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Effective Assessment of Response to Therapy in Patients with MDS

MMDS: Welcome to the *Managing MDS Clinical Briefs Interview*. Today, we're talking to Dr. Stephen Nimer. Dr. Nimer is the Director of the University of Miami Sylvester Comprehensive Cancer Center, where he is a Professor of Medicine, Molecular Biology, and Biochemistry. *Managing MDS (MMDS)* recently spoke with Dr. Nimer about the challenges of assessing response to treatment in patients with myelodysplastic syndrome.

Dr. Nimer, can you tell us how you assess response in patients with myelodysplastic syndromes?

Dr. Nimer: When you talk about assessing response to treatment in MDS, you first have to talk about the available treatments for this disease, and who needs to be treated.

Myelodysplastic syndromes are bone marrow failure syndromes, and so patients with MDS have cytopenias that are either isolated anemia or pancytopenia. MDS is also a predisposition state for the development of acute myelogenous leukemia or AML, and so there are really two concerns. The first concern is to treat the existing cytopenias, and the second is to minimize the potential for the patient to develop leukemia. When one is assessing response, one is really looking at the bone marrow and the peripheral blood to see the impact of treatment, keeping in mind that you may or may not have treatments that prevent the development of leukemia over a period that may last months or years.

In MDS, like in leukemia, there are both complete responses and partial responses. The International Working Group has established grades of responses and definitions, in terms of the disappearance of dysplasia from the bone marrow, and normalization of the blood count. As you would expect, complete responses require normalization of blood counts, with bone marrow blasts less than 5%, and disappearance of dysplasia. Interestingly, the chromosome abnormalities that are found do not have to

disappear for a complete remission to be documented, but logically, you would think that should be the case, meaning that the chromosomal abnormality should disappear, as well.

Partial responses are a different matter: unlike leukemia, where partial responses are not that meaningful, in myelodysplastic syndrome, partial responses do have meaning. In fact, we have learned from the randomized trials of 5-azacitidine that even people who do not achieve a partial response but who develop "hematologic improvement" can benefit in terms of prolonged survival. The important things to think about when you are treating the patient with myelodysplastic syndrome is, what is happening to the blood counts, what is happening to the percent blasts, and is there evidence for evolution of the disease, or is the disease dissipating.

MMDS: *How do you assess response in patients with 5q minus?*

Dr. Nimer: Lenalidomide is FDA-approved for the treatment of anemia in patients with 5q minus. Because lenalidomide works primarily on the anemia, that tends to be the criteria used for assessing response in these patients. However, responses can also be seen in people with 5q minus and other chromosomal abnormalities, or those with slightly increased blasts, as measured by a decrease in their percent blasts.

When treating with lenalidomide, one tends to give the medication until the response disappears. This means that you don't stop the treatment, but continue it, virtually indefinitely; in the 5q minus patients, we see a roughly 2-year median response duration. If the patient is not responding to lenalidomide and has significant myelodysplastic syndrome, one moves toward the hypomethylating agents, 5-azacitidine or decitabine, and then, one uses the traditional IWG response criteria.

MMDS: *What about patients with significant cytopenias? How would you assess response in these individuals?*

Dr. Nimer: Patients with MDS that require treatment tend to be those people with significant cytopenias or increased blasts. The important thing here is that the treatments for these patients require multiple cycles in order to see a response. It's not uncommon for patients getting 5-azacitidine to require 4 to 6 cycles until you begin to see a response. Because of this, it's very important that physicians understand this and not stop these medications early. In terms of how much of a response needs to be seen, again, if the patient isn't progressing, one tends to continue the 5-azacitidine

indefinitely. The survival benefit that has been seen in the two randomized trials of 5-azacitidine versus best supportive care or physician's choice really show that the patients need to continue on the medication in order to continue to derive benefit.

MMDS: *Is response assessment any different in patients who may receive a bone marrow transplant, or in the elderly?*

Dr. Nimer: For patients who are eligible for bone marrow transplantation, it is sometimes difficult, if the patient is not responding, to know when to give up the hypomethylating agent and when to move on to the transplant. It really requires a case-by-case assessment of how the patient is doing, what their comorbidities are, how good a donor is available, and patient preference. There are algorithms that you can refer to that take all of these factors into account.

The good news concerning MDS in the elderly is that the treatments tend to be very well tolerated, and because of this, it is quite routine to treat patients in their 80s with these medications. Again, if the patient is tolerating the medication, there is plenty of time to look for a response.

