agents or novel HMA combinations prior to HMA therapy. The paradigm in the US for a long time has been to use HMAs because they have been one of the only options available for so long, and so a high percentage of patients in the community are getting this therapy. We're really recommending against doing that. Ideally, these patients would get a second opinion at an expert center so that other therapies can be considered that may improve their quality of life (QoL) and transfusion burden, without having the potential

toxicity and possible disease changes that may develop as a result of using HMAs as monotherapy.

What are some of the more promising novel approaches under investigation for the treatment of MDS?

One of the agents that's the farthest along is imetelstat, which is a first-in-class telomerase inhibitor. In the earlier non-randomized portion of the IMerge trial, a high percentage of patients achieved TI on imetelstat treatment, and responses appeared to be particularly durable.[8] This has now gone into the randomized portion of the IMerge study, which is a 2:1 randomization of imetelstat versus placebo, with the primary endpoint being achievement of TI in this patient population.[9]

Along those lines, we are learning a lot more about the underlying drivers of disease pathogenesis, particularly for low-risk MDS patients. There is a complex pathway of pyroptosis or inflammasome activation that is ultimately an inflammatory form of cell death that drives the low blood counts in MDS. It has been shown by multiple groups that if these pathways can be blocked, effective hematopoiesis can be restored.[10] Investigations are continuing that involve the targeting of several steps in this pathway, including the most important end cytokine of this pathway, interleukin-1 beta (IL-1β). We and a couple of other centers will be evaluating canakinumab, an anti-IL-1β monoclonal antibody that is approved for the treatment of a range of periodic fever syndromes.[11] Central to the pathogenesis of this pathway is the nucleotide oligomerization domain (NOD)-like receptor protein-3 (NLRP3) inflammasome,[10] so there are a number of NLRP3-specific inhibitors that are going to enter clinical investigations in MDS.

Another important emerging target is IL-1 receptor associated kinase 4 (IRAK4). Promising phase 1 data on the IRAK4 inhibitor CA-4948 in patients with relapsed or refractory acute myeloid leukemia (AML) or MDS was presented by Dr. Guillermo Garcia-Manero at the ASH meeting[12]; these were higher-risk patients, but we would hypothesize that CA-4948 could also have benefit in low-risk MDS.

Lastly, there are a number of novel HMA doublets that may change the frontline standard of care for patients with high-risk MDS, such as azacitidine with magrolimab,[13] azacitidine with pevonedistat,[14] and azacitidine with sabatolimab.[15] We know that these drugs are synergistic, so if a doublet is tolerable in patients with low-risk MDS, then I think these will be very interesting to investigate further in the near future.

You presented phase 1b results for the combination of magrolimab and azacitidine at the 2019 ASH conference.[16] What are the latest findings for this and other HMA combinations?

The magrolimab and azacitidine doublet does have FDA breakthrough designation now for patients with high-risk MDS. The data, as recently presented, have shown the majority of patients, over 70%, responding, with a true complete remission rate above 40%, and the responses appear to be rapid and durable.[17] That trial is continuing to read out. There is also a randomized phase 3 trial called the ENHANCE study[14] that has been initiated, which is evaluating the combination of magrolimab and azacitidine versus azacitidine therapy alone for patients with high-risk MDS.

Also, far along in development is the combination of the NEDD8-activating enzyme inhibitor pevonedistat and azacitidine.[18]A phase 3 trial with the primary endpoint of event-free survival has been completed[19] and we are all eagerly awaiting the results. Similar to what was seen with magrolimab and azacitidine, the combination of pevonedistat and azacitidine shows synergistic activity, with the majority of patients responding and 40% to 50% of patients having true complete remissions and durable responses among patients with MDS. I think if that trial reads positive, it would support the approval of the medication.

The other combination that is exciting, but has had a setback, is azacitidine with the mutant p53 reactivator eprenetapopt (APR-246) for the treatment of *TP53*-mutant MDS.[22] The data have shown very nice synergism, both in a US trial[20] as well as in the Groupe Francophones des Myélodypsplasies (GFM) parallel trial.[21] However, the primary endpoint of complete remission was not met in the phase 3 study, according to a press release issued in December 2020, although responses were higher in the combination group as compared to azacitidine alone. The trial is ongoing, however, and future presentations may help us understand this combination better in the phase 3 trial setting.

