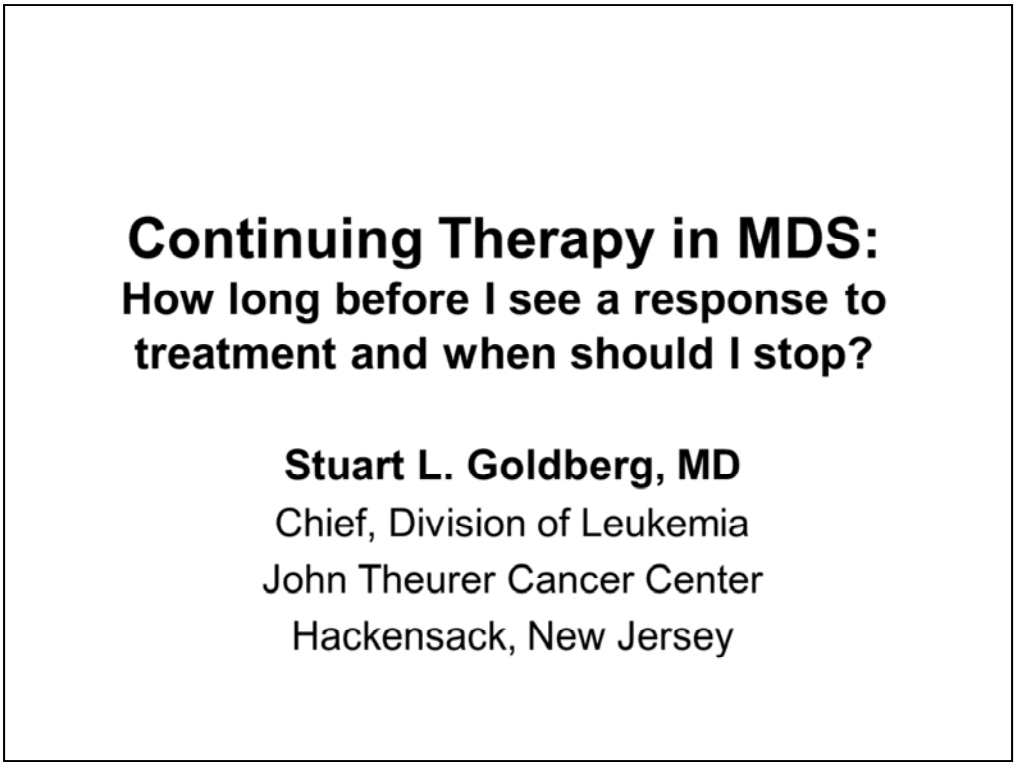
Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?

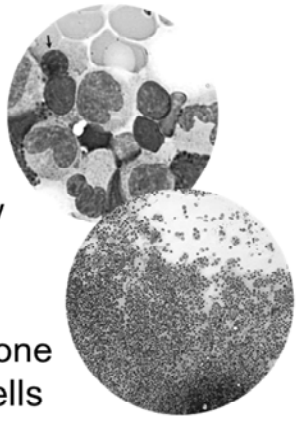


Hi, I am Dr. Stuart Goldberg from the John Theurer Cancer Center in Hackensack, New Jersey, and I am here with *ManagingMDS.com*. I would like to talk to you today about continuing therapy in myelodysplastic syndrome. One of the common questions I get is, “How long before I see a response to treatment and when I should stop treatment in a patient with MDS?”

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?

Myelodysplastic Syndromes

- A group of malignant hematopoietic disorders characterized
  - Clinically: bone marrow failure with cytopenias and a tendency to progress to AML
  - Pathologically: dysplastic morphologic abnormalities of bone marrow and peripheral blood cells



AML=acute myeloid leukemia
Bennett J, et al. The myelodysplastic syndromes. In: Abeloff MD, et al, editors. *Clinical Oncology*. New York NY: Churchill Livingstone; 2004. pp. 2849-2881.

These are common questions, and the answers are not very easy. As we all know, the myelodysplastic syndromes are a heterogenous group of bone marrow failure disorders. Clinically, they are characterized by the failure to make blood. So patients come with cytopenias, they come with low red counts and weak and tired. They come with low white counts and recurrent infections. They come with low platelet counts and bleeding. Pathologically when we do a bone marrow, we see dysplasia, we see change in the marrow. The marrows look ugly. The factories are broken, and they are not producing blood.

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?

