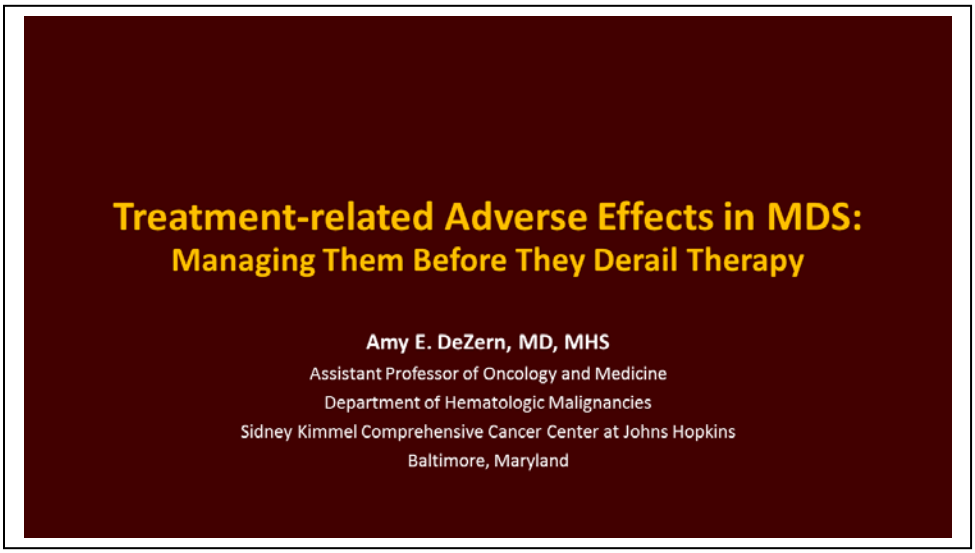
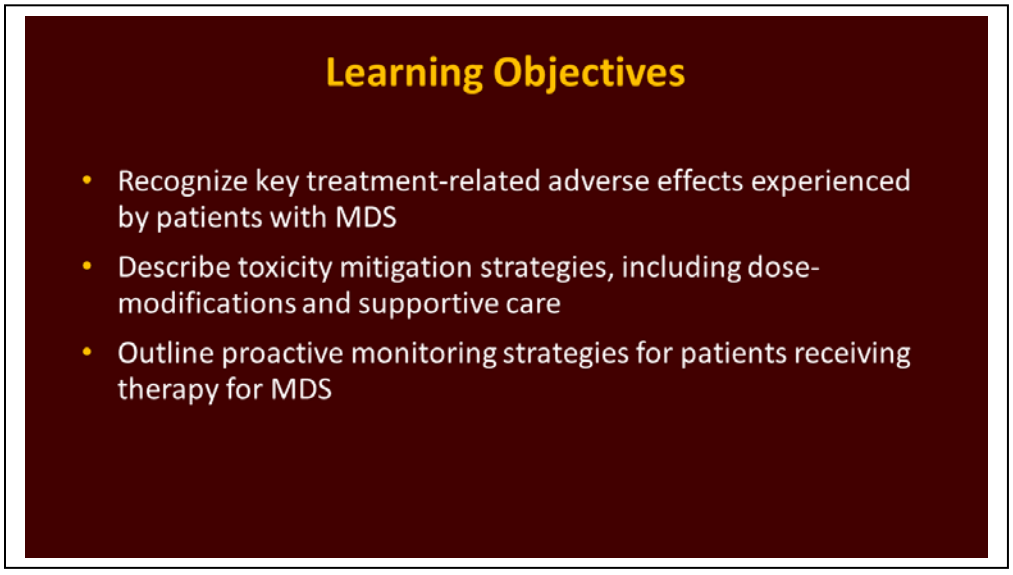
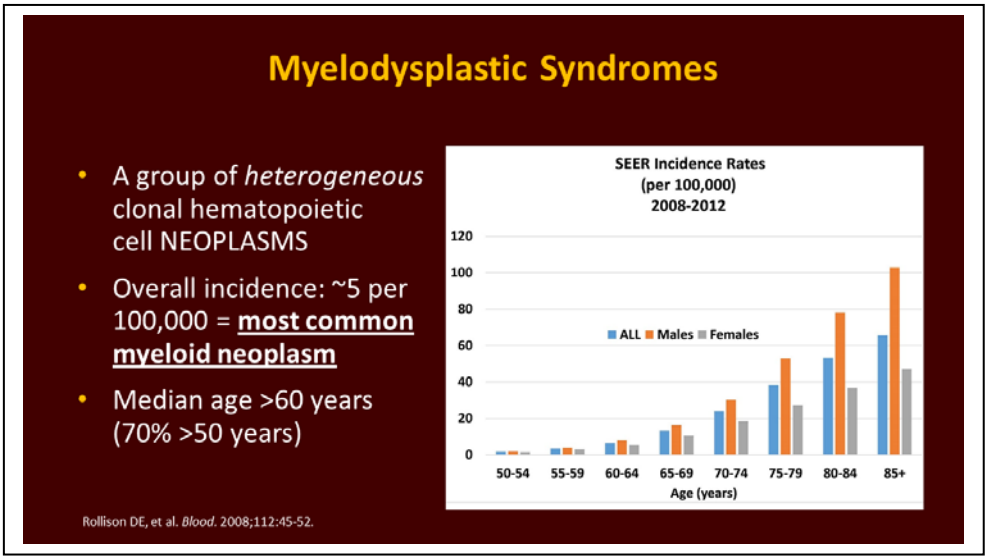


Hello and welcome to *Managing Myelodysplastic Syndromes* (MDS). My name is Amy DeZern, and I am an Assistant Professor of Oncology and Medicine in the Department of Hematologic Malignancies at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland. Today, I will be discussing treatment-related adverse effects in MDS and managing them before they derail therapy.

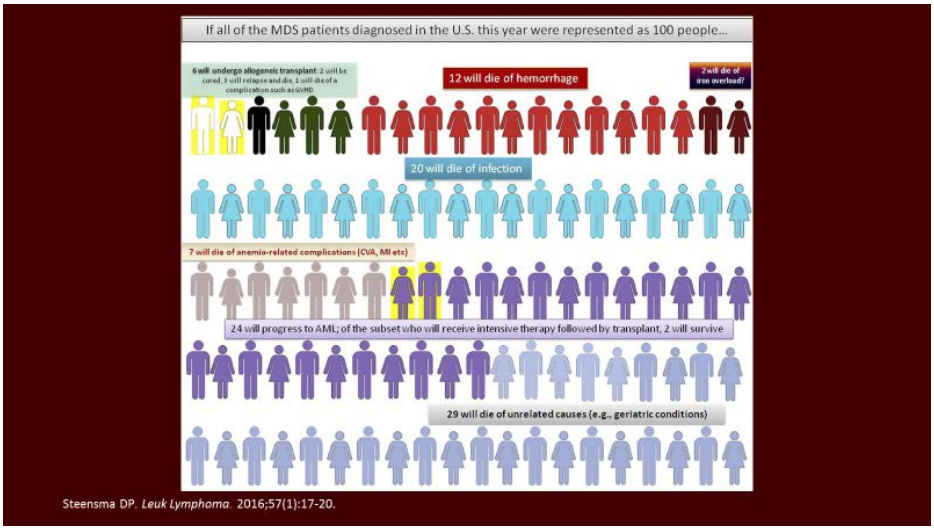


Our learning objectives are to help recognize key treatment-related adverse effects that can be experienced by our patients with MDS, many of whom are older. We will describe toxicity mitigation strategies, including dose modifications, as well as supportive care for this important group of patients. We will also outline proactive monitoring strategies for patients who are receiving ongoing therapies for their myelodysplastic syndrome.



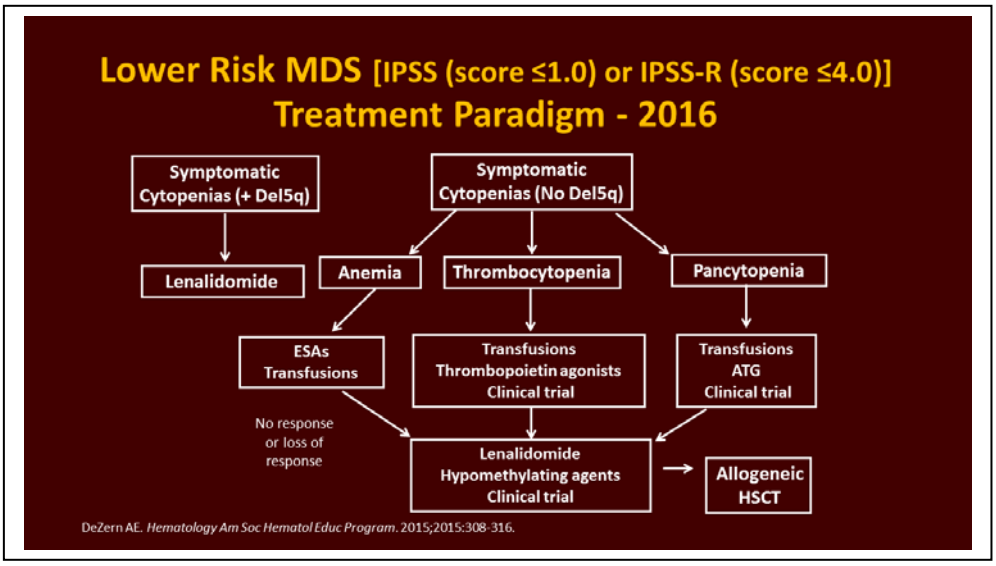
To begin, I will remind the audience that myelodysplastic syndromes are a group of very heterogeneous diseases. While they all fall under the umbrella term of myelodysplastic syndromes, there are really multiple diseases that are all clonal hematopoietic neoplasms. When considered together, the overall incidence of MDS is about 5 per 100,000, making it the most common myeloid neoplasm. In getting to our discussions of adverse-related effects as well as toxicities, I will remind you that the median age of these patients is over 60 years, with more than 70% of the group being over age 50. Certainly the incidence of myelodysplastic syndrome, as we know from the SEER database, increases with increasing age, and there is a 2 to 3 to 1 ratio of males to females who experience the disease.

