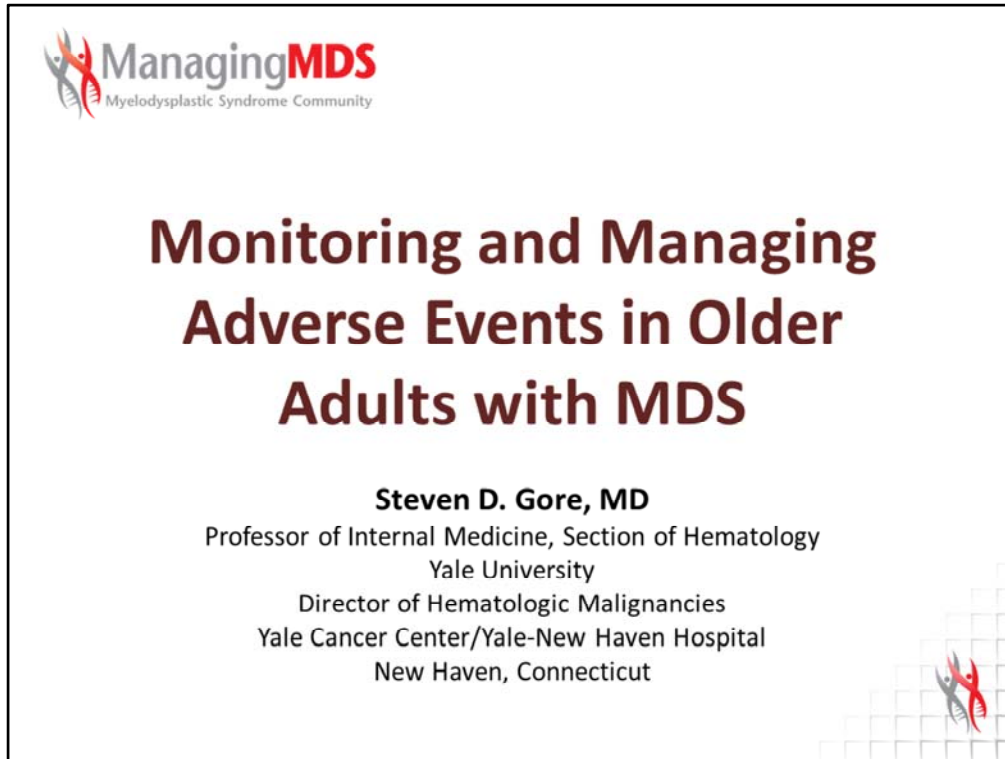# Monitoring and Managing Adverse Events in Older Adults with MDS

Welcome to *Managing MDS*. I am Dr. Steven Gore. In today's presentation, I will be reviewing monitoring and managing adverse events in older adults with myelodysplastic syndromes (MDS). Older adults with MDS have an increased risk for experiencing treatment-emergent adverse events, and ideally, they require tailored monitoring strategies for managing associated toxicities. In this activity, I will cover the major adverse events associated with the currently approved available therapies, as well as toxicities of notable concern in older patients with MDS. I will leave you with strategies to manage adverse events in older patients with significant comorbidities, while preventing the discontinuation of therapy and optimizing the benefit of treatment. Let's begin.
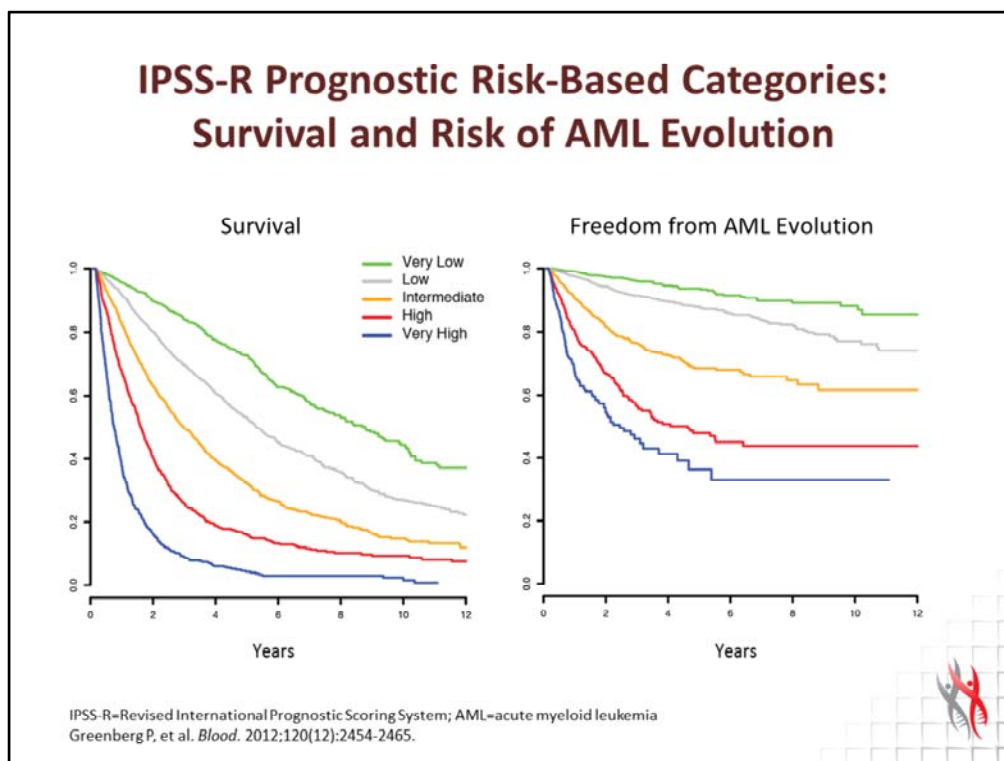
Establishing Goals of Treatment