The IPSS Risk Stratification Helps Divide Patients into Treatment Groups

	Score Value				
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blasts	<5%	5% to 10%	--	11% to 20%	21% to 30%
Karyotype*	Good	Intermediate	Poor	--	--
Cytopenias†	0/1	2/3	--	--	--

	Total Score					
	0	**0.5**	**1.0**	**1.5**	**2.0**	**≥2.5**
Risk	Low	Intermediate I		Intermediate II		High
Median survival, yr	5.7	3.5		1.2		0.4

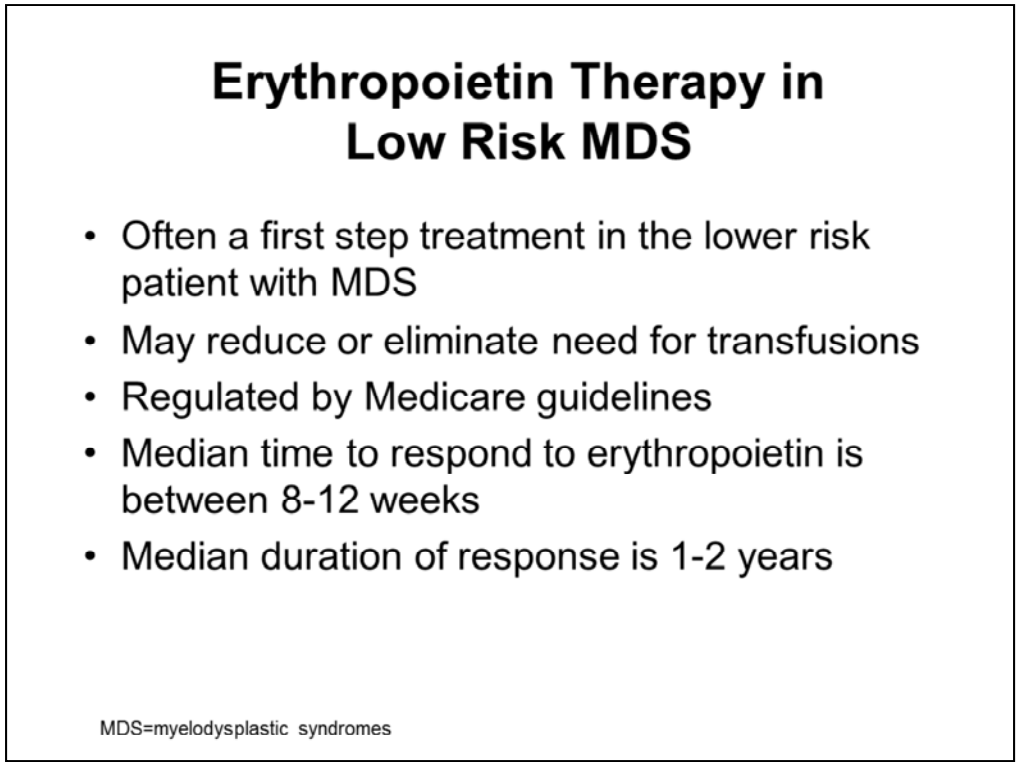
IPSS=International Prognostic Scoring System
*Good=normal, -Y, del(5q), del(20q); intermediate=other karyotypic abnormalities; poor=complex (≥3 abnormalities) or chromosome 7 abnormalities.
†Hb <10 g/dL; ANC <1800/mcL; platelets <100,000/mcL.
Greenberg P, et al. *Blood*. 1997;89:2079-2088.

One of the first things that we do with our patients with MDS is we try to put them in a treatment bucket, put them in a category so we can decide what their prognosis is and how we are going to go about giving therapy. To do this, we use the International Prognostic Scoring System or IPSS. The IPSS was developed in 1997 as a simple method of placing patients into prognostic groupings utilizing three categories: patients who had multiple lines of cytopenias did not do as well as patients with single cytopenias. The anemic patient does better than the patient who is anemic and thrombocytopenic; likewise, the patient with high blast percentages, moving closer to leukemia, may not do as well as the patient who does not have blasts, and finally; borrowing from the world of cytogenetics in leukemia, we learned that there are certain chromosomal abnormalities that send our patient toward poor prognosis and others that may send our patients to a favorable prognosis. So we look at the percentage of blasts, the type of cytogenetic abnormalities, and the number of lines of cytopenias to place patients into prognostic groupings. Typically, we then subdivide them into the lower categories, the low and intermediate risk group 1 where survival is measured in years against the high-risk categories. The intermediate 2 and the high-risk patients with survival is measured in months. When I approach my patient with MDS, I then have to think what is my goal of therapy? For my lower risk patient, it is trying to improve their quality of life. They may be very tired from the anemia, but because they do not have blasts, they do not have bad cytogenetics, they are not dying of the disease.

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?