Unfortunately, the outcomes for patients with myelodysplastic syndrome are not exactly where we hope they would be, and today I hope to take you through some of the ways that we can mitigate these lesser events to improve the outcomes for our patients.

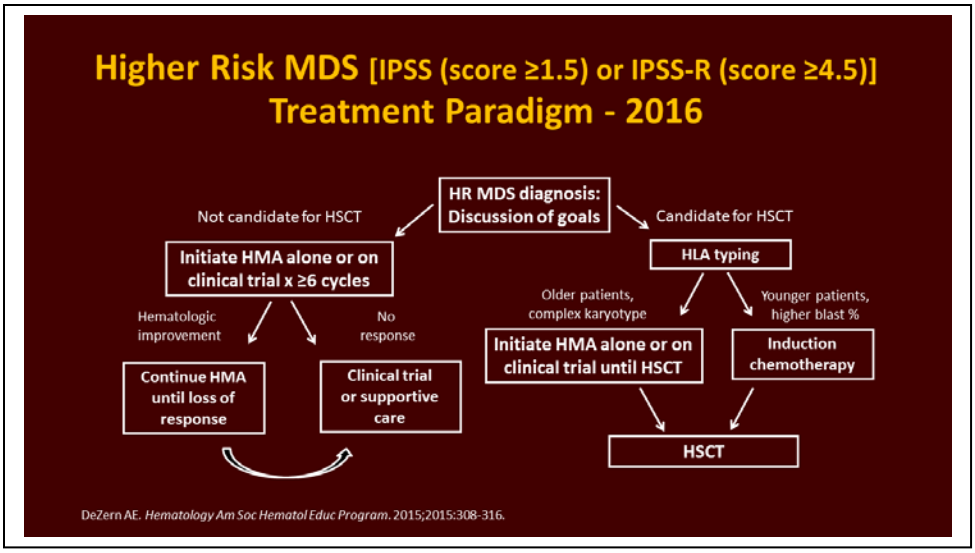


This is a graphical representation that shows the projected outcomes, if all of the MDS patients diagnosed in the United States this year were represented as 100 people. So, in the upper left corner, only a very small percentage, 6%, will undergo allogeneic transplant, the only potential cure for this disease. The patients who were cured after transplant are shown in yellow. Due to their cytopenias, as many as 12% will die of a bleeding complication, and while these patients are transfusion-dependent, many of them will have complications of the iron overload from the red cells they receive to improve their quality of life. A substantial portion, nearly a fifth, will die of infection. There is a fraction of patients with many of the comorbidities we see in the elderly who die of anemia-related complications,

and then, of course, there is the progression of the disease to acute myeloid leukemia, which can be a problem, and is why we must strive to keep our patients on therapy to prevent this. Then lastly, as I mentioned, this is an elderly population who suffers from MDS, and there are many unrelated causes that need to be optimally managed in these patients as well, as these will ultimately be causes of death in this patient cohort. Today, we will talk about the various ways that we can mitigate some of these complications with good modifications in our therapy.

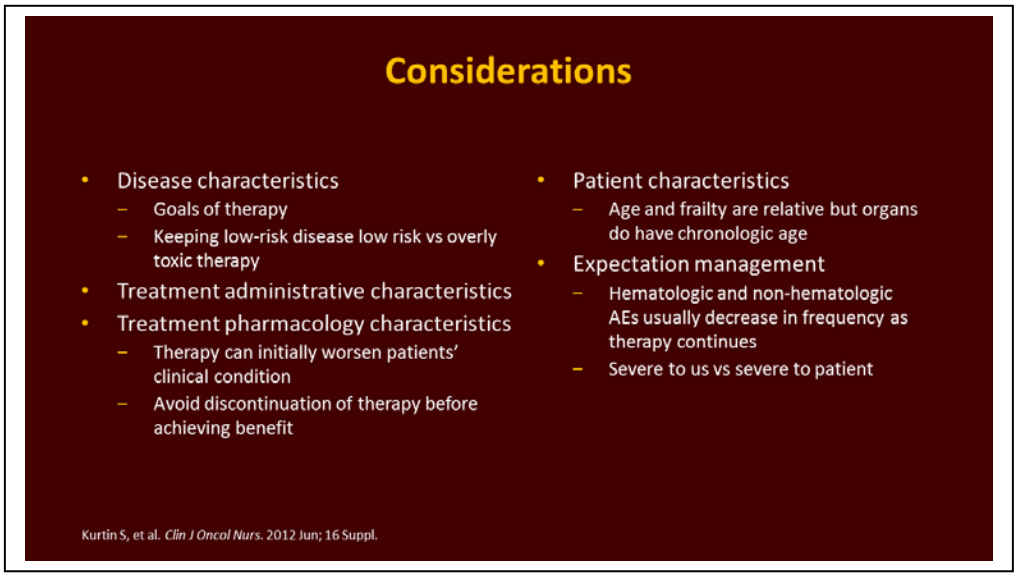


Everyone is aware that there are a relatively limited number of therapies that are currently approved for myelodysplastic syndrome. We divide our patients into lower-risk disease and higher-risk disease, and this can be very important as we think about how strongly to push these patients toward therapy. We will talk about several of these details, but in patients with lower-risk MDS who have an IPSS score of less than 1 or an IPSS-R score of less than 4, we have to consider whether they are even symptomatic. If they are not symptomatic, perhaps a watchful waiting approach is more appropriate. But in symptomatic patients, we look at their mutations (a deletion 5q or not) and then choose lenalidomide or other therapies, depending on which is their worse cytopenia. We will talk more about these additional options in this presentation.

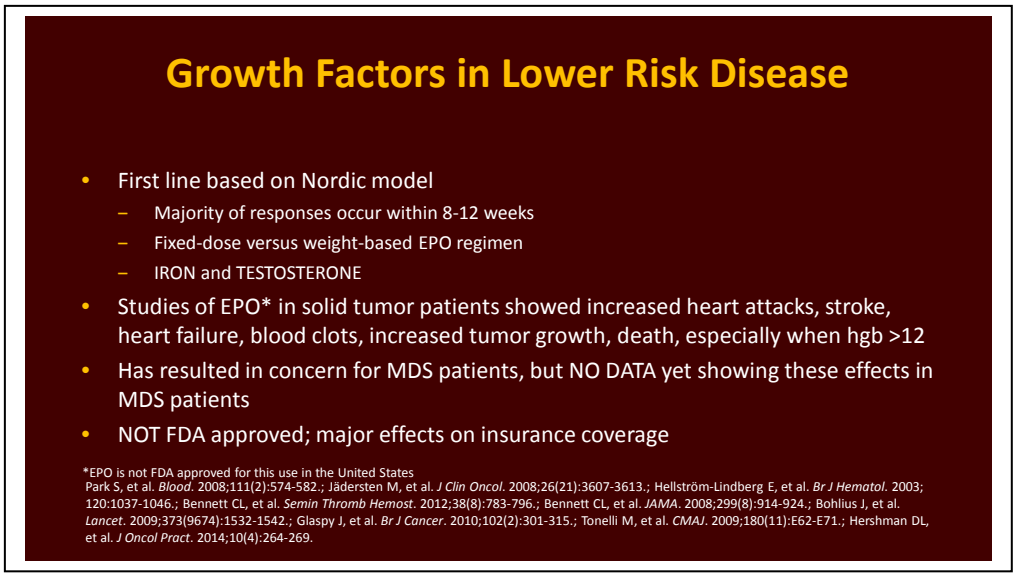


Higher-risk MDS, which describes about one-third of our myelodysplastic syndrome patients, are characterized by an IPSS score of greater than 1.5 or an IPSS-R score of greater than 4.5. These patients have different goals, because these are the ones who are more likely to fall into that group of patients on our graphical representation that will progress to AML. We tend to approach the higher-risk patients more aggressively and ask the patient to push through therapy more as we balance the adverse effects.

The considerations that we must have are related to these disease characteristics. That is why we must think about the goals of therapy in this older group of patients in terms of what complication may cause the most suffering to the individual. So, the goals of therapy are to, of course, increase a patient's quality of life and avoid some of the dangerous complications of the cytopenias that we have mentioned - infection, bleeding, and anemia. And then, if the low-risk disease is truly low risk, we would like to prevent it from progressing to a higher-risk form, while avoiding some of the toxic complications of the therapy, especially in lower-risk patients. We must think about how the treatments are administered, because this can affect the patient in terms of ease of access, as well as caregiver situations. We have to think about the pharmacology of the actual treatment. Because a very challenging concept for the patient to grasp, especially in lower-risk MDS, is that therapy can initially worsen their clinical condition. It may be that they are not feeling that badly because of their MDS, but once they embark upon a course of therapy, the complications of the therapy actually become more burdensome than the disease itself. However, we like to avoid discontinuations of therapies, because we have relatively limited options in this disease, and we do not want to cut something out before we have been able to see its benefit. Patient characteristics are always important when we embark upon therapy. As I have alluded to, as this is an older population, age and frailty are something to consider; but I always tell my patients that while age is certainly a state of mind and a relative condition, the organs themselves, especially the liver, the kidneys and the heart, do have a chronological age for the patient. I also think expectation management is extremely critical in all areas of oncology, but especially in myelodysplastic syndrome. If we can help the patients and their families to realize that both the hematologic and non-hematologic adverse events usually decrease in frequency as the patient goes through their therapy, this can be very helpful to get them to stay on their prescribed treatment strategy. Finally, I always try to keep in the front of my mind that something which is severe to me, compared to something which is severe to the patient, may not always be the same.