- Understanding disease
- Natural history
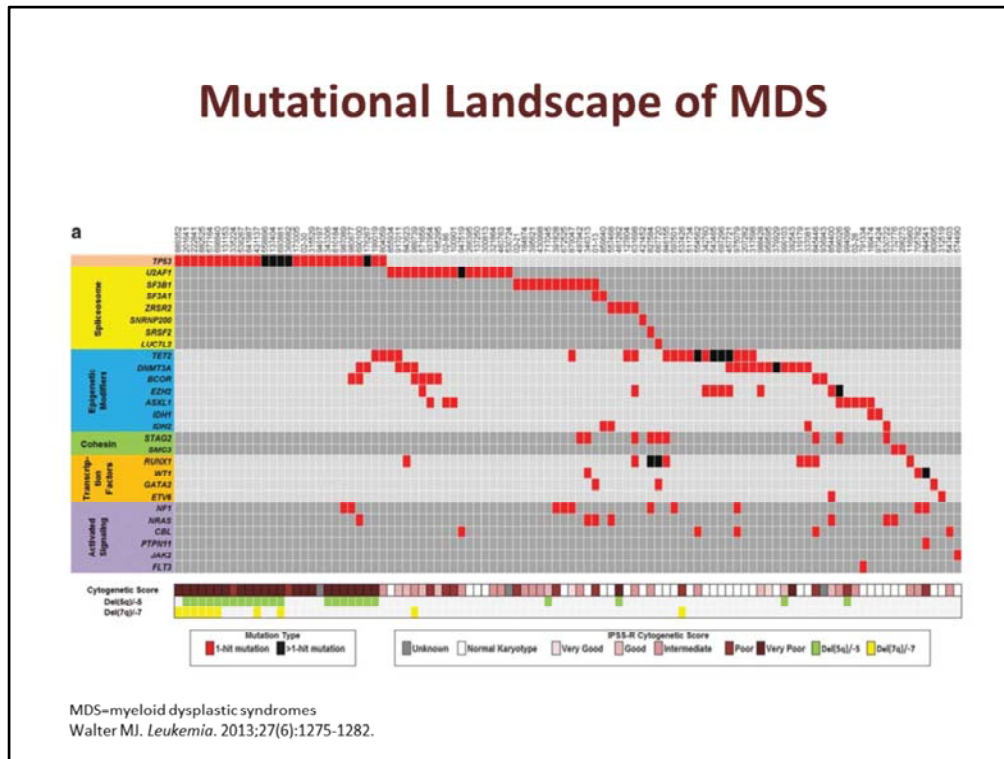- Patient hopes/expectations
- Palliative versus curative

For any patient with MDS, when one is starting to plan their therapy, it is really critical to establish the goals of treatment. This is particularly true in the elderly, because depending on what we are trying to accomplish, patients and physicians may be more or less willing to tolerate certain adverse events. In order for patients to help partner with a physician in establishing their goals for treatment of their disease, they need to understand their disease, which is by no means easy in this complicated set of diseases that, for the most part, patients are not familiar with. The natural history of their disease. The physician needs to understand what are the patient's hopes and expectations. Is this a robust older patient whose goal is cure, if possible, even if that means some risks of significant toxicities and even treatment-related death? Or is this a patient who really wants best quality of life, really wants to palliate their cytopenias? We really need to know what the patient's goals are. For some patients, all they really care about is getting to their granddaughter's wedding the next year and after that whatever happens, happens. Like I said, for other patients who are busy bungee jumping around in the jungles of Brazil, they want their shot at a cure, and there is everything in between. We need to establish whether our approach is going to be palliative or curative.

IPSS-R Prognostic Risk-Based Categories: Survival and Risk of AML Evolution

IPSS-R=Revised International Prognostic Scoring System; AML=acute myeloid leukemia
Greenberg P, et al. *Blood*. 2012;120(12):2454-2465.

We need to help patients understand the natural history of their disease. In order to do this, I usually use one of several prognostic models which are currently available based on the routine clinical data. The most commonly used one, of course, is the IPSS-R, the revised version of the old IPSS (International Prognostic Scoring System). I would note that many physicians still use the IPSS, and in my opinion, that is no longer adequate because it does not stratify patients clearly enough. There is also the World Health Organization Prognostic Scoring System (WPSS). The WPSS, which is used far less, has certain advantages because the WPSS was designed to be applied at any time in a patient's treatment course, whereas the IPSS-R theoretically only pertains to the patient at initial diagnosis. However, in my experience - and I usually calculate both the WPSS and the IPSS-R for each patient (I use an app for either of them on my phone) - almost to a patient, the two end up being very comparable. I think either way is really okay. As most of the audience is probably familiar, the IPSS-R divides patients into five risk categories. I personally think that it is important to emphasize the expected survival of a patient rather than the freedom from AML (acute myeloid leukemia) evolution. This concept of AML evolution, I think, is overplayed to patients because the AML associated with this particular disease is really just worsening MDS. I think when patients are presented with that, all they worry about is, do I have leukemia today? I deal with this by telling them that MDS is in fact a chronic leukemia; they have leukemia today, and this AML thing is just a name change that we do at 20% blasts. I really emphasize the survival. I actually do use these survival curves when appropriate, when a patient is robust enough intellectually, to be able to show them what can be expected and what the goals therefore would be if we were to try to change the natural history for that patient.