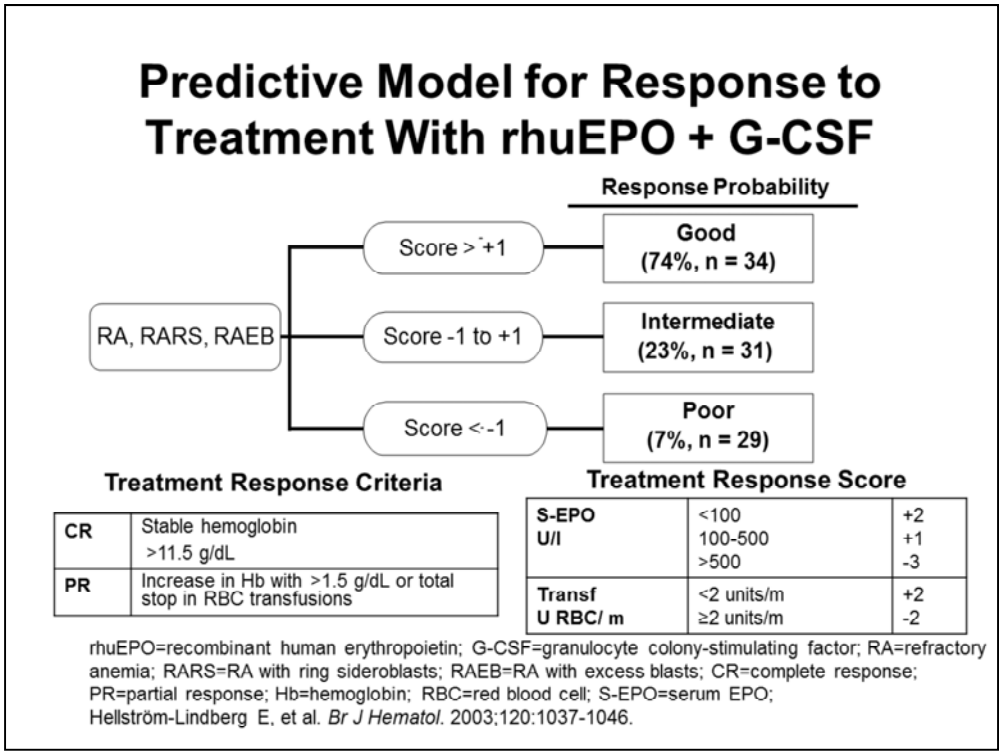
So I am trying to improve their quality. In the high-risk patients with blasts and cytogenetics and multiple lines of cytopenias, they may die, and so the goal is to improve the quantity of their life. If you keep remembering what your goal of therapy is, this may help you determine how long to treat the patient and when is time to go to a new therapy.

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?



For the typical patient who is anemic but is otherwise in a low-risk category, the patient who is just anemic but does not have bad cytogenetics, does not have lot of blasts, and maybe is just a little bit tired, often the first step is to think about transfusions and may be growth factors such as erythropoietin. Now erythropoietin in our elderly population is heavily regulated by the Medicare guidelines, so check with your state regulations to see how you are reimbursed. It should be noted that most patients when started on erythropoietin will have a reasonable chance of responding in having that red count come up, but it takes time. The way I explain this to my patient is if you put fertilizer on a dying plant, the plant may respond, but it takes some time for the plant to use that fertilizer. The median time to respond in most studies with erythropoietin is somewhere around 8 to 12 weeks. I have to tell the patient you have got to wait a month or 2 before we start to know if the erythropoietin is going to work. If it is fortunate enough to work, the response will usually last 1 to 2 years for patients who are treated early in the course of the disease.

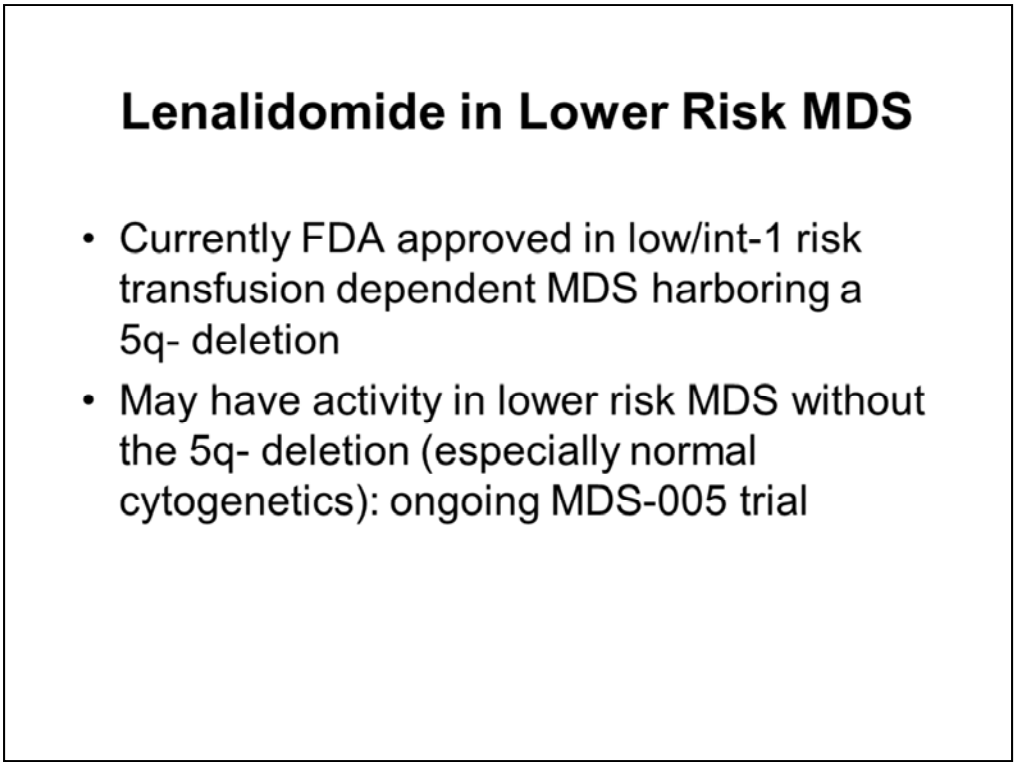
Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?