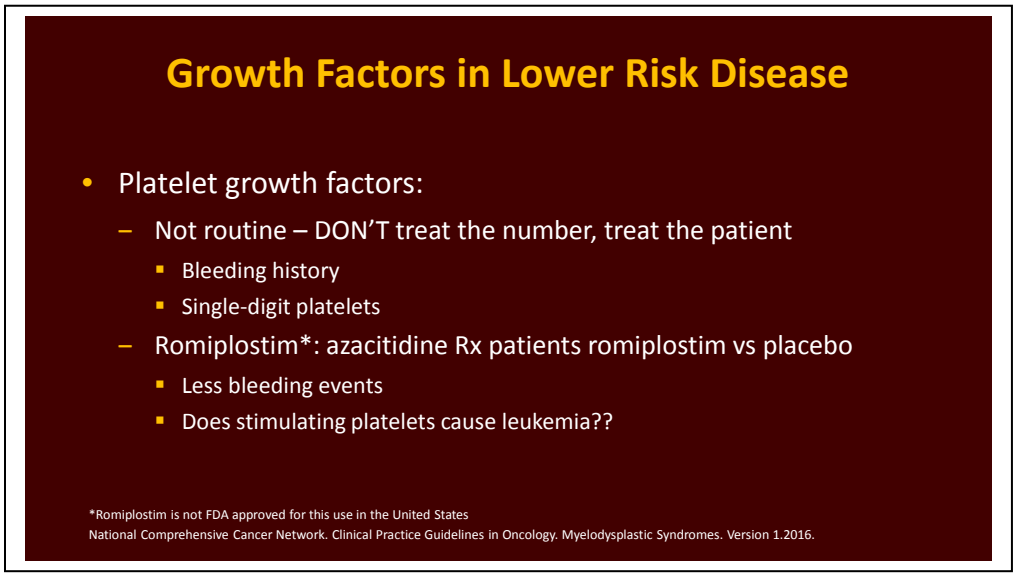
Let's first talk about growth factors. This is a very important group of therapies, especially in lower-risk disease. First, erythropoietin-stimulating agents (ESAs) are the most commonly used growth factor in myelodysplastic syndrome, but are not FDA-approved for this use. We often use the Nordic Group's model to show that, if we use something like an ESA in patients who have an erythropoietin level less than 500 and who are not heavily transfusion-dependent, the majority of these patients' responses will occur within 8 to 12 weeks. This gets back to that expectation management, if the patients are going to need to consistently receive the shots over that time period to ensure they receive benefit. A fixed-dose regimen versus a weight-dose regimen is very important, and again, explaining to the patient upfront



that their dose will be consistent and up-titrated over time, not based on their size but based on their response, is important. Maximizing the benefit of the erythropoiesis-stimulating agents can be enhanced by ensuring that our patients (especially females) are iron replete. We also need to ensure that male patients are testosterone replete, as testosterone deficiency is a very significant cause of anemia that is sometimes underappreciated, especially in elderly males. Unfortunately, studies of these erythropoietin-stimulating agents, or EPO, in solid tumor patients have shown an increase in myocardial infarctions and cardio- and cerebral-vascular events as well as clots. There are also warnings about increased tumor growth. This has resulted in a lot of concern and angst in some myelodysplastic syndrome patients, but it should be explained to the patient and their providers that no data yet shows that these effects are problematic in myelodysplastic syndrome, and that this is a very good first-line agent in lower-risk disease. The one thing that can be challenging in an adverse event that is not medically related, but still practical for the patient, is that since these are not FDA-approved in MDS, there is sometimes an impact on insurance coverage; an extra letter of approval or preauthorization can be very helpful in decreasing the patient's stress about this issue.

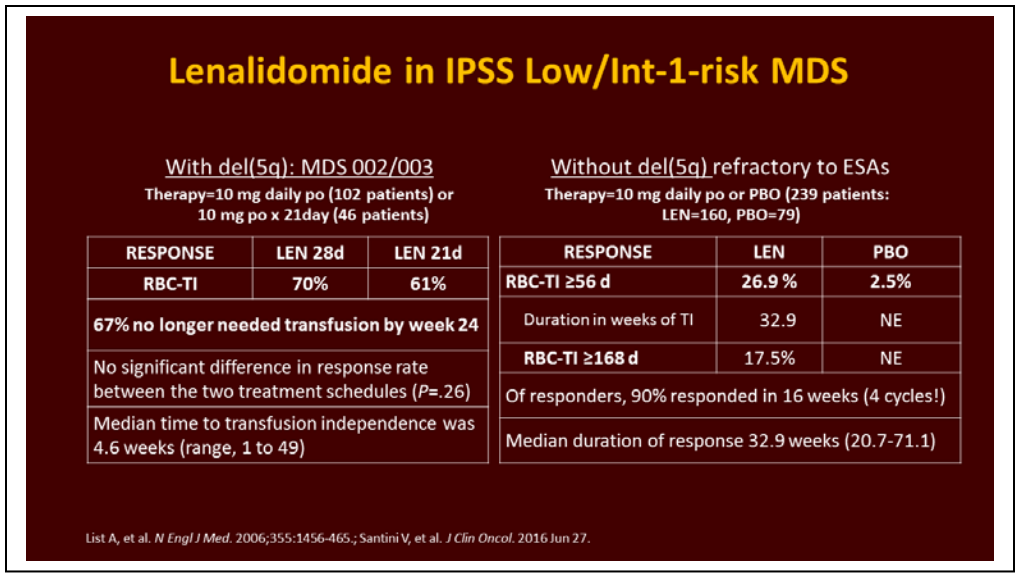
Further growth factor discussions often center on white cells. This is very important to recall for these patients: it is not routine to use white cell growth factors. It is not only about the absolute neutrophil count number but is also about the patient, and if they are, or are not, experiencing opportunistic active infections that are recurrent. Or, if they are having neutropenic fevers, there is some evidence, again from the Nordic Group, that if you combine erythropoietin-stimulating agents as well as G-CSF, you

may improve responses for anemia in patients who have refractory anemia with ring sideroblasts in particular. As with every medication, these are not without side effects, and sometimes white cell growth factors can make patients quite miserable, causing fever, bone pain, and, of course, injection site reactions. There is always the fear that stimulating the white blood cells could accelerate a patient's progression to leukemia, but this actually has not been borne out in the lower-risk group, which is reassuring. We can manage the fevers with acetaminophen, the bone pain with loratadine, and the injection site reactions sometimes with an EMLA cream if it is simply pain, or heat packs and sometimes even steroids if they are really having trouble tolerating them at the time of treatment. Pegfilgrastim requires less frequent dosing, but this is something we tend to discourage in MDS patients, because it has been associated with profound rises in the white count that are not safe and, in case reports, led to splenic rupture. This is why we tend to stick with G-CSF if we can. However, if frequent dosing is not possible because the patient is older or without a caregiver or themselves unable to give the shots, we can do lower doses at separate intervals, so that the patients can have an increase in their neutrophil count.



In my opinion, platelet growth factors are an open question in myelodysplastic syndromes. We saw in that original graphic that a portion of these patients do suffer with hemorrhage and this can be very problematic and even life-threatening, but again, we do not treat the number and we do not routinely use these. Bleeding history is very important to take in our thrombocytopenic elderly patients, as well as fall risk, and if patients do have platelet counts in the single digits, we have to think strongly about these. Romiplostim, which again is non-FDA approved for MDS at the current time, was compared in patients to a placebo, and they did have less bleeding events when they received this thrombopoietin mimetic. There was the question, which actually led to the trial being stopped early, of whether stimulating the platelets increased the blast count and thus increased the patient's acceleration to leukemia. Ultimately, when the study closed and was analyzed, this did not bear out, and the hazard ratio for progression to leukemia was the same in the romiplostim versus the placebo arm. So again, this is always an active discussion to have with patients, depending on their bleeding risk.

Lenalidomide is very commonly used in lower-risk disease. We think of it classically in the deletion 5q syndrome, as it was studied in the MDS 002 and 003 studies in patients who specifically had deletion 5q. 102 patients were given 10 mg of lenalidomide daily and about half that number were given 10 mg 21 out of every 28 days, which is a standard cycle. It should be noted that there was a tremendous response in terms of improvement from the anemia, augmentation of the hemoglobin, and actually



transfusion independence, or the RBC-TI as noted in the chart shown. The patients that received the 28-day cycle had transfusion independence at a rate of 70%, and patients on the 3-week cycle had a rate of 61%; two-thirds of the cohort with deletion 5q lower-risk MDS no longer needed transfusions by week 24. I personally like to start at the 28-day cycle, but I make note of this when we are thinking about adverse effects, that there was not a significant difference in the response rate between the two treatment schedules, because of the way the statistics were done in this trial. So, if you have a patient with deletion 5q, lower-risk MDS, who does need that week off, it is very reasonable to consider this. And again, getting back to that expectation management, if they can push through for at least a cycle and a little more, they have to get to that metric of median time to transfusion independence, which is the goal for all of these patients. On the other side of the slide, a more recently published article looked at patients with lower-risk MDS who did not have deletion 5q myelodysplastic syndrome. These were patients predominantly in Europe who were refractory to erythropoiesis-stimulating agents, and used a very similar dosing schedule. In this case, they had 10 mg daily by mouth 28 out of 28 days for every cycle, and 160 patients received the lenalidomide while 79 received the placebo. Certainly, you can see that the transfusion independence for the patients without deletion 5q was much less. It was only about 27%, which was reminiscent of the Phase 2 trial that had been done, but in this Phase 3, you can adequately tell patients that about 27% of the patients who do not have deletion 5q are going to have a meaningfully clinical benefit from lenalidomide. Something that I think is quite important, and probably what I use this study for the most, is that, of those who are going to respond, 90% of those responded within 16 weeks, or 4 cycles. So, again if you are having some adverse effects and the patient is trying to decide if they should push through or not, I tend not to push it past 16 weeks, because 90% have responded by that time. A patient who is really suffering with the toxicity of the drug is unlikely to have fallen to that 10%.