Mutational Landscape of MDS

MDS=myeloid dysplastic syndromes
Walter MJ. *Leukemia.* 2013;27(6):1275-1282.

Now, the IPSS-R is still not the last word because of the explosion in genomics which has happened over the past several years. What you see in this particular slide from Matt Walter from Washington University in St. Louis is a landscape of mutations found in a large variety of MDS patients. The details are not so important, but you can see that the mutations fall into a few categories. One is abnormalities of genes constituting the spliceosome, which is responsible for editing RNA. There is a variety of genes involved in epigenetic modifications. Then, you can see others as well, such as transcription factors and advanced signaling.

Impact of Mutations

Hazard Ratios for Death in a Multivariable Model		
Risk Factor	**Hazard Ratio (95% CI)**	**P Value**
Age ≥55 years vs. <55 years	1.81 (1.20-2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69-3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42-4.91)	<0.001
High vs. low	5.85 (3.63-9.40)	<0.001
Mutational status		
TP53 mutation present vs. absent	2.48 (1.60-3.84)	<0.001
EZH2 mutation present vs. absent	2.13 (1.36-3.33)	<0.001
ETV6 mutation present vs. absent	2.04 (1.08-3.86)	0.03
RUNX1 mutation present vs. absent	1.47 (1.01-2.15)	0.047
ASXL1 mutation present vs. absent	1.38 (1.00-1.89)	0.049

Bejar R, et al. N Engl J Med. 2011;364(26):2496-2506.

We know from this slide, from Rafael Bejar and Ben Ebert, that these various gene mutations may have significant prognostic information. In this paper, they looked at the impact of certain mutations on survival impact using just the old-fashioned or original IPSS risk group. You can see, for example, that if a patient has a TP53 mutation they are at increased risk of death no matter which IPSS risk group they are in. Similarly, with an EZH2 mutation, an ASXL1 mutation, and RUNX1 mutation. Now, how these mutations impact the IPSS-R or WPSS is not yet known, and the next generation of these prognostic scoring systems will most certainly integrate and incorporate the mutational profiling. However, one thing that I have noted anecdotally is that in the few patients where the WPSS gives me one reading and the IPSS-R gives me another reading, interestingly, it is often the WPSS that is the worst prognosis. It turns out that the patient has one of these bad risk mutations which I think tips them over. This is an evolving area, but this is also I think part of the emerging routine workup of a patient with MDS.
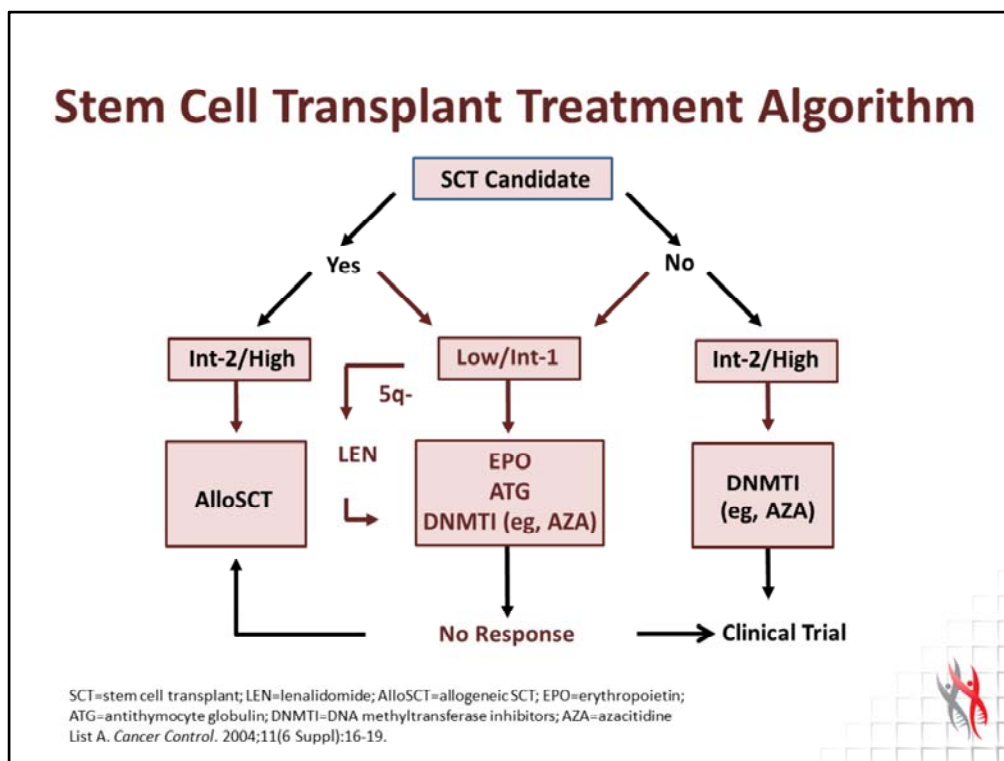
Goals of Therapy

- Select therapy best-suited for individual
  - Improve overall survival
  - Control symptoms
    - Improve blood counts
  - Decrease risk of progression to AML
  - Improve quality of life

The goals of therapy need to be selected to be best suited for an individual. We would like to improve overall survival for all patients when possible. We would like to control symptoms. This requires for most patients improving their blood counts. Again, decreasing the risk of progression to AML, I would just say decrease the risk of disease worsening. The cutoff for AML is less significant to me because the body does not know if there are 10% blasts or 15% blasts or 20% or 30% blasts. It is really how the disease impacts the bone marrow function. At all times if possible, we would like to improve the quality of life. This is really not trivial because some of the treatments which we offer patients, particularly in the elderly, may acutely, at least, decrease the quality of life. It is important to not only focus on survival when we are treating patients.

