

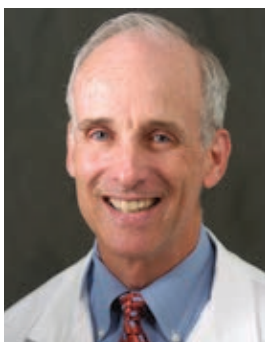
Myelodysplastic syndromes: etiologies, evaluation, and therapy

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DR HENRY [DH] It is my pleasure to interview Dr David Steensma, who is at the Dana-Farber Cancer Institute in Boston, where he is also an associate professor at the Harvard Medical School. Today we're going to talk about myelodysplastic syndromes [MDS], about which Dr Steensma has written and spoken as an expert. David, welcome to this interview.



DR STEENSMA [DS] Thanks, David. I'm glad to be here.

DH I thought perhaps the best thing for our listeners and readers might be for you to first define myelodysplasia, or MDS.

DS MDS are marrow failure syndromes in that they present with cytopenias due to the ineffective production of blood cells by the marrow. They are also neoplasms: they're clonal disorders, they are unstable and tend to evolve over time toward worsening marrow failure and acute myeloid leukemia. Those two things together really encompass the essence of MDS. There's some quibbling around the edges about just what is and is not MDS, especially with respect to older people who have mild cytopenias and have clonal mutations, but may not have other evidence of MDS, such as extensive dysplasia or excess blasts. Do those patients have MDS



or not? We're still trying to sort that out, where the boundaries are, and we can talk about that more in a few moments. Those are really the essentials of MDS: cytopenias, a clonal disorder, and currently it's diagnosed primarily by clinical picture and morphology – the finding of either extensive dysplasia or increased blasts in a patient with meaningful cytopenias.

DH In my practice, as I'm seeing patients who are living longer and getting older, we're seeing an uptick in the incidence of this as our population ages.

DS I think so, and it's hard to recognize – or tease out – whether that is in part because of increased recognition of MDS, ... as well as the population aging, or if there is a true increase in MDS incidence. We're also seeing more patients survive longer after treatment for other cancers, and we know the treatments that patients receive for other cancers – with radiation or with certain cytotoxic agents, – can be DNA damaging. It can lead, some years down the road, to development of MDS. As people are more likely to survive breast cancer or non-Hodgkin lymphoma or other neoplasms, the incidence of therapy-related MDS is rising.

DH I want to move to something I thought was interesting at the 2015 American Society of Hematology [ASH] Annual Meeting in Orlando, where there was an educational session on MDS. They mentioned the revision of the World Health Organization [WHO] classification of tumors of the hematopoietic and lymphoid tissues ... Here we are 8 months later. Anything you could discuss about where we are with this new edition of the WHO classification?

DS Yes, the WHO classification was last revised in 2008, and the proposal has been put forward to make some additional changes to all of the myeloid

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disorders classifications [online Table 1].¹ That includes acute myeloid leukemia [AML], where the most important changes have been made, myeloproliferative neoplasms, and MDS.

The changes in MDS in the 2016 WHO proposal are really pretty minor. One of them is the loss of the old term, *refractory anemia*, which has been with us since a paper was published in 1938 about anemia that was refractory to liver therapy and to iron – obviously, that included a very heterogeneous group of patients.² That refractory anemia term eventually got adapted by the MDS community, but it's a little bit misleading. Many patients with MDS, of course, don't have anemia or their anemia is not truly refractory, so those terms are now going away. If we have a patient with MDS with 12% blasts, we'll call him MDS with excess blasts, instead of refractory anemia with excess blasts. A minor terminology thing, but I think a step into the modern era.

The other change is incorporation of the finding that many patients with ring sideroblasts have mutations in *SF3B1*, a splicing factor. The previous threshold for defining MDS with ring sideroblasts, of finding at least 15% ring sideroblasts among erythroid precursors, was somewhat arbitrary.

The new definition of MDS with ring sideroblasts was that, yes, you can get there by having 15% or more ring sideroblasts, but you can also get there if you have fewer ring sideroblasts as long as you have the *SF3B1* mutation. That *SF3B1* mutation is the one mutation that we know about associated with MDS that implies a more indolent or benign natural history; all the other mutations described and associated with MDS are either neutral or bad. *SF3B1* is the one more favorable one. That's where the prognostic part comes in.