There are some models that we can use to help predict who is going to respond to erythropoietin. Our Scandinavian colleagues have elegantly over the last decade published several different models, and here is one, and that is that patients who have a low endogenous erythropoietin level as well as those patients who are not already transfusion dependent are the most likely to respond. It makes sense. If your kidneys are already chugging out as much as EPO, giving a little extra is not going to help, and likewise, if the plants are already dead and not making any blood, giving them some fertilizer is not going to wake it up either.

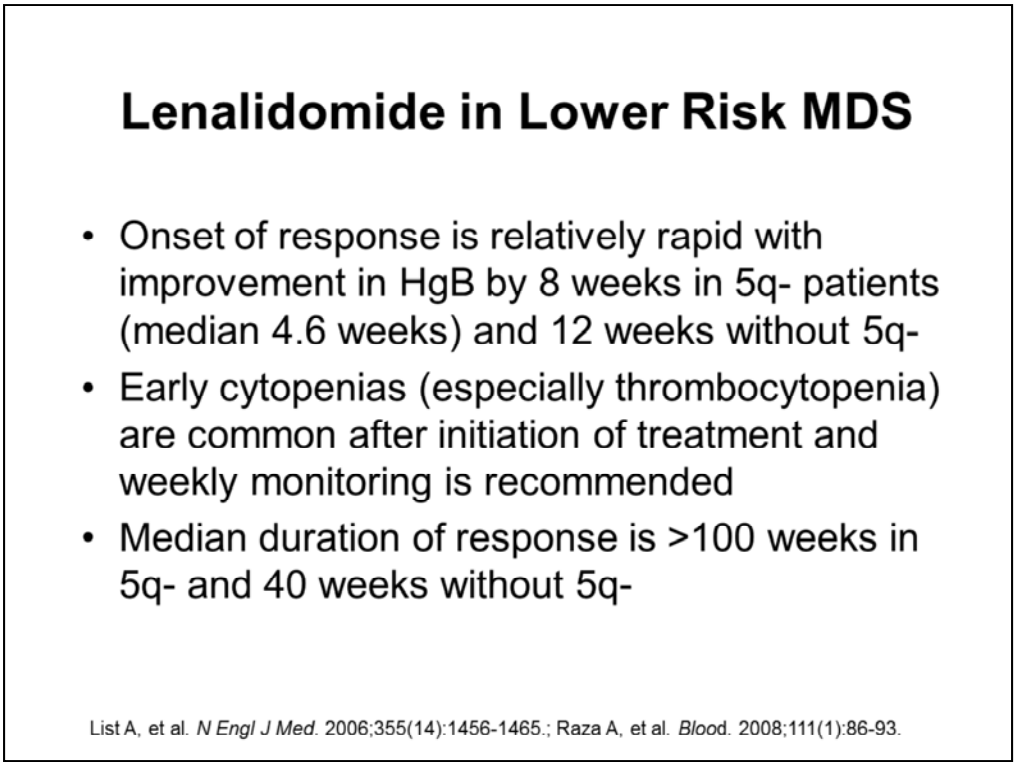
Now there are some regulations on EPO use and some cautions. We know that erythropoietin can stimulate not just red cell production but may stimulate solid tumors. So Medicare stepped in and said we should not probably use these in solid tumors. Likewise, if you drive your hemoglobin very high, you may get thrombotic events, you may get hypertension, you also get thrown out of being a cyclist because these are how these athletes are cheating. You want to make sure that you keep within the regulations, and in our state where there is a REMS program to advise our patients about the potential dangers of erythropoietin supplementation which really do not apply to our anemic patients with MDS, but nonetheless, we go through the regulations.

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?