Monitoring and Managing Adverse Events in Older Adults with MDS

Stem Cell Transplant Treatment Algorithm

SCT=stem cell transplant; LEN=lenalidomide; AlloSCT=allogeneic SCT; EPO=erythropoietin; ATG=antithymocyte globulin; DNMTI=DNA methyltransferase inhibitors; AZA=azacitidine
List A. *Cancer Control.* 2004;11(6 Suppl):16-19.

This is an old treatment algorithm that several of us, including Alan List and several others, came up with in about 2004 when azacitidine was being launched commercially. I think that the overall approach still holds to a great extent. When one is looking at the patient we can ask, "Is this patient now, or will this patient ever be, a candidate for stem cell transplantation?" Well, many more patients are eligible now in 2017 than were in 2004. For example, the increasing development of reduced-intensity transplantation has made many more patients candidates. The development of alternative donor transplantations, including haploidentical donors, has provided donors for more patients. Just because somebody is a 72-year-old with MDS does not mean a priori they are not stem cell transplant candidates. Of course, we come back to: What are the patient's goals and how robust is the patient? What are the comorbidities? What are the patient's wants in life? Once we have determined whether we are going to try to get the patient to stem cell transplant, if that is something the patient wants, we can stratify the patients into higher and lower risk disease categories. Again, this is an old slide so it falls back on the IPSS, the original IPSS. We can certainly adopt the IPSS-R categories with the caveat that that intermediate category in the IPSS-R or WPSS is the one that we are not always so sure what to do with. Looking down the pathways for lower risk patients, however, we want to stratify them; are therapies that may include erythropoietic-stimulating agents (ESAs) if the primary problem is anemia, may include immunosuppressive therapies, although in the elderly group (as you will see this is something we tend not to apply as much), or we may offer DNA methyltransferase inhibitors or aza-nucleosides; and more about that later. For the specific subset of patients with del5q MDS in lower risk, lenalidomide of course is uniquely active. For the higher-risk patients, however we want to stratify them or identify them, our only approved drugs are aza-nucleosides. Some patients will be candidates for induction chemotherapy based on cytarabine, and we would always like to enroll patients in clinical trials whenever possible.

Monitoring and Managing Adverse Events in Older Adults with MDS

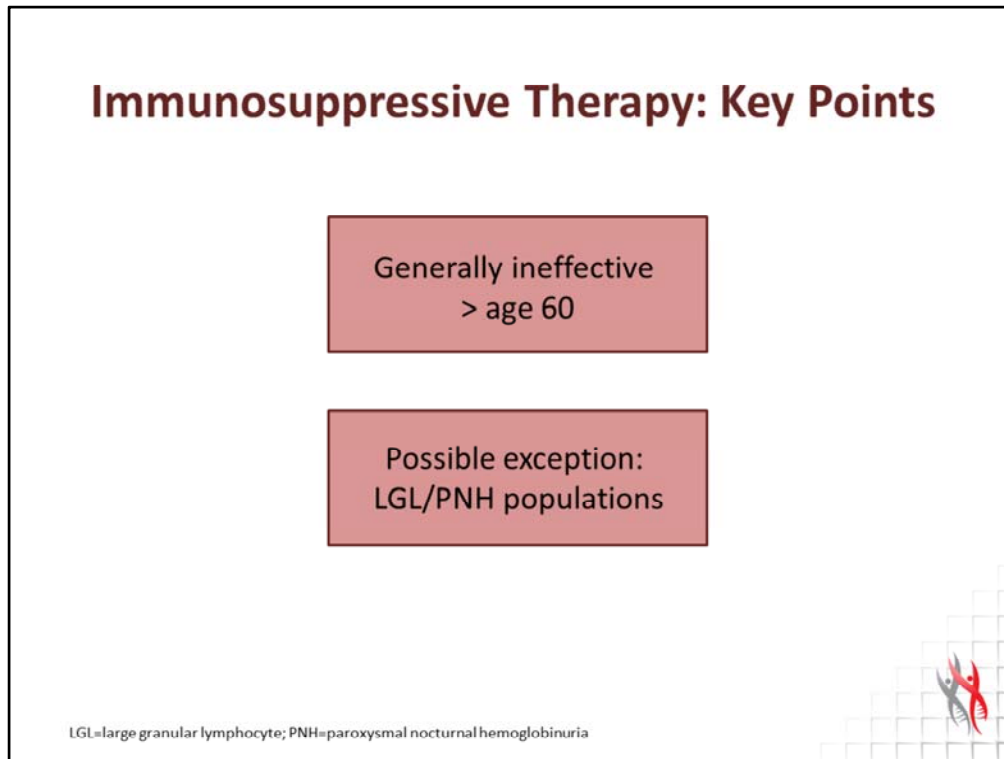## Erythropoietic-Stimulating Agents (ESA): Key Points

- Baseline erythropoietin level

- Adequate dosing

- Adjustment for refractory anemia with ring sideroblasts (RARS)