DH That's on a bone marrow specimen not blood, and is it a cytogenetic? How is that ordered?

DS That's a molecular genetic test, so you usually have to do it by a next-generation sequencing panel. Many institutions have incorporated that testing into their routine hematopathology workflow when MDS is suspected, but it is also orderable by a number of reference labs as a stand-alone test. It turns out that you don't need to do the test on marrow, you can do the molecular genetic test on blood and it is almost as sensitive as in marrow. Most of the circulating cells in MDS patients are clonal cells, and they bear the same mutations that the marrow does. When we've correlated one with another, the marrow and blood mutation profiles are virtually identical.

DH That's really helpful. More and more, I see in my practice that we can do tests on blood, we don't necessarily have to do [them] on the marrow, and this works in solid tumors as well.

DS It is a very welcome development, isn't it?

DH Absolutely, it saves us a lot of biopsies. We move

next to the diagnostic and prognostic systems. We've often talked about the International Prognostic Scoring System [IPSS] or the Revised International Prognostic Scoring System [IPSS-R]. Could you elaborate on that?

DS For a number of years the most widely used prognostic scoring system in MDS has been the 1997 IPSS, developed by Peter Greenberg and colleagues. That was based on about 800 patients with de novo MDS, most of whom just got supportive care, and it had 4 different risk groups with quite distinct clinical outcomes – the lowest-risk patients living more than 5 years, the highest risk with median survival of less than a year. That was based on a relatively small number of patients, and it was problematic because it didn't reflect the broad range of chromosome findings in MDS, it didn't have any sensitivity to the severity of cytopenias, just whether there were zero, one, two, or three cytopenias.

A major international effort, starting in about 2008, began in order to come up with a new prognostic scoring system. The result was the IPSS-R, which was published in 2012 [online Table 2 and Table 3].³ The IPSS-R is based on more than 7000 patients from 10 different countries and combines almost 20 different data sets. Again, it's only valid at the time of diagnosis, and only in adult patients. Most of the patients in the IPSS-R series got supportive care only. While IPSS-R is not perfect, it is definitely an improvement in some respects on the original IPSS. There are 5 risk groups in IPSS-R, it includes a much broader range of cytogenetics, and it's sensitive to the severity of cytopenias so that it treats someone with a platelet count of 9,000 differently from somebody with a platelet count of 99,000.

The IPSS-R is a step forward. The next step – and this is ongoing – is to incorporate molecular testing results into the IPSS. At the 2016 ASH annual meeting in December, we'll see a proposal describing some of the initial results. There are clearly four or five mutations that are IPSS or IPSS-R independent.

DH You've already mentioned *SF3B1*. Maybe you could mention the *TET2*, *DNMT3A*, and *ASXL1*. Are they good or bad, and are those also next-generation molecular testing?

DS All of these are next-generation molecular testing, and one does get those specific gene results in most of the panels that are institutionally generated or commercially available for MDS. In the first cut of the multivariable survival model with genotyping data from the first 2,000 patients, there were 4 bad actors – mutated genes that, if present, have an IPSS-R independent negative prognostic value. One of them, not surprisingly, is *TP53*. *TP53* mutations and deletions are bad across oncology and all sorts of different tumor types, and MDS is no exception. Those patients tend to do very poorly even if they get transplanted.

The other 3 are *RUNX1*, which encodes a transcription

factor; *EZH2*, which encodes a histone methyltransferase; and *NRAS*. Those findings are likely to be reflected in the final IPSS-RM, which is the revised IPSS with molecular data that is currently in development.

DH Very interesting. Do you think that will be discussed at this year's ASH?

DS It should be. It may not yet be the final version that will be discussed, but there will definitely be an update. Many of the other mutations, including some of the ones that you mentioned, like *DNMT3A*, don't seem to have an overall prognostic value that is independent of the IPSS-R. It's always worse to have a mutation in MDS than to not have a mutation – with the exception of *SF3B1* – but *DNMT3A*, perhaps just because it's so common across all different IPSS risk groups, does not fall out as an independent predictor.