Let's talk about some hematologic adverse events associated with lenalidomide from the original deletion 5q study, which characterized these very nicely. In the patients that received the 28-day cycle, over half had grade 3 or grade 4 neutropenia, really markedly depressed absolute neutrophil counts. 44% had thrombocytopenia, which is what we often think of as the largest toxicity of lenalidomide, and bleeding events are something to be concerned about. Anemia was not a big problem for these patients, even though that was part of their eligibility to get on a trial. And then overall leukopenia was relatively low, but we worry far less about the total white count than we do about the neutrophils. So, I do counsel patients strongly about neutropenic precautions and the risks of having a low absolute neutrophil count when we are using lenalidomide. There were very low rates of febrile neutropenia in this original study, and in the registration trial for lenalidomide in deletion 5q patients, growth factors

for white cell support were permitted when the patients had fever; this is how I tend to avoid this adverse effect if I can. Something I will mention is that, in this original trial, rash as a non-hematologic adverse event of lenalidomide was not reported here, but it has been as high as 20% in the other trials, and I think lenalidomide rash is one of the biggest adverse effects that we have to think about for these patients.

Most Frequently Observed Hematologic Adverse Events: del 5q MDS Safety Data

N=148	Grade 3 or 4
Neutropenia	55%
Thrombocytopenia	44%
Anemia NOS	7%
Leukopenia NOS	6%

- Grade 3 or 4 febrile neutropenia reported in 4.1% (6/148) of MDS patients
- In registration trial, G-CSFs were permitted for patients who developed neutropenia or fever in association with neutropenia
- Patients may require the use of blood product support and/or growth factors

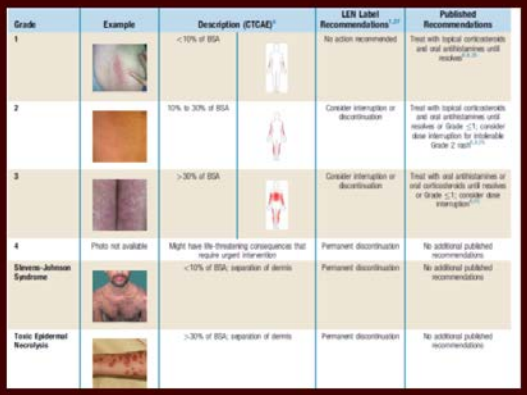
- RASH NOT reported here but as high as 20% in other trials

List A, et al. *N Engl J Med*. 2006;355:1456-1465.

When there was an analysis done at the Celgene Global Drug Safety database, it showed that a non-serious rash was the leading cause of permanent discontinuation of lenalidomide in these patients, and this is what I have seen in my own practice as well. I show here a lovely reference from about a year ago that shows some different examples of the rash, and you can see there is a variety. The grade 1 rash is an erythema covering less than 10% of the body surface area. This is something I forewarn patients about, so that we do not get overly concerned about it. If it is really bothering them in terms of pruritus or is aesthetically displeasing, I will prescribe topical corticosteroids or oral antihistamines. If it involves more of the body surface area, we have to have a discussion about it; we need to consider holding the drug for a few days, and again using those topical steroids or otherwise, to see if we can get the patient to tolerate it. A grade 3 rash, which is more than 30% of the body surface area, sometimes requires oral corticosteroids in order to get it to resolve. In these cases, I do discontinue lenalidomide, at least temporarily, until we can get the rash to resolve. Beyond that, to me it is nearly an absolute contraindication to continue it or even allow for dose interruptions. If you are having Stevens-Johnson syndrome or anything above a grade 4 reaction, we have to really consider that

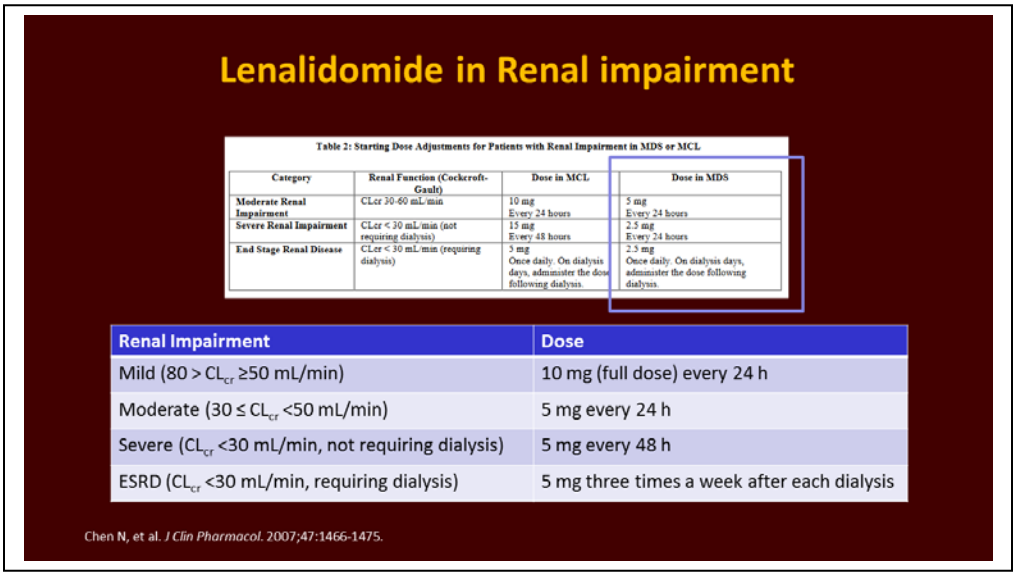
Lenalidomide Rash

- An analysis of the Celgene Global Drug Safety database showed that non-serious rash was the leading cause of permanent early discontinuation of LEN in patients with MDS treated in the post-marketing setting

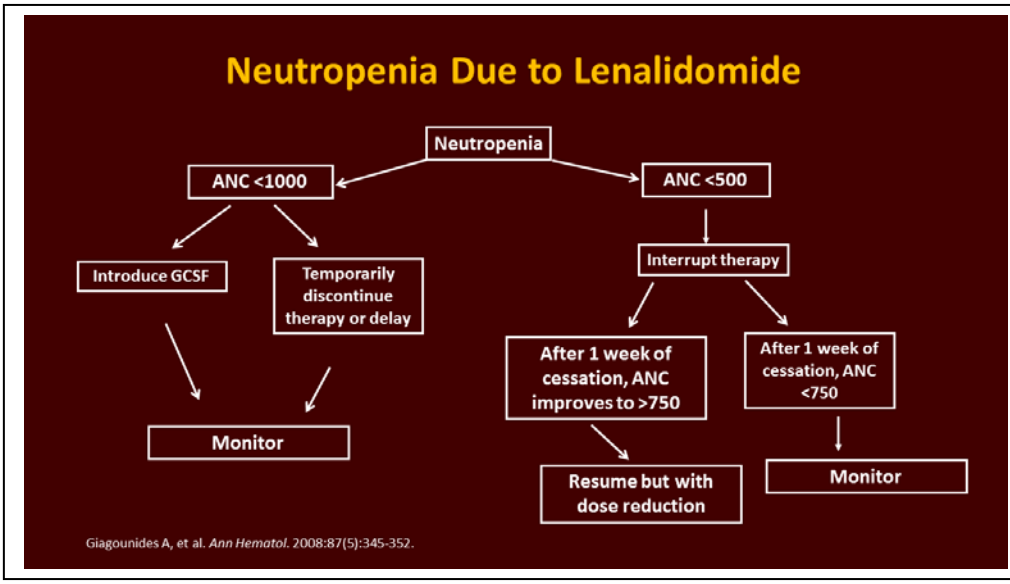


Tinsley SM, et al. *Clin Lymphoma Myeloma Leuk*. 2015;15 Suppl:S64-69.

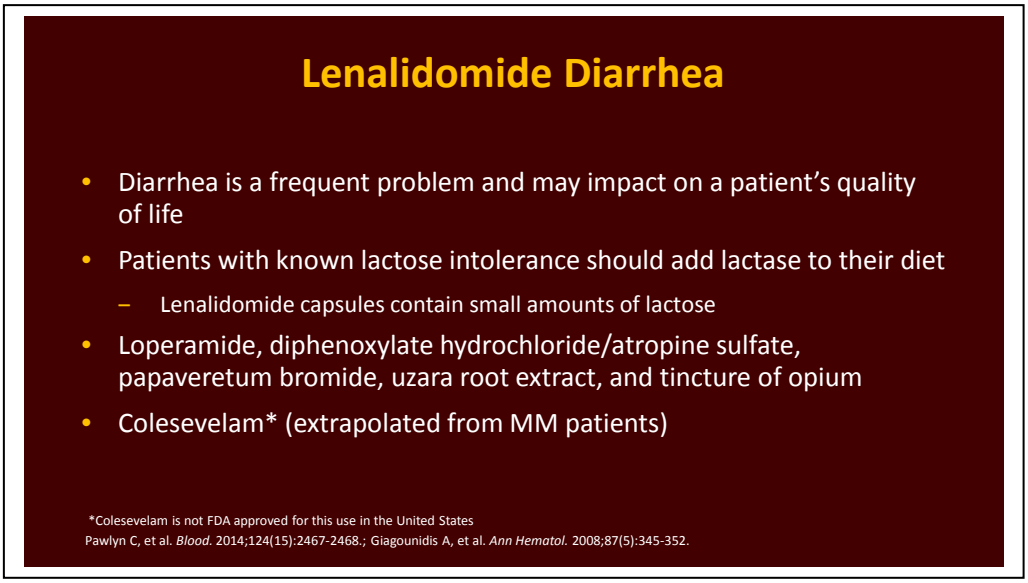
the medicine is probably not worth it for these patients. So, again, grade 3 and below, we can use supportive management with some dose interruption, but it is not an absolute contraindication to re-initiate the drug and see if a patient and their skin can tolerate it. But it is a reason that, once I start lenalidomide, I ask the patients to call me very soon if they notice any rash, and I see them so that we can decide what steps should be taken.