- Adequate trial

- Knowing when you're done

- Not important: venous thromboembolism (VTE), disease progression, overcompensation

Let's talk about erythropoietic-stimulating agents for patients with lower-risk MDS, and I have summarized a few key points here. ESAs are only effective in patients whose endogenous EPO (erythropoietin) levels are not terribly high. As you know, the erythropoietin is made by the juxtaglomerular complex of the kidney in response to the circulating hemoglobin. Somebody with a normal EPO axis who is anemic because of their MDS should be cranking out a lot of EPO and if their endogenous EPO level is high, we can give erythropoietin or darbepoetin till the cows come home and patients will not respond. It is critically important to get a baseline EPO level. In patients whose EPO level is greater than 500 units per mL, it is pretty much agreed that patients are not likely to respond. As a matter of fact, the closer you look at the data, the response rate probably falls off at about 100. If the level is less than 200, I will often consider ESAs; less than 100, I am enthusiastic about it; between 200 and 500, I discuss with the patient. The next point is that the patient needs to receive adequate dosing. For most patients that may require more than the so-called "standard" 40,000 units of erythropoietin a week (or comparable dosing schedules of darbepoetin). Most papers that have demonstrated efficacy have used minimal doses of erythropoietin of 60,000 units per week, sometimes higher; for darbepoetin, 300 mcg weekly or 500 mcg every other week; again, much higher than is used in their indications. For patients with refractory anemia with ring sideroblasts (RARS) in the case of erythropoietin, most patients will not respond unless G-CSF (granulocyte colony-stimulating factor) is added to somehow sensitize the cells to the erythropoietin. It is not clear that that
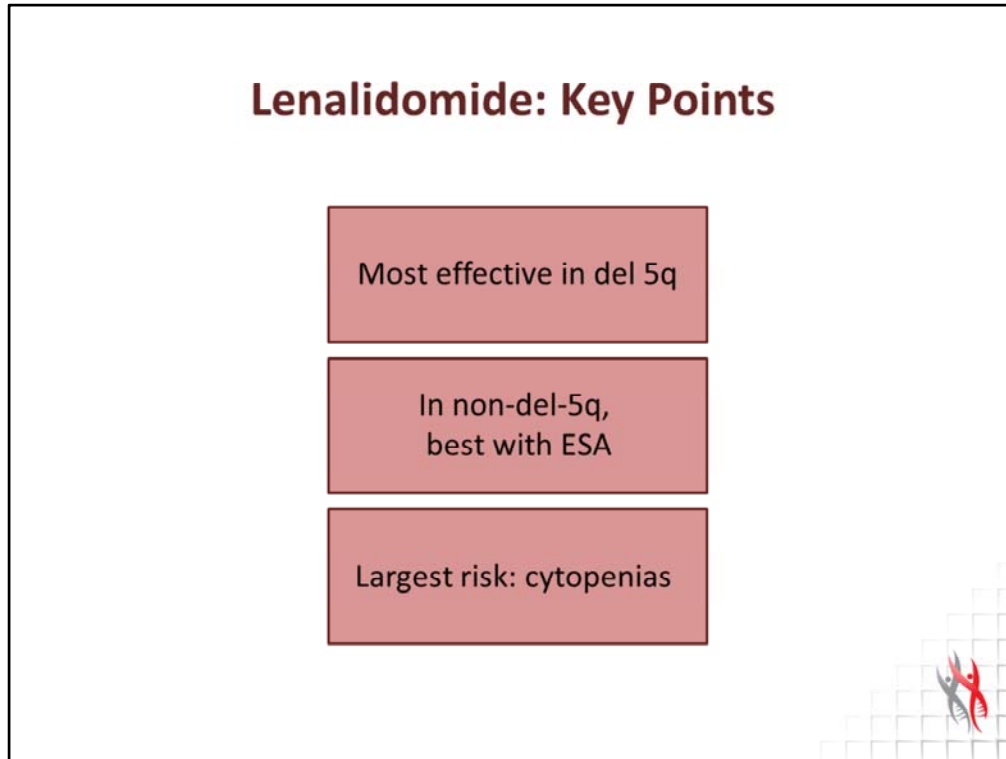
is true with darbepoetin and it is not clear if the erythropoietin dosage is pushed much higher. What is an adequate trial of ESA therapy? Well, in general, patients should receive ESAs we think for about 12 weeks, and if you have given 12 weeks of ESAs at a decent dose, they are probably not going to respond if they have not already. It is important to know when you are done and stop it. I see a lot of patients who have been on ESAs for years and years and years and they have been getting transfused every other week, and I think it is kind of silly. What physicians worry about in the use of ESAs and other diseases does not always apply in MDS. For example, patients with MDS are probably not at an increased risk of venous thromboembolic disease with ESAs. ESAs are not known to promote disease progression, and we are rarely fortunate enough to have somebody whose hemoglobin overcompensates to where one would need to stop the EPO or darbepoetin because the hemoglobin has gotten too high. That would be a remarkable response.