DH In my practice, many of our primary care colleagues will send us a small monoclonal protein and ask, 'Is it myeloma? Is this the monoclonal gammopathy of unknown significance [MGUS]?' It seems to have a correlate in the MDS world that maybe some of us, as we get older, are developing clonal hematopoiesis of indeterminate potential [CHIP]. I look at the definition of CHIP, I guess the correlate for the MDS, and some of this may be just a pre-MDS event that never happens. How would you discuss or describe this CHIP phenomenon that we sometimes see, especially in our seniors?

DS We've long known, as you said, about MGUS, and monoclonal B-cell lymphocytosis that never becomes myeloma or chronic lymphocytic leukemia [CLL]. CHIP is effectively the myeloid equivalent of that, though not all the CHIP mutations are associated with myeloid neoplasms, some are lymphoid instead. What we've found from large genome-wide association studies, is that a very substantial proportion of the older population have acquired somatic mutations in genes that are associated with hematologic malignancies, but don't meet criteria for those malignancies. They may not have cytopenias at all, or they may have only very mild cytopenias and no dysplasia, no increase in blasts. By age 70, 10% of the population has one of these CHIP mutations.

DH Really?

DS It's really high, isn't it?

DH Yes.

DS By age 100, it's about 35%. It's probably like prostate cancer; it's just something that evolves and is really common with aging, but isn't always clinically meaningful.

There are several reasons that is clinically important. The first, if we have somebody who has a mild cytopenia and they don't meet criteria for MDS, and someone sends

off a mutation test and it comes back with a *DNMT3A* mutation as a sole mutation, we don't know if that is just somebody who has a clonal mutation and that's not why their blood counts are a little low, or if this an MDS that's about to develop. The rate of developing MDS for this scenario seems to be about 0.5%-1% per year, so about the same order of magnitude of MGUS becoming myeloma or another disorder. It doesn't always go to MDS. Sometimes it becomes a myeloproliferative neoplasm. Sometimes it becomes AML directly. Occasionally – rare, but occasionally – it will become a lymphoid neoplasm. We had to come up with a name for this state, and we called it CHIP.

The other two scenarios clinically where this is meaningful is in somebody who has a staging marrow that's done for, let's say, myeloma or non-Hodgkin lymphoma, and somebody sends off one of these genotype panels looking for lymphoma-associated genes. Then you get things you weren't looking for, *SF3B1* or *U2AF1*, things that are MDS associated genes, but there's no evidence of MDS.

Then finally, in our older donors for bone marrow transplant, let's say we have a 65-year-old man who is going to have a bone marrow transplant, and his 67-year-old sister is a human leukocyte antigen [HLA] match and signed up to be a donor. If she has one of these mutations, these CHIP mutations, that may make her a less-than-ideal donor. There may be a higher likelihood of post-transplant MDS or AML in that population if someone with CHIP is a donor. These are some of the very practical things that we're facing in this new era of molecular testing.

DH Fascinating. I would then take that to mean for the busy clinician that if you are thinking MDS, use the IPSS-R and/or the new WHO criteria to diagnose MDS first before you worry about next-generation molecular sequencing that might determine a CHIP in someone's peripheral blood.

DS Correct.

DH Alright, great. Then I wanted to move on to therapy. You've diagnosed MDS, and in the ASH and American Society of Clinical Oncology meetings we are certainly waiting to hear that there are some better therapies, but I think thus far we have the hypomethylating agents [HMAs] – azacitidine, decitabine, and then the immunomodulatory drug, lenalidomide. Can you discuss their use in MDS?

DS Those are the 3 US Food and Drug Administration approved drugs – azacitidine and decitabine, which are quite similar DNA HMAs, which get used mostly in higher-risk patients, and where azacitidine is the only drug that has shown a survival advantage compared with conventional care. Those data are limited to high-risk patients. We don't know that HMAs help lower-risk patients live longer. Then

lenalidomide works best in lower-risk patients with chromosome 5q deletions, but has some utility in lower-risk patients with non-del[5q], especially normal karyotype patients where the platelet count is still preserved [online Figure 1].⁴

The drug class that is used most commonly in MDS, but doesn't have a specific FDA-approved label for MDS, are the erythropoiesis stimulating agents [ESAs]. Unlike the solid tumor world where there's a lot of concern about survival and tumor progression in patients treated with ESAs, we've never seen that in MDS. In fact, comparisons of treated and untreated patients suggest that the treated MDS patients with ESAs do a little bit better, and there's no suggestion of increased leukemia progression. Some of the safety concerns that we think about with ESAs in the solid tumor world may not apply to MDS. In most series, ESAs are the most commonly used drugs for MDS.