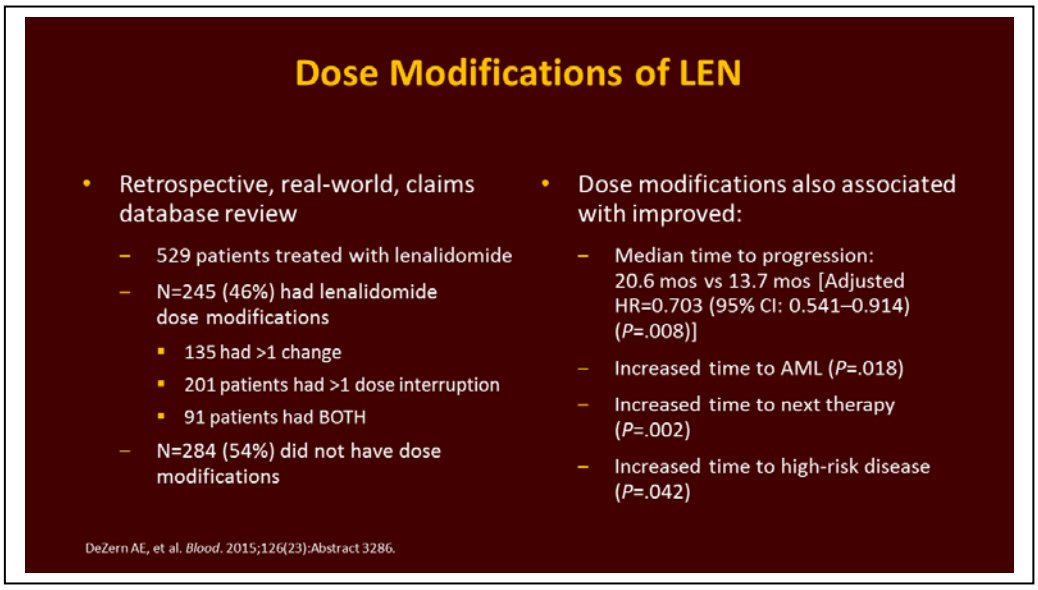
The next thing that is always a consideration is how to dose in some of our older patients who have renal impairment. At the top of this slide, I show the package insert for lenalidomide for patients who have renal impairment, and I think this is the place where we most often look for dose adjustments. A study was done that specifically looked at the pharmacokinetics of lenalidomide, and even examined this in patients on dialysis. If these are some of our older patients with lower-risk MDS with whom we are trying an oral medication, we certainly do not want them to have some of those medication-related hematologic adverse toxicities – but I would like to see if they may be able to tolerate the dose, maybe even for the 16 weeks. For these patients, I adjust the dosing for renal impairment as listed in the lower table. So, if they just have mild renal impairment, I give them the full dose. If they have moderate renal impairment, which is defined as a creatinine clearance of less than 50 mL/min, those are the patients that I start at 5. I should note that even though the original studies started at 10, and this was how these drugs came to approval, if the patient has renal impairment or is a little bit older, starting at 5 is not wrong and you can always up-titrate if necessary. Patients with severe renal failure who are not on dialysis should receive every-other-day dosing. There is also one study concerning the rare patient on dialysis who needs lenalidomide, suggesting that dosing three times a week can be considered.



Here, I show a flowchart that is from a lovely review article by Dr. Giagounides a number of years ago, looking at how to best deal with neutropenia due to lenalidomide. If the neutrophils fall less than 1,000, we can talk about G-CSF and temporarily discontinue or delay therapy. If they fall below 500, interruption of therapy really is mandatory. Depending on how quickly the cytopenia resolves, we can decide what to do after cessation. Thinking back to the previous slide, these dose reductions can be appropriate, even with reportedly normal renal function, if the patient is really suffering from lenalidomide adverse events.

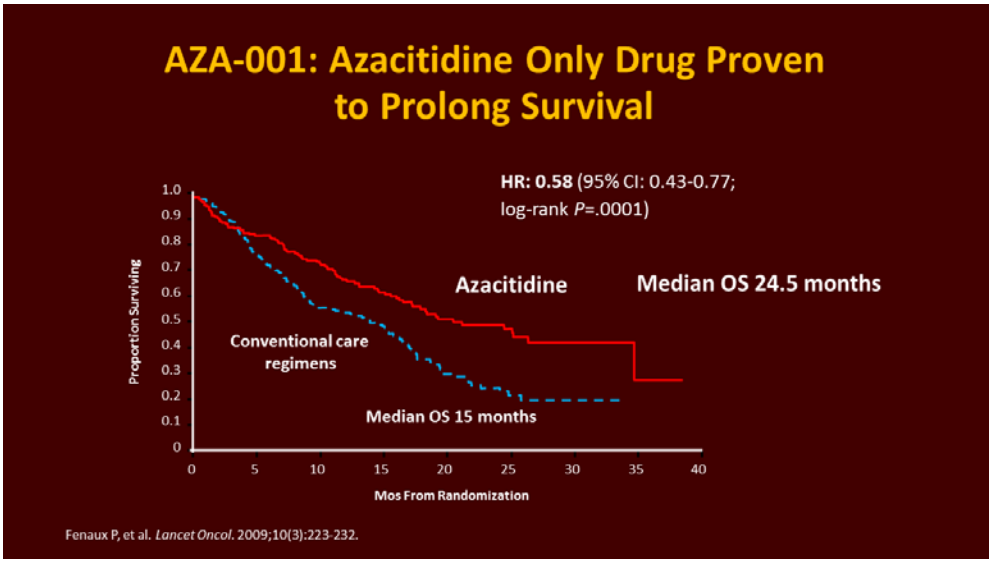


Last, but certainly not least, is lenalidomide-associated diarrhea. This is a really frequent problem, and is probably the biggest complaint that patients have after rash. If patients, especially older patients, have become lactose intolerant, they can add lactase to their diet, and I often remind them that lenalidomide capsules contain small amounts of lactose. Loperamide can be used, as well as other antidiarrheal agents. I will just mention a pearl that is much more recent: colesevelam is a medication that is approved for hypercholesterolemia, but there was a study in multiple myeloma patients who were also being treated with lenalidomide. In these patients, colesevelam was shown to control the lenalidomide-associated diarrhea very well. It is a bit of a more potent agent, but if you have patients who are really suffering from this adverse effect of therapy, this is something that I keep in the back of my arsenal, if the more traditional regimens like loperamide or tincture of opium are not working.

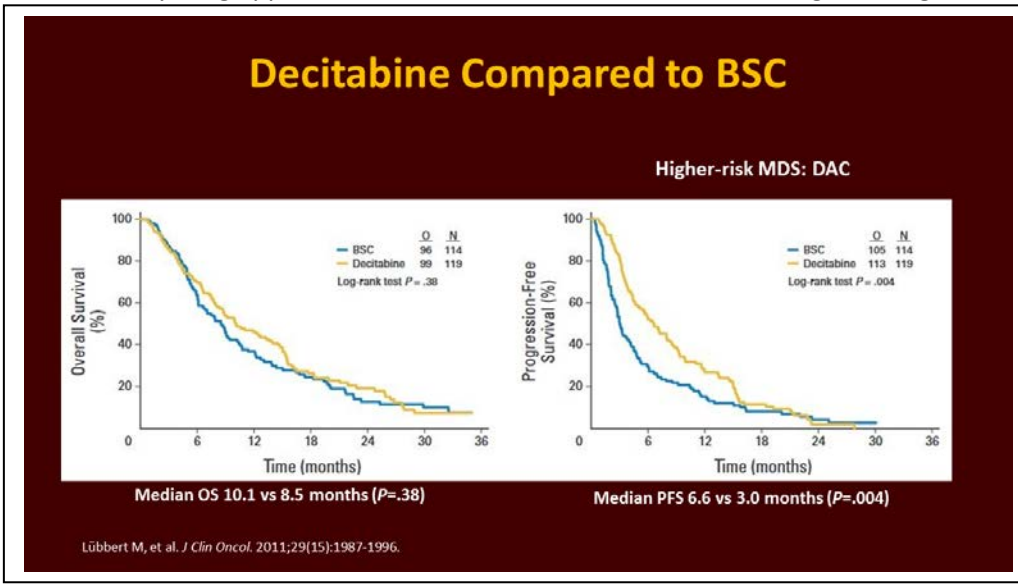


Here are some dose modifications of lenalidomide. This was a recent abstract which will soon be published that looked at 529 patients with lenalidomide, and it suggested that dose modifications are common and acceptable. This speaks to the fact that dose modifications can be associated with improvements in time to progression, a longer time before the patient gets AML, and a longer time of tolerating the therapy, as well as increasing the time to the next therapy. I think this is important and comforting for patients as well as for us as clinicians, that it is okay to dose-modify so that the patient can achieve tolerance of adverse events such as neutropenia, renal impairment, or rash. Once we hit upon the right dose for an individual patient, they will be able to tolerate the adverse events and stay on therapy longer.

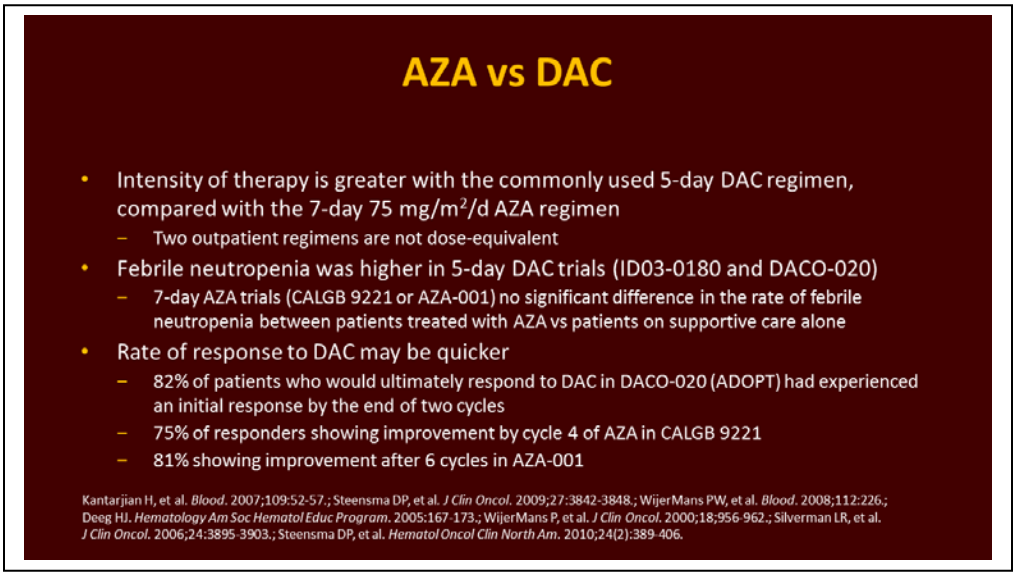
Let's move forward to higher-risk disease. Based on the AZA-001 study, azacitidine was the only drug proven to prolong survival, and this is why this is one of the three after lenalidomide, and then with decitabine, that are approved medicines in MDS.