Immunosuppressive Therapy: Key Points

Generally ineffective
> age 60

Possible exception:
LGL/PNH populations

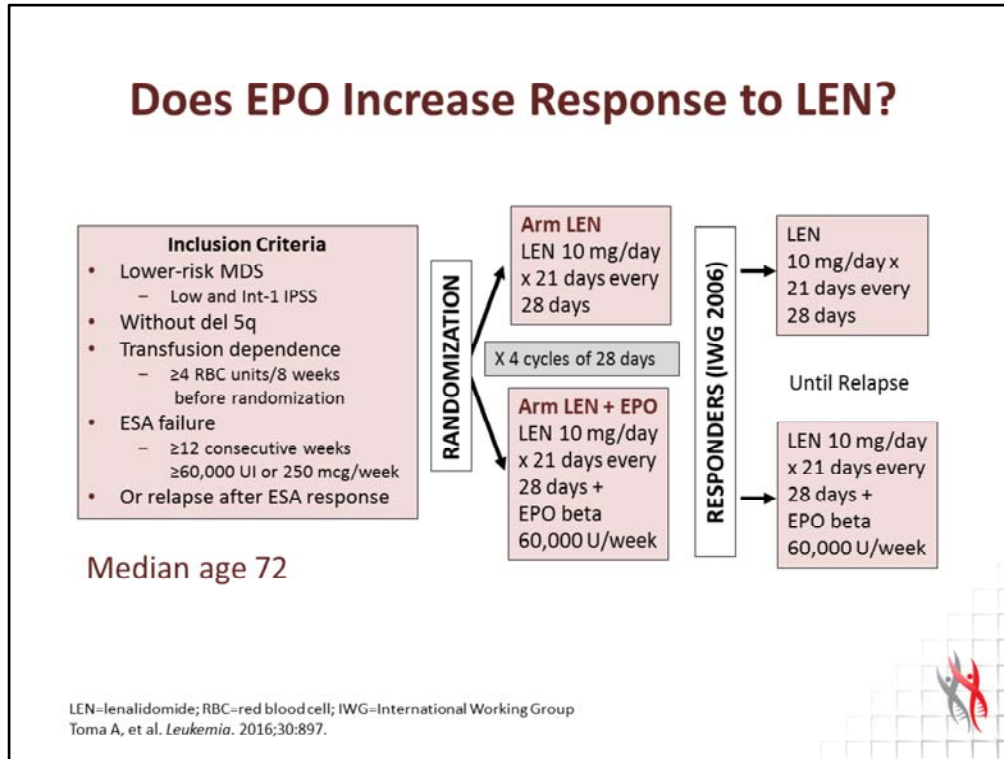LGL=large granular lymphocyte; PNH=paroxysmal nocturnal hemoglobinuria

What about immunosuppressive therapy? Well, the best-studied immunosuppressive therapy is anti-thymocyte globulin. Most studies have suggested that, in general, this is not effective in patients greater than age 60, so probably not germane to this discussion in great detail. A possible exception would be patients who have cells with a large granular lymphocytic phenotype or PNH (paroxysmal nocturnal hemoglobinuria) population. Those patients may respond to immunosuppressive therapy. In the older patients, I will tend to start with cyclosporine; again, effects are often disappointing. I'll particularly do that in a patient who has an LGL-MDS kind of overlapping picture. Of course, cyclosporine may not be well tolerated in the elderly because of the renal toxicity.

Lenalidomide: Key Points

Most effective in del 5q

In non-del-5q, best with ESA

Largest risk: cytopenias

We know that lenalidomide is a highly active drug in lower-risk patients with del5q and anemia. Lower-risk MDS patients with del5q who are transfusion dependent have about a two-thirds chance of developing transfusion independence with lenalidomide. There is a recent study from France which looks at the use of lenalidomide in non-del5q MDS. Originally, Dr. Raza led a multicenter study looking at the efficacy of lenalidomide in anemic patients with MDS in non-del5q and found a 25% response rate, kind of disappointing. This was replicated in the Celgene-sponsored MDS-005 study led by Valeria Santi from Firenze, Italy, which showed exactly the same response rate in a randomized placebo-control trial. The French, as I will discuss in a minute, looked at lenalidomide in non-del5q with or without erythropoietic stimulating agents, and I will talk about that in a minute. The largest risk of lenalidomide in all patients, and especially in the elderly, is the development of cytopenias secondary to treatment. This is most profound in patients with del5q whose platelet count in particular can drop precipitously as can their neutrophils and one needs to watch that very, very carefully. This is true to a lesser extent in the non-del5q as well.

Monitoring and Managing Adverse Events in Older Adults with MDS

Does EPO Increase Response to LEN?

Inclusion Criteria
- Lower-risk MDS
  - Low and Int-1 IPSS
- Without del 5q
- Transfusion dependence
  - ≥4 RBC units/8 weeks before randomization
- ESA failure
  - ≥12 consecutive weeks ≥60,000 UI or 250 mcg/week
- Or relapse after ESA response

Median age 72

RANDOMIZATION

Arm LEN
LEN 10 mg/day x 21 days every 28 days

X 4 cycles of 28 days

Arm LEN + EPO
LEN 10 mg/day x 21 days every 28 days + EPO beta 60,000 U/week

RESPONDERS (IWG 2006)

LEN 10 mg/day x 21 days every 28 days

Until Relapse

LEN 10 mg/day x 21 days every 28 days + EPO beta 60,000 U/week

LEN=lenalidomide; RBC=red blood cell; IWG=International Working Group
Toma A, et al. *Leukemia.* 2016;30:897.

Here is the outline of the French study asking the question, "Does erythropoietin increase the response to lenalidomide in non-del5q?" You can see the inclusion criteria were lower risk MDS using the old IPSS scoring system, non-del5q transfusion dependent, and they had to have either failed to respond to an adequate trial of erythropoietic stimulating agent at an adequate dose as you can see, or relapsed after their ESA response. Such patients were randomly assigned to standard dosing of lenalidomide of 10 mg per day for 21 days out of 28, with or without erythropoietin 60,000 units per week. As you can see, the median age was 72.