ESAs don't work very well if the patient's endogenous serum erythropoietin level is greater than 500 U/L. In that case, the kidney is already doing as much as it can, working as hard as it can, and we can't really supplement that pharmacologically.

That's about it for approved therapies. I think that there are some real unmet needs, and we can talk about what those are in a minute.

DH You anticipated one of my questions, the growth factors. The ESAs you discussed very well, and off-label use of the thrombopoietins [TPOs], which seem to be a little more stem cell active than just influencing platelets. I've seen TPO tried off-label in my practice to try and stimulate a bone marrow for any of the 3 cell lines, especially the anemia, with a little worry that you might take a high-risk MDS and convert to leukemia. Any comment on TPOs off-label in MDS?

DS Yes, we're certainly seeing an increased use of these agents, eltrombopag and romiplostim. I use them from time to time for patients with MDS in my own practice. It is true that sometimes there are responses in other lineages besides just the platelets. It seems to be more common to see responses in other lineages with eltrombopag than with romiplostim, or at least it is better studied there. We don't entirely understand it, but occasionally one does see an anemia improvement or a neutrophil improvement in a patient treated with eltrombopag.

There are some patients with MDS who also have idiopathic thrombocytopenia purpura, so these agents may be particularly helpful in the patient whose platelet count is low out of proportion to the other cytopenias, because they may have a slightly different pathophysiology. The caution with these agents is that there are blast cells in some patients that have functional TPO receptors, and these agents certainly can stimulate growth of an immature cell population. For the most part, when you see that blast increase and then stop the TPO agonist, those cells revert to where they were before, but it is a very concerning thing to see.

I tend to use these drugs most commonly in my practice for the patient who is platelet transfusion dependent, where we're just really struggling with transfusing them with platelets – for example, somebody who is allo-immunized and who is coming in multiple times per week for platelets, and still having minor hemorrhage. In that case, I'm willing to sort of bite the bullet on a blast risk and use a TPO agonist even though, yes, their blasts may increase from 6% to 18%. I would almost rather have that increase in blasts than have them bleed to death.

These TPO agonist drugs will probably never be approved for MDS, partly because a few years ago a romiplostim study – the randomized study that was going for registration – was stopped early because of an excess of progression in patients who were getting the study drug. There is a randomized study of eltrombopag still ongoing in Europe.

DH To continue with that anemia theme, I've actually had a patient or two on some new developing drugs – lus-patercept, so-called ACE-536; sotatercept, ACE-011. Any thoughts that those might in certain patients be useful to decrease the transfusion requirement?

DS This class of agents certainly is quite interesting. The one that is being developed in MDS is luspatercept, although there was another agent – sotatercept – which in an early-phase clinical trial showed almost identical results, but isn't being moved forward for commercial reasons. These drugs are activin receptor ligand traps; they're basically antibodies that bind up members of the transforming growth factor beta superfamily, especially GDF11, which may inhibit a late stage of erythropoiesis.

For reasons that are unclear, luspatercept seems to be most effective in patients with MDS with ring sideroblasts or an *SF3B1* mutation or both, probably because these patients have a different type of erythropoietic defect from other patients with MDS. The defect may be at a later stage of red cell development, and that may be where GDF11 is most active and so luspatercept is particularly effective.

If I had to guess which drug has the best chance of being approved for MDS in the next year or two, it would be luspatercept, just because there was such a high transfusion freedom rate in the phase 1-2 studies, and because there's an ongoing phase 3 placebo-controlled registration trial of luspatercept in MDS with ring sideroblasts or *SF3B1* mutations. I would love to see another active agent available for us in MDS.

DH As you said, I think that these work downstream from erythropoietin in the early red cell development, so the transforming growth factor beta superfamily works after that step has failed.