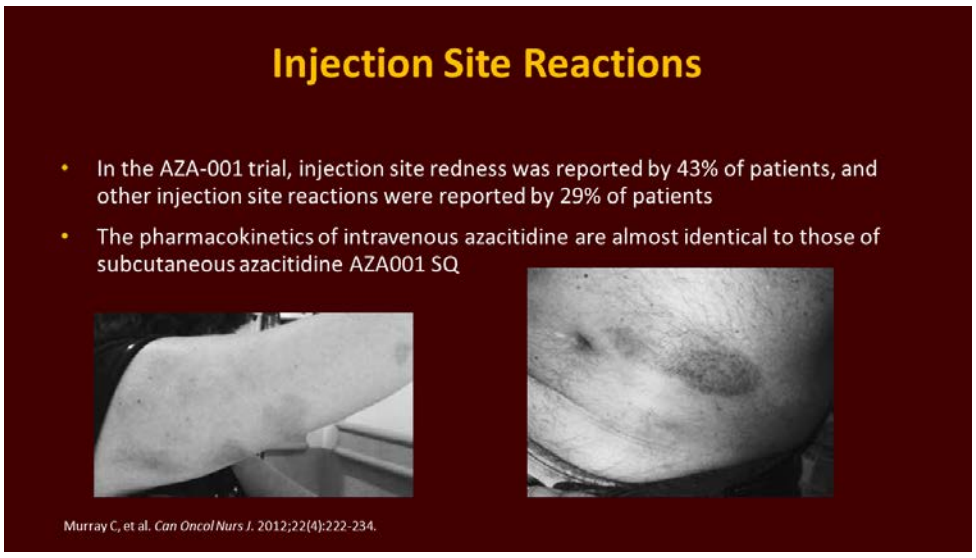
I show you the azacitidine and decitabine curves together because, in actuality, while azacitidine has been the only drug approved to extend survival, decitabine is still a good drug. I mention this in terms of adverse effects intolerance for patients, because both are very routinely used in the upfront setting for higher-risk patients.



In terms of azacitidine versus decitabine, I'll note that the intensity of therapy is greater with the more commonly used 5-day decitabine regimen. This was slightly different than the regimen that was used in the previous study resulting in the survival curves on the previous slide. It is more intense compared to the 7-day 75 mg/m^2/day azacitidine regimen, and so these two very commonly used outpatient regimens are not dose equivalent. I always mention to patients, as well as their providers, that febrile neutropenia rates were higher in the 5-day decitabine trials than they were in the 7-day azacitidine trials. I think that this is important, in terms of expectation management for the patient, as well as in attempting to avoid hospitalizations as well as this adverse event of therapy. There was no difference in the CALGB study, as well as the AZA-001 study, of febrile neutropenia in patients who were receiving azacitidine versus those who were receiving supportive care. This is something to consider – that, in terms of what the goals of therapy are and expectations for the patient, the rate of response to decitabine may be quicker. 82% of patients who ultimately responded to decitabine had this response by the end of 2 cycles, whereas with azacitidine, about 75% of the responders did not have improvement until cycle 4. You then gather a few extra percentage

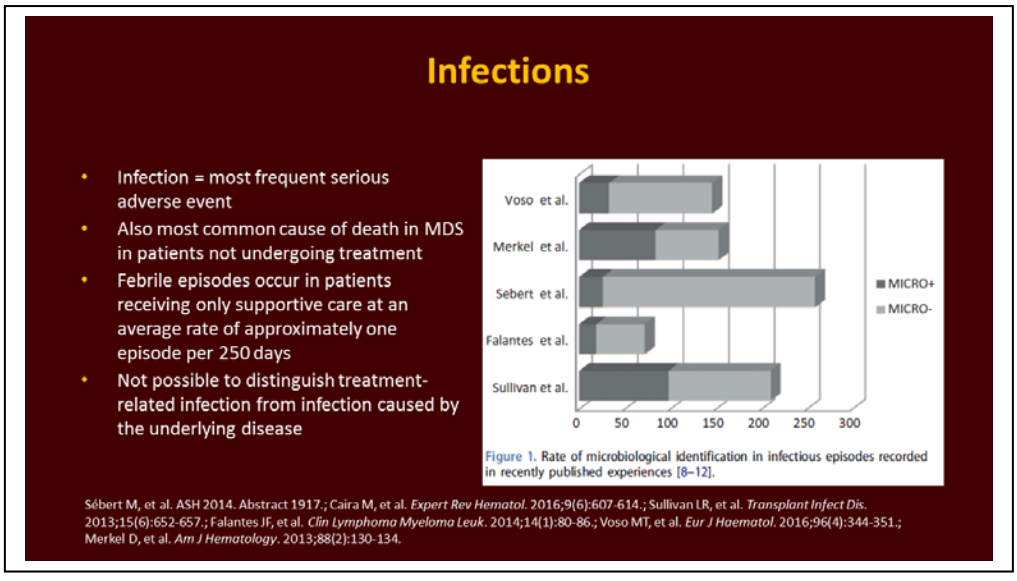


patients after 6 cycles in the AZA-001 study. So, these are conversations to have with your patient about dose intensity, as well as time to response, in terms of how we manage the adverse effects.



I will remind you that, in the AZA-001 trial, these patients were given the drug subcutaneously. I would say that it is more common these days, for patient comfort and expediency, to give it through an IV for ease of administration, even at the local clinic. Subcutaneous administration may still be done, but this is always a discussion to have; injection site redness was reported in 43% of the patients in the AZA-001 study.

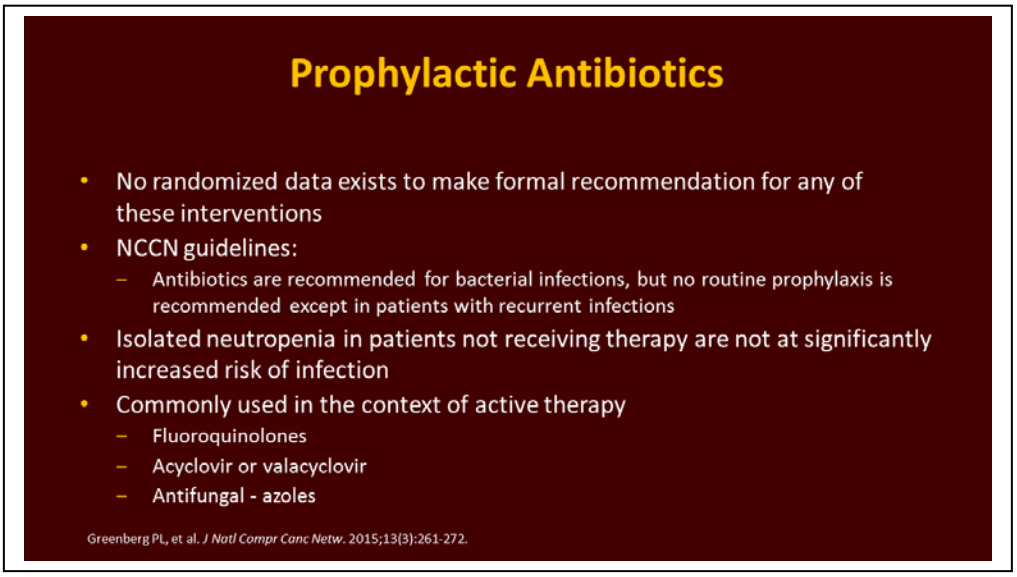
While it hasn't been studied head-to-head, it is assumed that the pharmacokinetics of intravenous azacitidine are almost identical to those of the subcutaneous azacitidine. So, that can reassure us that, if patients are having some of these unsightly or painful injection site reactions, it is okay to switch to intravenous for the patient.



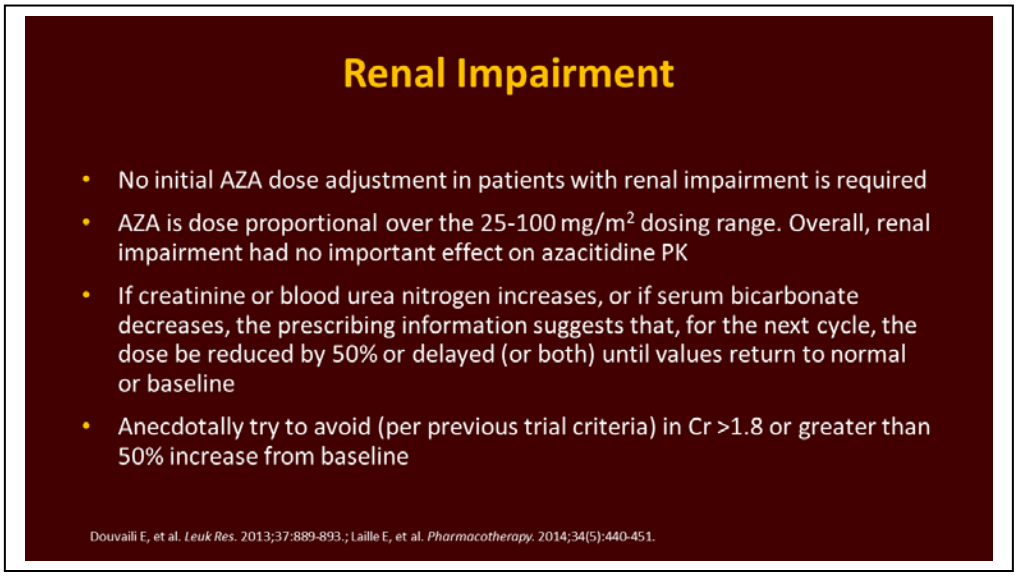
In terms of infection, I mentioned some of the dose intensity issues between azacitidine and decitabine, but infection still remains the most frequent serious adverse event for these patients. It is also the most common cause of death in MDS patients who are not undergoing therapy. Febrile episodes occur in patients receiving supportive care only, without any treatment for their MDS, at a rate of about one episode for 250 days. It is slightly higher in some of the studies with decitabine or azacitidine, but it is not always possible to distinguish treatment-related infection from infection caused by the underlying disease. That is why I often prepare patients, and tell

them to always notify us of febrile neutropenia. We can then decide how we'll manage it, and may not necessarily hold therapy for this reason, if there is no documented infection.