MMDS: *How do you distinguish myelodysplastic syndromes from acute myelogenous leukemia?*

Dr. Nimer: This question comes up frequently. One of the important principles here is that, although there are definitions based on the percent blasts in the bone marrow and the exact cytogenetics, sometimes you need a bit of time. So, if a patient has acute leukemia, you may catch them at the point where they don't quite have leukemia, but they're on their way there. In these cases, if your suspicion is that the patient has leukemia, and does not have high enough blast counts, but has neutropenia and thrombocytopenia, you have two choices: you can either decide to treat the disease as leukemia, or you can or observe the patient for a while.

If you choose to treat for leukemia, there are regimens involving hypomethylating agents that are effective in treating acute myelogenous leukemia, such as the 5- or 10-day decitabine treatments. If, alternatively, you elect to wait for definitive development of leukemia, and if you do serial peripheral blood assessments, CBCs and serial bone marrow evaluations, and you find that the patient at one point had 10% blasts but now has 22% blasts, then it is likely that the patient had leukemia to begin with. If the patient has myelodysplastic syndromes, these features tend to be

consistent over time. This means that, if the patient has 5% to 10% blasts, a few months later he or she would still have 5% to 10% blasts, as MDS is a more stable condition.

So, in addition to using percent blasts and cytogenetics, you can also use time to see how the patient is doing, and whether the patient really has leukemia or not. While you're treating patients with MDS, they may develop leukemia, and so, even though it takes a few cycles to see the response to hypomethylating agents, you have to be aware that the patient may progress while on these treatments. If that happens, you'll need to move on to an algorithm that allows the patient to be treated for leukemia.

MMDS: *Is there any way to reliably predict response to treatment in patients with MDS?*

Dr. Nimer: We need to think about molecular prognostication of myelodysplastic syndrome. Raf Bejar and others have published work in the *New England Journal of Medicine* and in other papers, indicating that there are a number of genes that, when mutated, confer either a good or a bad prognosis in patients with MDS. The question is, how do you incorporate that information into the clinical prognostication, which is a system that we are all very comfortable with using.

First of all, we are not quite at the point where doctors around the country can get these panels on a routine basis for their patients. Moreover, specific genetic mutations really haven't been completely confirmed in terms of their ability to predict treatment outcomes. Given that there are really two or three main treatments for myelodysplastic syndrome, the question also is, if you can change the predicted response percentage for a patient, will that actually mean that you will change the treatment? One of the more important abnormalities to screen for in this process is the p53 mutation, because if the patient has a P53 mutation, they may not respond to anything. Certainly for the hypomethylating agents, p53 mutations are involved in a poor prognosis, so for these patients, you may consider stem cell transplantation earlier, for example, or even a more aggressive treatment or something experimental for patients who have those mutations.

Regarding mutations other than p53, there are panels that you can run, but, at the moment, most physicians are still using clinical criteria to assess prognosis and to determine treatment strategies.

MMDS: *Are there any side effects of treatments that require monitoring or assessment?*

Dr. Nimer: There are toxicities and side effects of these treatments that we have to watch for. Lenalidomide, which is used to treat anemia, and in particular 5q minus anemia (although note that 20% of non-5q minus MDS patients will respond), the main side effect is myelosuppression, and it occurs quite quickly. We learned from clinical trials that, when starting patients on lenalidomide, you need to start monitoring CBCs very soon after initiating therapy. The patient starts out with low blood counts, which can go even lower, so you need to monitor the platelet count in particular in these patients, as they may require a platelet transfusion or an interruption of the medication. Because of this cytopenias for lenalidomide are very important.

For 5-azacitidine and decitabine, bone marrow suppression and cytopenias are, again, the main side effects of these agents. As the patient's bone marrow improves, however, these tend to be less and less of a problem. The current approved schedule for decitabine is a 5-day schedule of 20 mg/m^2, and it tends to be more myelosuppressive than the 7-day subcutaneous 5-azacitidine treatments. Nonetheless, both have the side effect of cytopenias, and one needs to monitor CBCs during treatment processes.

MMDS: *Do you have any final thoughts for us today, Dr. Nimer?*

Dr. Nimer: I do. Myelodysplastic syndromes have gone from a disease where there were no treatments at all, other than supportive care, to a disease with a natural history and changing treatments, such as lenalidomide, 5-azacitidine, and decitabine. I haven't talked about erythropoietic growth factors like erythropoietin today, but these treatments are changing the natural history of the disease, as they're allowing patients to go on to bone marrow transplantation without other forms of therapy. They're well-tolerated in the elderly, as well.

Today, given the data that we've talked about, it really is the unusual patient with myelodysplastic syndrome, no matter how elderly, who is not offered some form of therapy for their disease, unless they have significant comorbidities. I hope this information has been useful for you. Thank you for your attention.

MMDS: Thank you, Dr. Nimer.