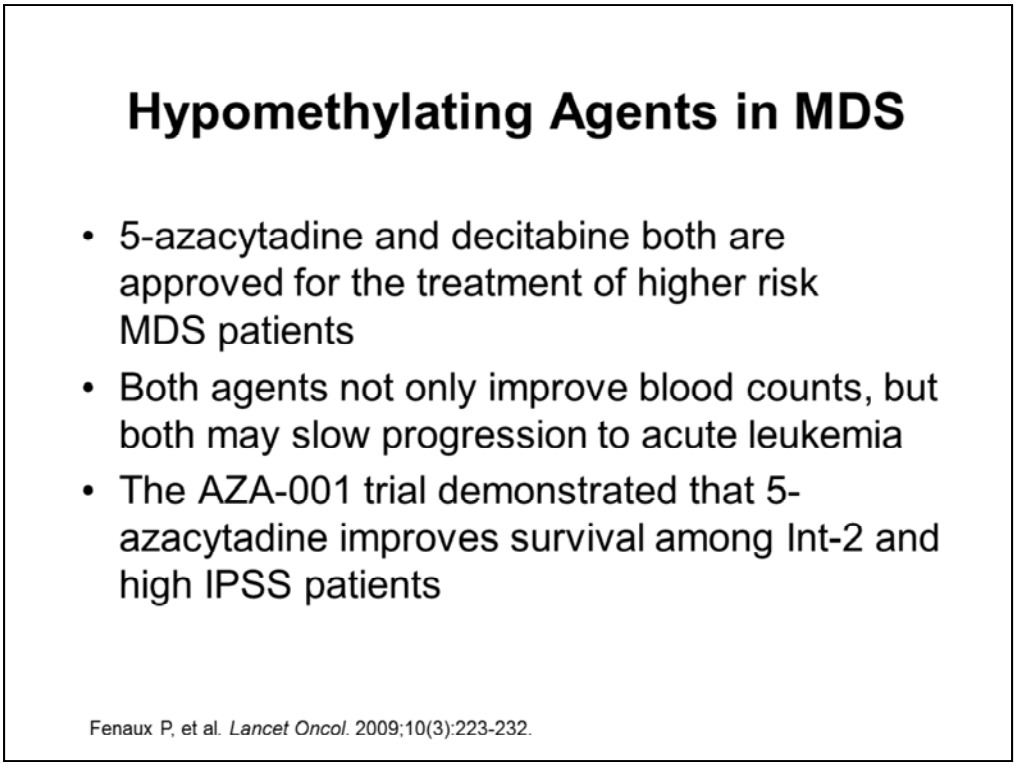
Occasionally, our patients have received growth factors and they are still anemic, they are still tired, they are still weak, and now we start to think about specific therapies for myelodysplasia. One of the first stages we often will come up with is the oral agent lenalidomide. It is convenient because it is an oral agent and therefore it may be an appropriate choice for the anemic patient who has got low-risk disease where once again our goal is to improve their red cell production and give them improved quality. It is currently FDA approved for patients with low- or intermediate-risk group 1 patients who are transfusion dependent, who harbor a 5q minus deletion. Off-label however, we can use this agent, and I have used this agent, in patients who do not have a 5q minus deletion, especially in those patients who have normal cytogenetics where maybe one-third of patients will respond as opposed to the two-thirds of patients who respond with 5q minus. We will learn more about whether lenalidomide can be used in patients who do not have 5q from the ongoing registration trial MDS-005, a placebo-controlled study. There are toxicities that you need to know with lenalidomide and that is especially early on in the treatment, the agent itself can cause cytopenias, especially thrombocytopenia. So when you start lenalidomide, it is recommended that the patients be monitored once a week to make sure they do not drop dramatically in their platelet count. We also can see some mild neutropenia. Rashes are common, and although the package insert talks about thrombosis, that is typically not seen in the MDS patients. That is more with a higher dosage used in multiple myeloma. I do not prophylax my patients with aspirin with MDS whereas I may do that in patients with multiple myeloma.

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?