There are other doublets showing responses. Probably the furthest along is the combination of sabatolimab, which is a TIM-3 inhibitor, with azacitidine. Recently presented results of a phase 1b study also showed promising activity and durability of responses for this HMA combination.[22]

What advances are you most looking forward to over the next few years with regard to the treatment of MDS?

I think we are actively making major advances in achieving transfusion independence and decreased transfusion burden in low-risk MDS patients that have anemia. What we really need to do, and what I'm hopeful for, is to change the natural history of this disease. We want to be able to treat patients with pancytopenia or other cytopenias, we want to be able to decrease their risk for ultimately transforming to high-risk MDS or AML, and of course, we ultimately hope this will lead to an improvement in overall survival and associated QoL improvements. If we can fundamentally target the underlying drivers of this disease, either through targeting inflammatory pathways, or maybe in rare patients through targetable mutations such as IDH1 or IDH2, then ideally we can change the natural history of the disease in these patients.

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REFERENCES

1. Efficacy and safety study of luspatercept (ACE-536) versus epoetin alfa for the treatment of anemia due to IPSS-R very low, low or intermediate risk myelodysplastic syndromes (MDS) in ESA naïve subjects who require red blood cell transfusions - full text view - clinicaltrials.gov. Accessed March 17, 2021. https://clinicaltrials.gov/ct2/show/NCT03682536

2. Della Porta M, Platzbecker U, Santini V, et al. The commands trial: A phase 3 study of the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anemia due to IPSS-R very low-, low-, or intermediate-risk MDS in erythropoiesis stimulating agent-naive patients who require RBC transfusions. *Blood*. 2020;136(Supplement 1):1-2. Accessed March, 16,2021. doi:10.1182/blood-2020-140284.

3. Platzbecker U, Germing U, Götze KS, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): A multicentre, open-label phase 2 dose-finding study with long-term extension study. *Lancet Oncology*. 2017;18(10):1338-1347. Accessed March 15, 2021. doi:10.1016/S1470-2045(17)30615-0

4. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med*. 2006;355(14):1456-1465. Accessed March 14, 2021. doi:10.1056/NEJMoa061292

5. List AF, Sun Z, Verma A, et al. Combined treatment with lenalidomide and epoetin alfa leads to durable responses in patients with EPO-refractory, lower risk non-deletion 5q [del(5q)] MDS: Final results of the E2905 Intergroup Phase III Study - an ECOG-ACRIN Cancer Research Group study, Grant CA180820, and the National Cancer Institute of the National Institutes of Health. *Blood*. 2019;134(Supplement_1):842-842. Accessed March 15, 2021. doi:10.1182/blood-2019-127274

6. Madanat Y, Sekeres MA. Optimizing the use of hypomethylating agents in myelodysplastic syndromes: Selecting the candidate, predicting the response, and enhancing the activity. *Semin Hematol*. 2017;54(3):147-153. Accessed March 15, 2021. doi:10.1053/j.seminhematol.2017.06.001

7. Germing U, Oliva EN, Hiwase D, Almeida A. Treatment of Anemia in Transfusion-Dependent and Non-Transfusion-Dependent Lower-Risk MDS: Current and Emerging Strategies. *Hemasphere*. 2019;3(6):e314. Published 2019 Oct 30. Accessed March 16, 2021. doi:10.1097/HS9.0000000000000314

8. IMerge: Phase 2/3 Clinical Trial to Evaluate Imetelstat in Transfusion-Dependent Participants With Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) That is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment. Accessed March 21, 2021. https://www.geron.com/patients/imerge-study/

9. Geron Corporation. A Study to Evaluate Imetelstat (Grn163l) in Transfusion-Dependent Subjects with Ipss Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) That Is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment. clinicaltrials.gov; 2021. Accessed March 16, 2021. https://clinicaltrials.gov/ct2/show/NCT02598661

10. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 inflammasome: An overview of mechanisms of activation and regulation. *Int J Mol Sci.* 2019;20(13):3328. Accessed March 15, 2021. doi:10.3390/ijms20133328

11. MD Anderson Cancer Center. Phase 2, Open-Label, Study of Subcutaneous Canakinumab, an Anti-Il-1b Human Monoclonal Antibody, for Patients with Low or Int-1 Risk IPSS/IPSS-R Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia. clinicaltrials.gov; 2020. Accessed March 16, 2021. https://clinicaltrials.gov/ct2/show/NCT04239157