Outcomes

	L (n = 65)	LE (N = 66)	P
Erythroid response	15 (23)	26 (39)	0.044
Multivariate			
LE versus L	5	1.6 – 15	0.005
EPO < >100	4	1.3 – 12.6	0.016
CBN genotype	0.38	0.16 – 0.92	0.026

- DVT in four patients
- 25% myelosuppression
- Lenalidomide dose reduced in 30-35%

L=lenalidomide; LE=lenalidomide-EPO; DVT=deep vein thrombosis
Toma A, et al. *Leukemia*. 2016;30:897.

Here are the outcomes. Looking at the top section in the lenalidomide-only arm, 15 out of 65 patients had an erythroid response. In the lenalidomide plus EPO, it was about double that, 26 patients out of 66 or almost 40%. In multivariate analysis, the addition of erythropoietin was an important factor for response. As you can see again, the endogenous EPO level greater than or less than 100 was also significantly important. They also looked at the genotype of an important lenalidomide binding factor called cereblon and found a significant impact there; that is not a clinically available test and that genotyping test I think will need a validation. Now, there has been another trial run by Dr. Alan List from Moffitt in the Eastern Cooperative Oncology Group which was presented at ASH this year which had a similar design (although patients could not have received erythropoietin before) and it shows essentially the same result in a bigger study that is not yet published.
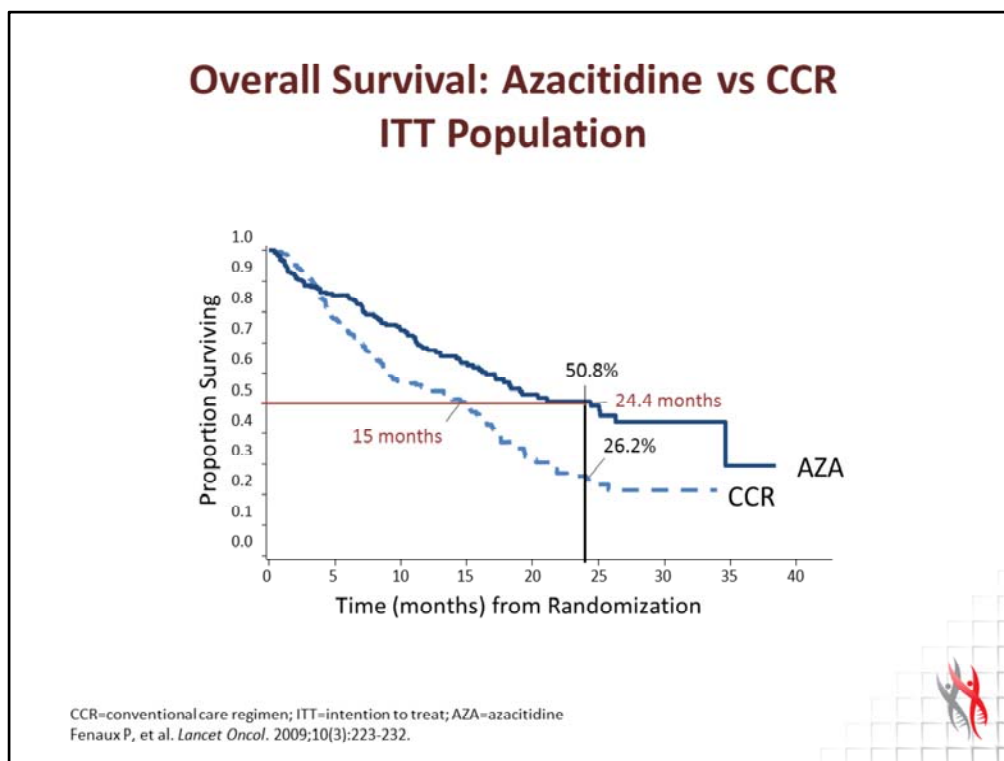
Luspatercept

- Soaks up SMADs which are increased in MDS and inhibit red blood cell growth

- Phase 2 trial

- Low/int-1; Hgb <10; EPO >500 or non responsive

- 26 patients: 57% with ringed sideroblasts

- 40% HI-E

	Ringed sideroblasts	SF3B1 mutation
RR	7	6
NR	6	9

Platzbecker U, et al. *Leuk Res.* 2015;39(1):S25.

Luspatercept is a drug under development, which has a very exciting promise in patients, particularly with anemia and refractory anemia with ring sideroblasts. This is a protein which soaks up SMADs which include TGF beta. These are increased in patients with lower-risk MDS and they seem to inhibit red blood cell growth. What I am showing here is an older study presented at the International MDS meeting two years ago by Uwe Platzbecker from Germany. This was a phase 2 trial in lower-risk patients with MDS who were anemic and who either had an elevated EPO level predictive of nonresponse to ESAs or who were ESA nonresponsive. Here, we are only showing 26 patients, 57% of whom had ring sideroblasts, and you can see that there is a 40% erythroid response rate. The response rate was quite high in patients who had ring sideroblasts or the SF3B1 mutation which goes along with RARS. There is an international randomized phase 3 placebo-controlled study in patients with ring sideroblasts which is about to wrap up, and we will hear more about this drug coming soon.

Monitoring and Managing Adverse Events in Older Adults with MDS

Overall Survival: Azacitidine vs CCR ITT Population

CCR=conventional care regimen; ITT=intention to treat; AZA=azacitidine
Fenaux P, et al. *Lancet Oncol.* 2009;10(3):223-232.