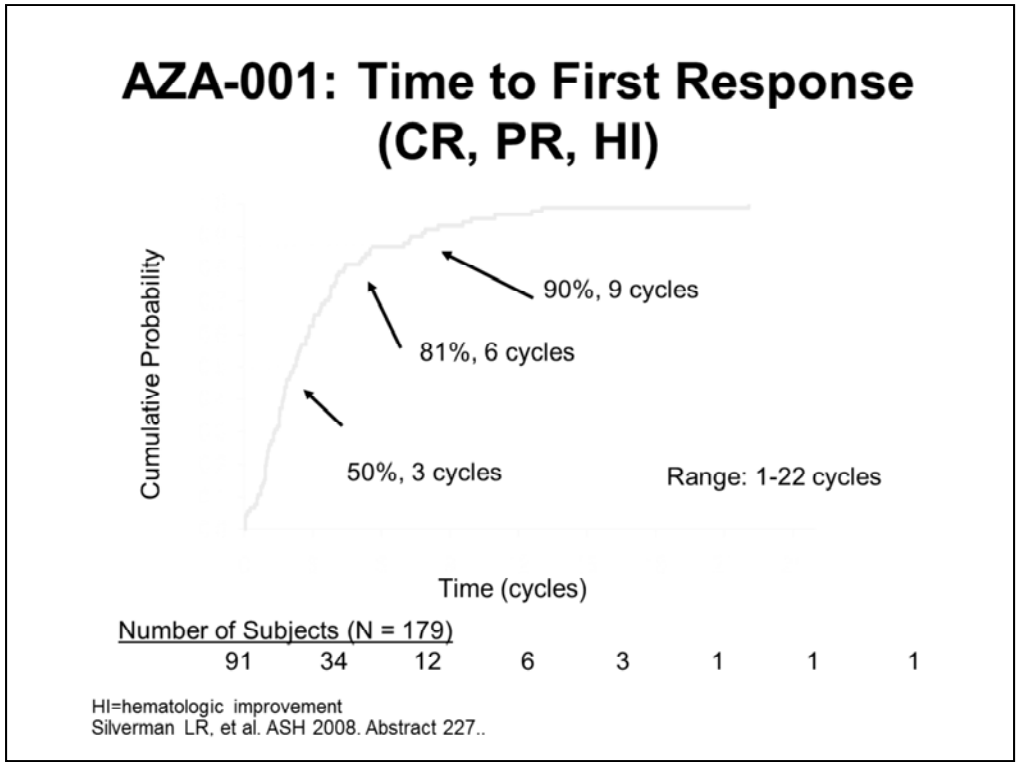
One of the nice things about lenalidomide though is the response onset is very rapid. Typically, we will see improvement in hemoglobin in the 5q minus patient within 4 to 6 weeks, and it is rare if the patient has not responded by 8 weeks to see a response. So a patient with 5q minus deletion, I may give them a 2- to 3-month trial and if they do not respond then move on to something else. For the patient who does not have 5q, it takes a little bit longer, maybe 12 weeks to see a response to that agent, but once again, 3 or 4 months if I am not seeing response, it is time to move on to other therapies. For the patient who is fortunate enough to respond, the median duration of response can be quite long, for the patient with 5q minus, it may last 2, maybe even 3 years, and for the patient without 5q, the emerging data is about a year, but we have to see more data especially from the MDS-05 trial.

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?



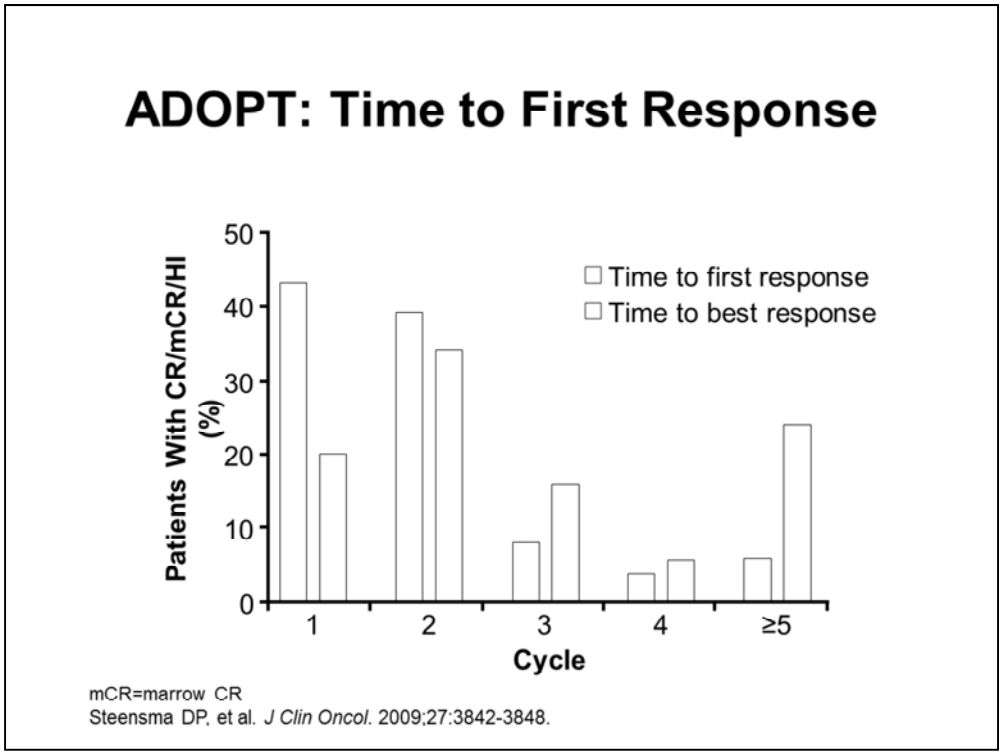
The major drug that is used in the patients with higher risk disease is the hypomethylating agents, 5-azacitidine and decitabine. These are really forming the backbone of the treatment of the aggressive patient with MDS. One of the nice things about the hypomethylating agents is that not only do they improve the blood counts that make our patients have improved quality, but they also may improve quantity. Both agents have been shown to slow progression to acute leukemia. Both agents have been shown to improve quality of life parameters against placebo. And in the AZA-001 trial, a large international study compared 5-azacitidine against best supportive care, we saw that 5-azacitidine improved survival among the higher risk patients with intermediate risk 2 or high IPSS score. In that specific study, the median survival for these higher risk patients was only 15 months if treated with conventional care or supportive care, but it improved to 24 months with the addition of 5-azacitidine, and at the same time that they were getting the chemotherapy, the patients felt better. In general, hypomethylating agents are fairly well tolerated with very minimal problems with side effects. These are the drugs that can be tolerated in older individuals. Once again, we do see local injection reactions. We also can sometimes see rashes. We can see cytopenias from the drugs, and they must be used with caution in patients who have both renal and hepatic impairment. You will want to check the package insert if you are unfamiliar with the administration.