12. Garcia-Manero G. A phase 1, open label dose escalation trial evaluating the safety, pharmacokinetics, pharmacodynamics, and clinical activity of orally administered CA-4948 in patients with acute myelogenous leukemia or myelodysplastic syndrome. In: ASH; 2020. Accessed March 17, 2021. https://ash.confex.com/ash/2020/webprogram/Paper140889.html

13. Gilead Sciences. Enhance: A Randomized, Double-Blind, Multicenter Study Comparing Magrolimab in Combination with Azacitidine versus Azacitidine plus Placebo in Treatment-Naïve Patients with Higher Risk Myelodysplastic Syndrome. clinicaltrials.gov; 2021. Accessed March 16, 2021. https://clinicaltrials.gov/ct2/show/NCT04313881

14. Millennium Pharmaceuticals, Inc. A Phase 1b, Open-Label, Dose-Escalation Study of MLN4924 plus Azacitidine in Treatment-Naïve Patients with Acute Myelogenous Leukemia Who Are 60 Years or Older. clinicaltrials.gov; 2020. Accessed March 16, 2021. https://clinicaltrials.gov/ct2/show/NCT01814826

15. Novartis Pharmaceuticals. A Randomized, Double-Blind, Placebo-Controlled Phase III Multi-Center Study of Azacitidine with or without MBG453 for the Treatment of Patients with Intermediate, High or Very High Risk Myelodysplastic Syndrome (MDS) as per IPSS-R, or Chronic Myelomonocytic Leukemia-2 (CMML-2). clinicaltrials.gov; 2021. Accessed March 16, 2021. https://clinicaltrials.gov/ct2/show/NCT04266301

16. CD47 antibody magrolimab in combination with azacitidine effective in MDS and AML patients. Moffitt Cancer Center. Accessed March 17, 2021. https://moffitt.org/for-healthcare-professionals/clinical-perspectives/clinical-perspectives-story-archive/cd47-antibody-magrolimab-in-combination-with-azacitidine-effective-in-mds-and-aml-patients/

17. Sallman DA, Asch AS, Kambhampati S, et al. The First-in-Class Anti-CD47 Antibody Magrolimab Combined with Azacitidine Is Well-Tolerated and Effective in AML Patients: Phase 1b Results. Presented at: 62nd ASH Annual Meeting and Exposition, December 5-8, 2020. Abstract 330. Accessed March 21, 2021. https://ash.confex.com/ash/2020/webprogram/Paper134728.html

18. Swords RT, Coutre S, Maris MB, et al. Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML. *Blood*. 2018;131(13):1415-1424. Accessed March 14, 2021. doi:10.1182/blood-2017-09-80589

19. Sekeres MA, Watts AM, Radinoff A, et al. Efficacy and Safety of Pevonedistat Plus Azacitidine Vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes (MDS) from Study P-2001 (NCT02610777). Presented at: 62nd ASH Annual Meeting and Exposition, December 5-8, 2020. Abstract 637. Accessed March 21, 2021. https://ash.confex.com/ash/2020/webprogram/Paper135840.html

20. Sallman DA, DeZern AE, Garcia-Manero G, et al. Eprenetapopt (APR-246) and Azacitidine in TP53-Mutant Myelodysplastic Syndromes [published online ahead of print, 2021 Jan 15]. *J Clin Oncol.* 2021;JCO2002341. doi:10.1200/JCO.20.02341

21. Groupe Francophone des Myelodysplasies. A Phase 1b/2 Study to Evaluate the Safety and Efficacy of APR-246 in Combination with Azacitidine for the Treatment of Mutation Tp53 (Tp53) Mutant Myeloid Neoplasms. clinicaltrials.gov; 2020. Accessed March 16, 2021. https://clinicaltrials.gov/ct2/show/NCT03588078

22. Brunner AM, Esteve J, Porkka K, et al. Efficacy and Safety of Sabatolimab (MBG453) in Combination with Hypomethylating Agents (HMAs) in Patients with Acute Myeloid Leukemia (AML) and High-Risk Myelodysplastic Syndrome (HR-MDS): Updated Results from a Phase 1b Study. Presented at: 62nd ASH Annual Meeting and Exposition, December 5-8, 2020. Abstract 657. Accessed March 21, 2021. https://ash.confex.com/ash/2020/webprogram/Paper136855.html

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