DS That's the thought, yes.

DH I thought we would finish up with a case of mine

to see if you would comment. This patient, 73-year-old retired pediatric anesthesiologist, has been through a lot and is still going strong with her MDS. She is transfusion-dependent every 2 weeks now. She has a white cell count that is okay, around 4-5, with a normal differential, so she's okay there. Her platelet counts remain normal, 200-plus – not too high, not too low. Her mean corpuscular volume runs in the 103–105 range. She's had a couple of bone marrow biopsies over the past 4 years. Always hyperplastic, 90% cellular, some dyserythropoietic and platelet abnormality changes as well. Erythropoietin level is 300 mU/ml; ESA therapy didn't work. Blast count is 2%. Her cytogenetics, which actually haven't been repeated in a couple of years, trisomy eight. She has not had the next-generation sequencing lately, and has had, and responded to, and then progressed after ESA therapy, a TPO mimetic, lenalidomide, azacitidine. She actually was on luspatercept and got a response up to 4-5 weeks for transfusion, then it leaked back down to 3, now to 2 weeks. This unfortunately, probably similar to your practice, is the kind of patient where we start looking for other things. Anything you would comment or do differently, or suggest by way of clinical trial?

DS I think this is a patient in whom next-generation sequencing could be helpful, because there is the possibility of identifying a targetable mutation – 5%-10% of patients with MDS will have a mutation in *IDH1* or *IDH2*, for instance. There are targeted agents out there in clinical trials for patients with those mutations, though of course most patients don't have targetable mutations. That being said, David, you said the patient was 73 and in reasonable health otherwise?

DH Yes.

DS Given the lines of therapy that this patient has been through, reduced intensity conditioning transplant, if the patient does not have a *TP53* mutation, has at least a 40% long-term success rate. The morbidity and mortality of the procedure, while still substantial, are lower than they were even 5 years ago. I would give serious consideration for a patient like this to refer for transplant. If *TP53* mutation is present the outcome is worse but there are still some long-term survivors.

I don't think we do enough stem cell transplants in the United States for MDS for a variety of reasons. I'm not a transplant specialist myself, so I don't have a dog in this fight except for getting the best thing for my patients. I would

think about it for this patient, a referral for transplant would be reasonable. We do them in our center for patients who are up into the mid-70s if the patient's health is reasonable otherwise, so she certainly this patient could be a candidate.

Once an HMA such as azacitidine or decitabine stops working for the patient, if they have IPSS higher-risk disease, the median survival is less than 6 months. If they have IPSS lower-risk disease and HMA has failed them, the median survival is still only about 15 months, so they certainly are a high-risk group.

DH I think that's really something I'll consider in her. Before leaving her, if a clinician seeing a patient like this wants to do next-generation sequencing on peripheral blood and does not have it in his or her university, perhaps in a community practice, can you name a place to which you might send out?

DS Sure. Some of the send-out labs that do this testing include NeoGenomics, Genoptix, Mayo Med Labs, and Foundation Medicine. Those are the first few that come to mind.

DH This has been so helpful and so interesting. Anything else you might want to comment by way of when to refer, or when to consider clinical trial in patients like this?

DS Very few patients with MDS go on clinical trials, even compared with the national average for adults with tumors – which is pretty low to begin with. There are a lot of reasons for that. The MDS patients tend to be older patients and they don't always travel well to large academic centers. But we definitely – if I can make a plug for trials – need to do better, both as clinical trialists in designing trials that doctors would actually want to refer their patients into because they have a high likelihood of success, and as community-based doctors in sending patients at least for an opinion at some point to a major center. Often there are trials available, and that's the only way that we're going to ever move forward.

DH I can't thank you enough for all this interesting information. I've been speaking with Dr David Steensma at the Harvard Medical School and at the Dana-Farber Cancer Institute. Dave, thank you so much for taking the time today to do this.

DS My pleasure, thanks for having me.

DH You're very welcome.

References

- Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405. [Erratum *Blood*. 2016;128(3):462]
- Rhoads CP, Barker WH. Refractory anemia: analysis of 100 cases. *JAMA*. 1938;110:794-796.
- Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-2465.
- Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. *Blood*. 2014;124(18):2793-2803.