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?



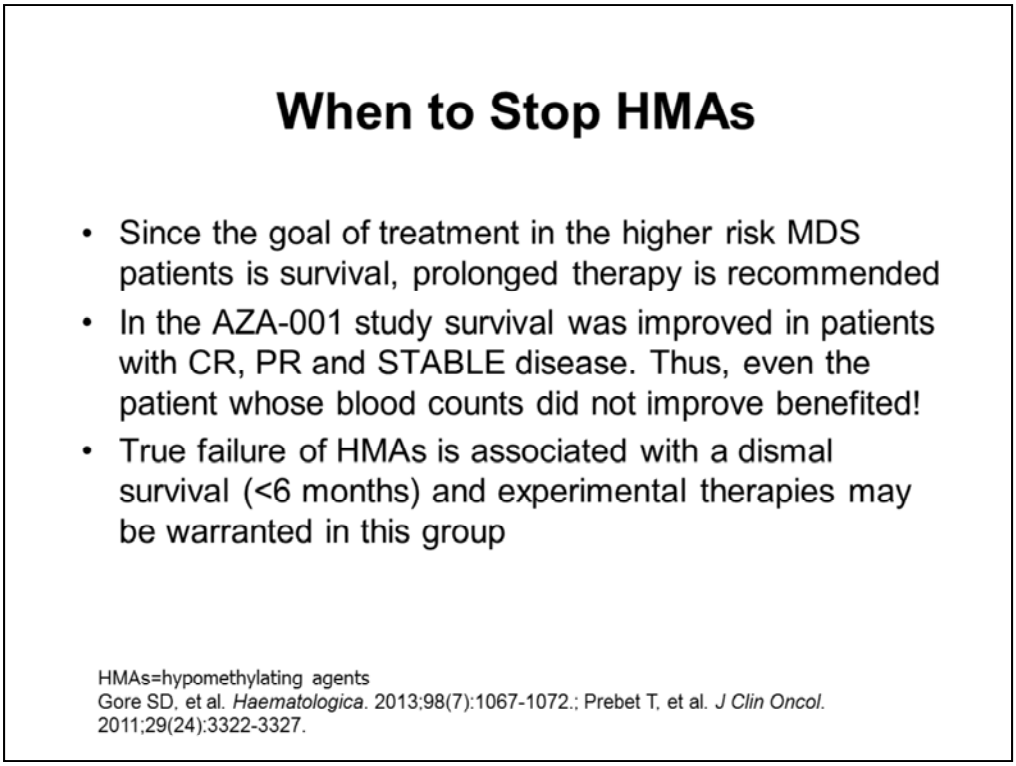
One thing about all the drugs in MDS is they take time to work, and in the AZA-001 trial, we saw that it takes between 4 and 6 months to have the first response to patients with hypomethylating agent with 5-azacitidine. So do not give your patients 5-azacitidine and then expect the next month their blood counts to get better. In fact, during their first 2 cycles, it is not uncommon as we clear out the dead bad cells, it is not uncommon for us to see the blood counts get worse. I tell my patients when I start them on 5-azacitidine that they are going to need more transfusions during the first 1 to 2 months and hopefully during the 3rd and 4th month we might stability, and as we get into the month 5 and 6, we may start to see good responses. But as you see from this curve, the patients who have not responded by 6 cycles rarely respond. I will give a patient a good 6-month trial before I declare this a success or a failure.

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?



Likewise, in the ADOPT trial, the registration study for decitabine utilizing the 5-day regimen which you can see once again it takes several months to see the response. One of the things that I often will see is the patient gets very disappointed during the first cycle, stops treatment, and then they have been exposed to all the side effects without having a chance of the benefit. I tell patients, we are going to start you in a drug, close your eyes and we will talk in 4 to 6 months. At that point, then we will know if this is the right thing for them.