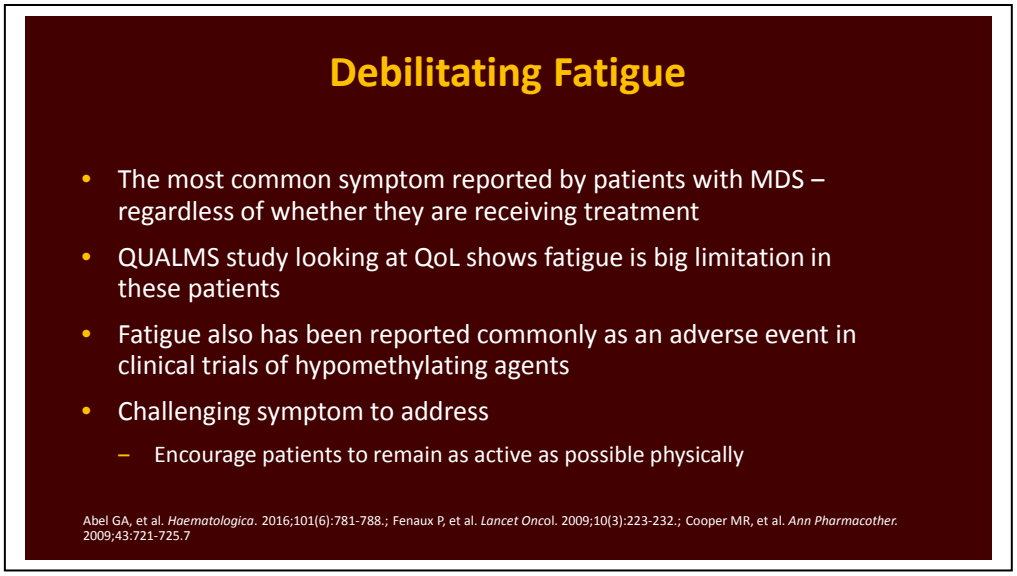
On the right side of the slide, it shows that in the minority of patients, represented by the darker blocks on the bar graph, there is not a positive organism identified in this febrile neutropenia, and so that is why it is a challenge for us to know how to manage this adverse event. Many people use prophylactic antivirals, antibacterials, and antifungals as supportive care in this patient population to avoid this serious adverse event.



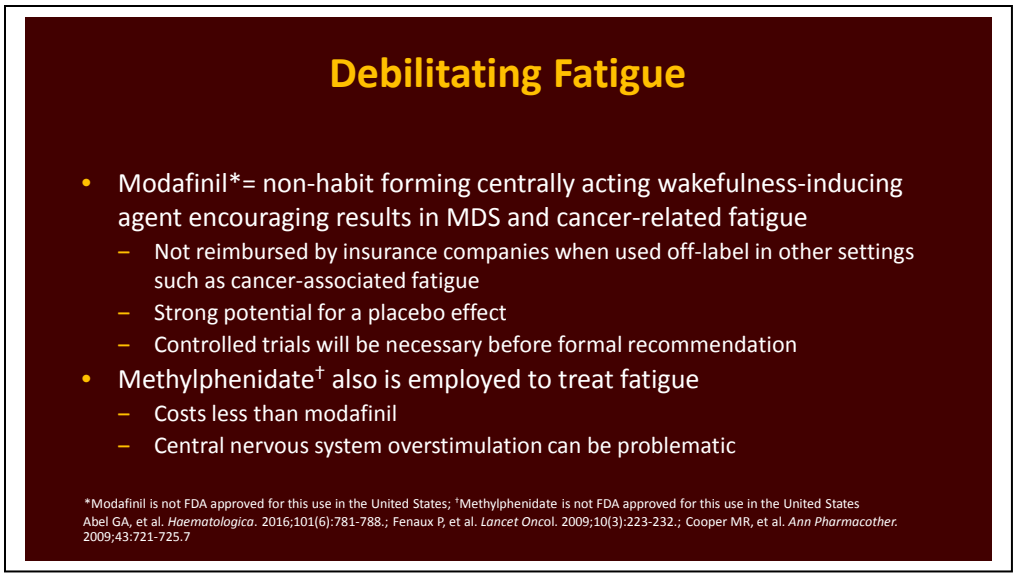
This brings up the question of prophylactic antibiotics. There are not any randomized data to make truly formal recommendations for these interventions. The NCCN Guidelines do say that antibiotics are recommended for bacterial infections, but actually no routine prophylaxis is necessary except in patients who have these recurrent opportunistic infections. As I mentioned, it is not at all uncommon to add an antiviral and antifungal in today's environment, but it can be a challenge and a pill burden for these patients. Without really strong evidence that it is truly beneficial, it is always a discussion with the patient at the bedside. And again, sometimes it is not even about the number, but about the patient. There are certainly older patients who have neutrophil counts in the 200s and never have a fever and do not have any problems with opportunistic infections. We must consider the patient in front of us, because sometimes the prophylactic anti-infectives can have side effects of their own. That being said, I have listed here what is most commonly done in these patients in community practice.



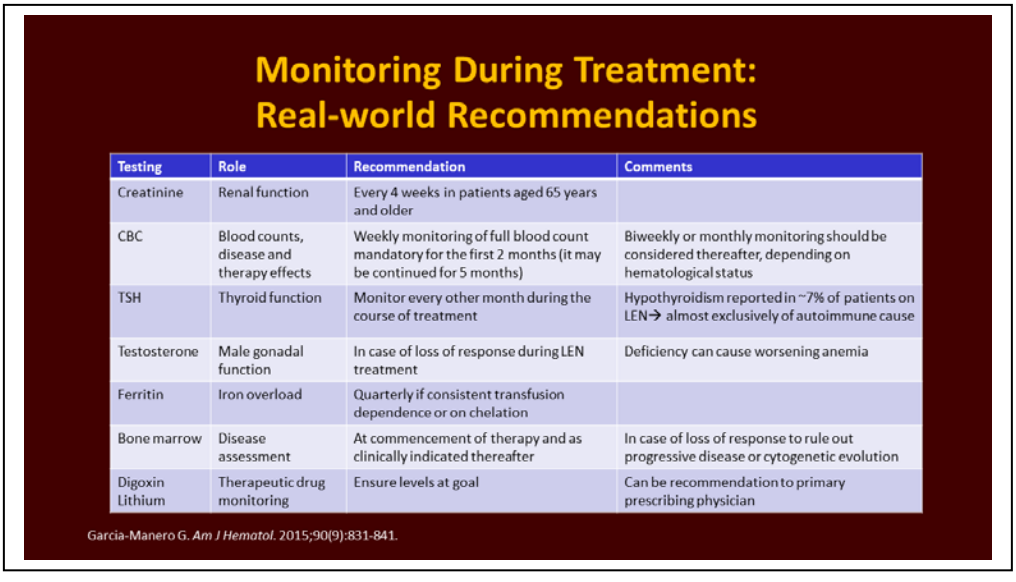
Again, renal impairment in our older patients with their chronologically-aged kidneys is something to think about. There is not an azacitidine dose adjustment that is required. Azacitidine is dose proportional over quite a dosing range. The standard, as we mentioned, is 75 mg/m^2 for 7 days. Over the range suggested here, there have been nice studies looking at the pharmacokinetics that can reassure us about this. Anecdotally, I tend to try and avoid it in a creatinine over 1.8 and so sometimes if I have a patient on a 7-day cycle, I will stop it for 4 or 5 days, if their creatinine increases over the course of the cycle. Alternatively, I might shorten a cycle or dose reduce on subsequent cycles, if the patient has experienced problems with this after they have been treated with azacitidine.



I think fatigue is probably one of the most challenging symptoms in all of medicine, but particularly in MDS. I think this is something that is important to discuss with patients, and talk through the fact that their MDS causes fatigue, as well as their therapy for this disease. Again, it is that balance of the considerations of therapy and the risks/benefits for the patient. It is the most commonly reported symptom in all MDS studies. More recently, there is something called the QUALMS which is the Quality of Life Assessment tool in Myelodysplastic Syndrome, and it really speaks to what a large limitation fatigue is for these patients. This has always been the most commonly reported adverse event in any clinical trial of azacitidine or decitabine, and it is an incredibly challenging symptom to address. I do encourage patients to remain as active as possible. We will talk about transfusions in a moment.