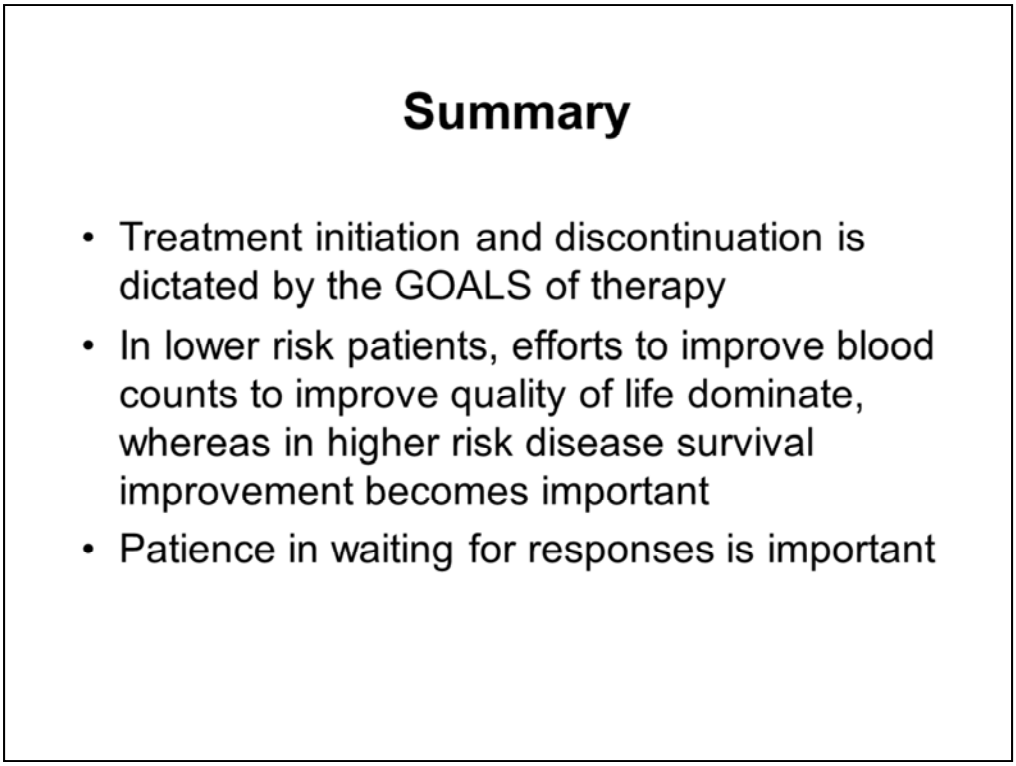
Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?



For the patient who does not respond after 6 cycles, unfortunately we do not have a lot of other options, we start to think about experimental treatments. But one of the hardest questions that I get is a patient has been doing okay on these drugs and starts to lose their response or is still requiring transfusions, should I stop my hypomethylating? And then, we go back and say what is our goal of treatment? In a higher risk patient, survival is our goal, and therefore, prolonged therapy even in the patient who may not have the best blood count response may still be warranted. A recent analysis by Dr. Gore and colleagues of the AZA-001 trial, the randomized trial comparing 5-azacitidine against supportive care showed that of course patients who are having response, a CR or PR, are going to have longer survival. But interestingly, patients who had stable disease, so if the blood counts were still low and still requiring transfusions but the transfusion requirements had not greatly accelerated even though they were continuing to require transfusions, they still benefited in survival. And if survival is our goal, we keep the therapy going even if the blood counts are poor. Now, a true failure of the hypomethylating agents where now all of the sudden blood counts are decreasing despite our use, their transfusion requirements are getting worse, or we start to see the appearance of blasts, this is a very bad sign for our patients because we know that there is a dismal survival, less than 6 months, for a patient who has truly failed hypomethylating agents. With this, we then have to think about experimental therapies. So, in general, with my patients with hypomethylating agents, I try to give them every chance to respond, and if there is even a question of whether they were responding or not responding, I might give them another cycle or 2 to try to keep them on therapy in hope that they can

get stability and therefore translate to longer survival.

Continuing Therapy in MDS:
How long before I see a response to treatment and when should I stop?



Well, hopefully that short introduction to how I approach the initiation and discontinuation goals of treatment in MDS can be helpful to you. In summary, lower risk patients, I try to focus on improving quality of life by improving blood counts, but in higher risk patients, I am thinking about survival, and that guides how long I am going to continue treatment and which treatment. And remember, all of these therapies take time, so patience is truly a virtue both for the doctor and for the patient. I may have to remind them that these are slow therapies, that they have to sort of go through the motions to get through that first couple months to have a just chance of having the long-term pay off that we want. For more information about MDS, check out *ManagingMDS.com*.