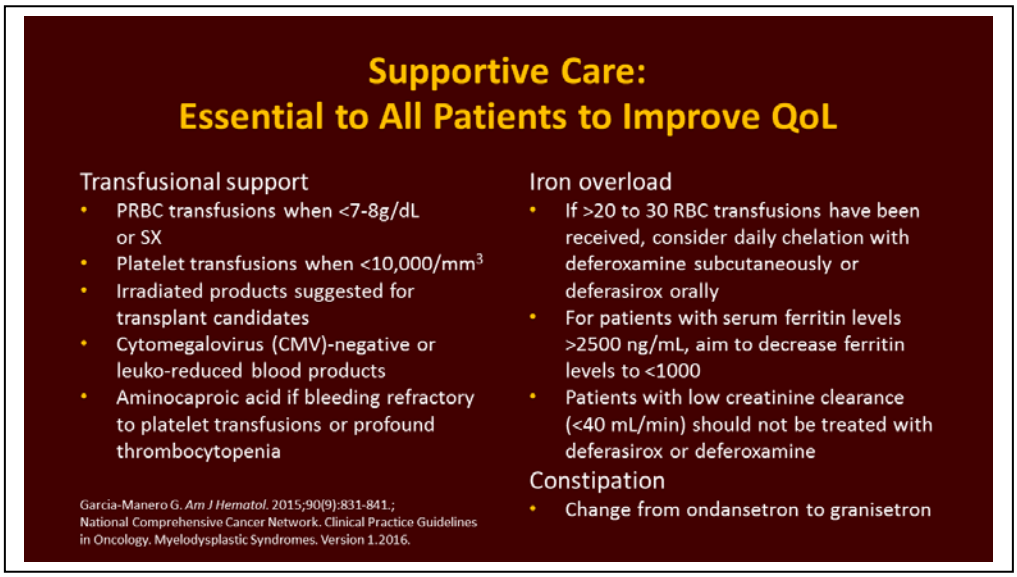


I personally tend to not to recommend stimulating medications, but modafinil, which again, is not FDA-approved in MDS, is a non-habit-forming wakefulness-inducing agent. It has been described in cancer-related fatigue and has had some encouraging results. Again, it is not reimbursed, and this can be challenging. There is also a strong placebo factor which is not necessarily a bad thing, but it is hard to make a formal recommendation with the limited data available. Methylphenidate is something I am seeing prescribed to patients, either by their psychiatrist or sometimes by their primary care doctor, much more frequently as an agent to treat fatigue. It certainly costs less than modafinil, but it can cause overstimulation. I think we really have to decide with the patient how debilitating the fatigue is, because some of the symptoms of these agents, such as irritability and excessive crankiness, can be a challenge, even if they are "less tired."



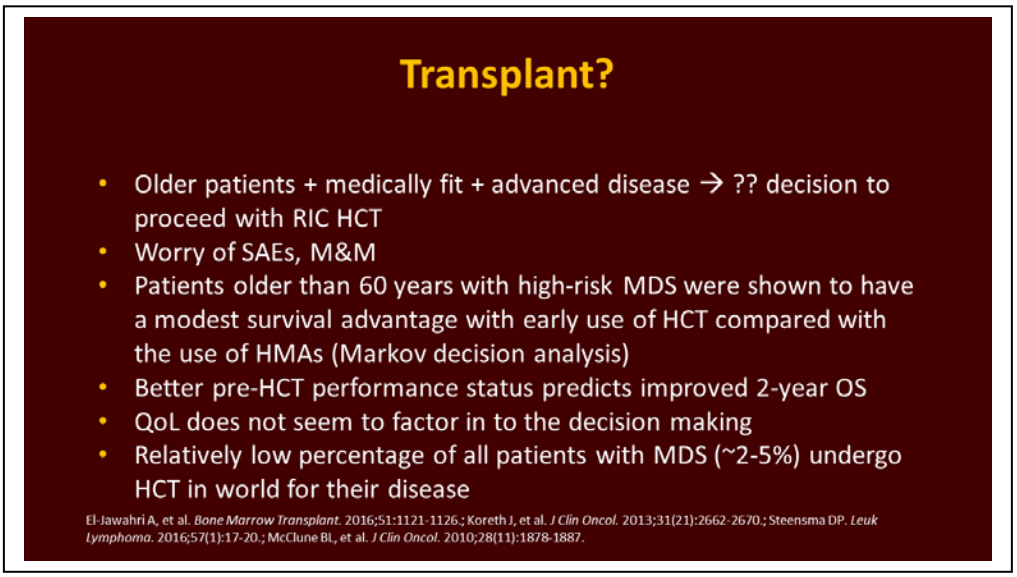
So, I will leave you over the next couple of slides with some real-world recommendations about how to monitor these patients, again always trying to avoid the adverse effects if we can. We have talked a lot about renal function. I tend to check the creatinine at least once a cycle in patients who are much older, maybe 75 or 80, sometimes twice a week during the week of therapy to make sure there is no change. Obviously, the blood counts need to be monitored frequently, both on lenalidomide and either of the hypomethylating agents weekly; I think this is quite important, so that we can find out if the patient is experiencing neutropenia that will require a dose interruption or modification. Thyroid function is really important. Obviously, this is a cause of fatigue if you are hypothyroid or sometimes even hyperthyroid, and I tend to monitor it about every other month.

What is interesting, particularly in patients treated with lenalidomide, is that about 7% of patients were noted in all those trials to have hypothyroidism that was of an autoimmune cause. I have mentioned testosterone can be very helpful in older patients, and I often check it at the time of initiation of therapy and then later on if there is loss of response. If they become testosterone-deficient over the course of their therapy, I will usually bring in an endocrinologist or one of my internal medicine colleagues to make sure that we supplement testosterone if that is appropriate. Obviously, iron supplementation is very important for these patients; it is always a balance if they are becoming iron-overloaded from their transfusions. Regarding bone marrow, I do monitor it certainly at the beginning of therapy but only as clinically indicated thereafter. And therapeutic drug monitoring is something that sometimes goes unrecognized, but if you have an older patient with cardiac dysfunction on digoxin or someone who has psychiatric illnesses on lithium, all of the drugs that we have talked about for therapy for MDS can alter these levels, and we need to ensure that they remain at goal levels, and not subtherapeutic nor at toxic levels.



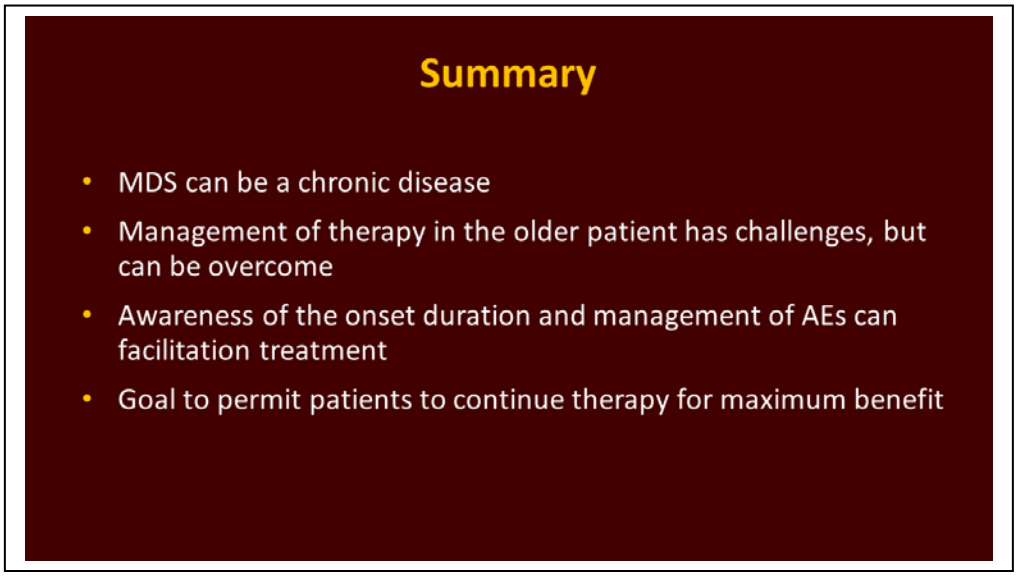
We have talked about supportive care, and I know you all know this well. Transfusional support guidelines are listed here, usually red cell transfusions if the anemia is worse than 7 or 8 g, or if the patient is symptomatic. Platelet transfusion is only if they are bleeding or less than 10,000. Irradiated products are very important. CMV-negative or leuko-reduced blood products are most common. And then, I do occasionally use aminocaproic acid if bleeding is hard to control and the patients are refractory. This is a very expensive medicine, especially for our older patients who might only have Medicare, and sometimes, this can be a true limitation to this aspect of supportive care. Remembering back to that initial graphic, iron overload is a problem in these patients. The recommendations for chelation I have listed here are from the National Comprehensive Cancer Network guidelines, and if they have had 20 or 30 or more red cell transfusions in a lifetime, chelation is important. Just in terms of managing adverse events, the iron chelators are challenging to tolerate, especially in older patients who might be a bit more prone to dyspepsia or GI upset or are already suffering from some mild diarrhea from their therapy, and this is something that we have to keep in balance. There is a guideline to ferritin levels, for when to begin as well as to remind us that these drugs are renally cleared, so that we must be respectful of their creatinine. It is always a balance, particularly with the iron chelators, if the patient is really having adverse effects from the iron overload or they are having more adverse effects from the therapy itself. The last thing I will mention in terms of quality of life and supportive care is constipation, especially with azacitidine. Obstipation was well-reported in the trials and is a common complaint for patients; it is especially a challenge when an elderly patient becomes obstipated. So, I tend not to give ondansetron or Zofran as the antiemetic when I am using azacitidine, and I use granisetron which does not have that side effect. That can be very helpful in

patients continuing to have regular bowel movements during their week of therapy in cutting out this adverse effect.



Lastly, a discussion on potential treatment-related adverse effects in MDS cannot go without having transplant noted. It is always a discussion in older patients who are medically fit, who do have higher-risk for more advanced disease. How do we decide if they should proceed with a reduced-intensity transplant? Again, just like all the discussions we have had about the regular therapies, there is always the worry of severe adverse events of transplant, as well as morbidity and mortality. In patients who are older than 60 years with high-risk MDS, they do have a survival advantage when transplantation is used early, compared to just using azacitidine or decitabine. This was a Markov decision analysis that was published out of the Dana-Farber Cancer Institute a few years ago that is very helpful in counseling these patients and it is something to consider. If the patient had a better pre-transplant performance status, this is going to predict about a 2-year overall survival, and is a reason to have this discussion before they may or may not have any adverse events of azacitidine or any other therapy. Quality of life has been looked at in terms of this, and should be factored into either the patient's or the doctor's decision to go to transplant, in terms of adverse events or not, and this is not an issue. That being said, there is still a very low percentage of all patients with MDS who undergo transplant, the potentially curative pathway, for their disease.

I hope that I have given you examples of how MDS therapies can be tolerated over the lifetime of a chronic disease. There are always challenges in these patients, especially because they are older, but they can be overcome. Awareness of these adverse events and



their management can facilitate good treatment for a longer time, and allow our patients to remain on therapies and achieve maximal benefit.

I would like to thank you all for viewing this activity. For additional resources, please view the other educational activity on *managingmds.com*.