Let's move on to the treatment of higher risk patients with azacitidine and decitabine. I mentioned before that azacitidine and decitabine can be used in lower-risk patients with good effect on the hemogram. Whether this is a good long-term strategy or not, I think is beyond the scope of this particular talk. Again, we are supposed to be focusing on toxicity, and I think that the points that I will make about azacitidine and decitabine, in terms of toxicity and adverse events, can be extrapolated from the higher-risk discussion to lower-risk patients whom you may choose to treat with the aza-nucleosides. The slide that we are showing right now is from the now classic AZA-001 study. It was initiated after the US approval of azacitidine and was run by Pharmion Corporation, subsequently Celgene, and was published in *Lancet Oncology* by Pierre Fenaux from France. As I am sure most of you know, this trial took patients with higher-risk MDS, including what used to be called RAEBT - which is now called AML with myelodysplastic-related features and less than 30% blasts - and randomized patients between the standard dosing schedule of azacitidine versus one of three preselected conventional care regimens: either observation with transfusional support, low-dose cytarabine, or intensive cytarabine-based induction therapy. This important trial showed an improvement in median survival in the azacitidine-treated group; it was really quite remarkable.
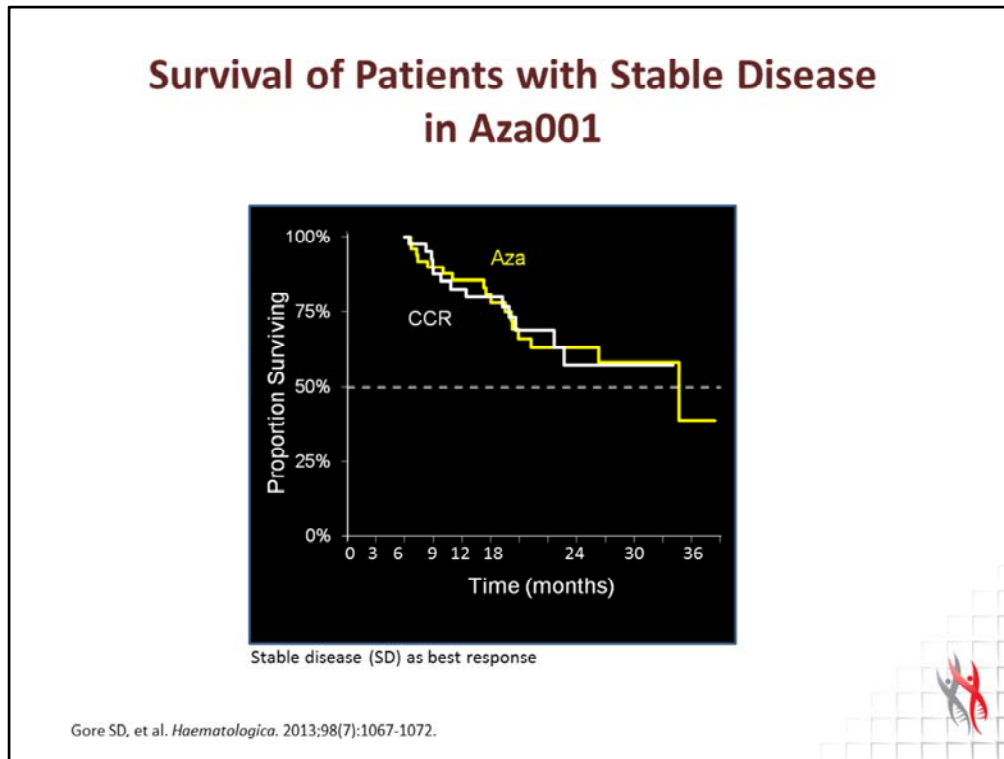
Azanucleosides: Key Points

- Adequate dosing
- Adequate number of cycles
- Management of cytopenias
- Prophylactic antibiotics
- Appropriate discontinuation
- Real-life experience

We do believe that aza-nucleosides, particularly azacitidine, have been shown to improve survival; unfortunately none of the current studies of decitabine have demonstrated that. Because we would like to improve survival, we really need to understand how to mitigate toxicity. I should note also that, for azacitidine in the setting of lower-risk MDS, its impact on survival has not been studied. That is why I am limiting my discussion to higher-risk MDS. Here are the key points. Aza-nucleosides need to be given in adequate dosing. I think that particularly in the elderly, many physicians will undertreat patients because they are afraid of the toxicity, but there is little bit of "no pain, no gain" here. We have to be willing to tolerate cytopenias and get them through it in order to see the net effect. If you are going to be dose reducing from the get-go, then probably that patient is not really a candidate to get aza-nucleosides, at least not under your direction, because they are not likely to get the benefit. They are going to get all the pain, none of the gain. One needs to give an adequate number of cycles of drugs to know that patients are not responding. That may require even greater than 6 cycles, but certainly a minimum of 6 cycles to assess hematologic response. I personally do not think that the marrow response by itself has been shown to be meaningful. Many studies will look at marrow CRs in which the marrow is cleared of blasts, but there is still no improvement in the hemogram. A variety of studies have suggested that such responses are not associated with improved survival, and again for me, I do not think that it is really worth the toxicity of the drug to continue the aza-nucleoside in that setting; that is just my opinion. Management of cytopenias is very important. While I do not, in general, give prophylactic antibiotics to patients
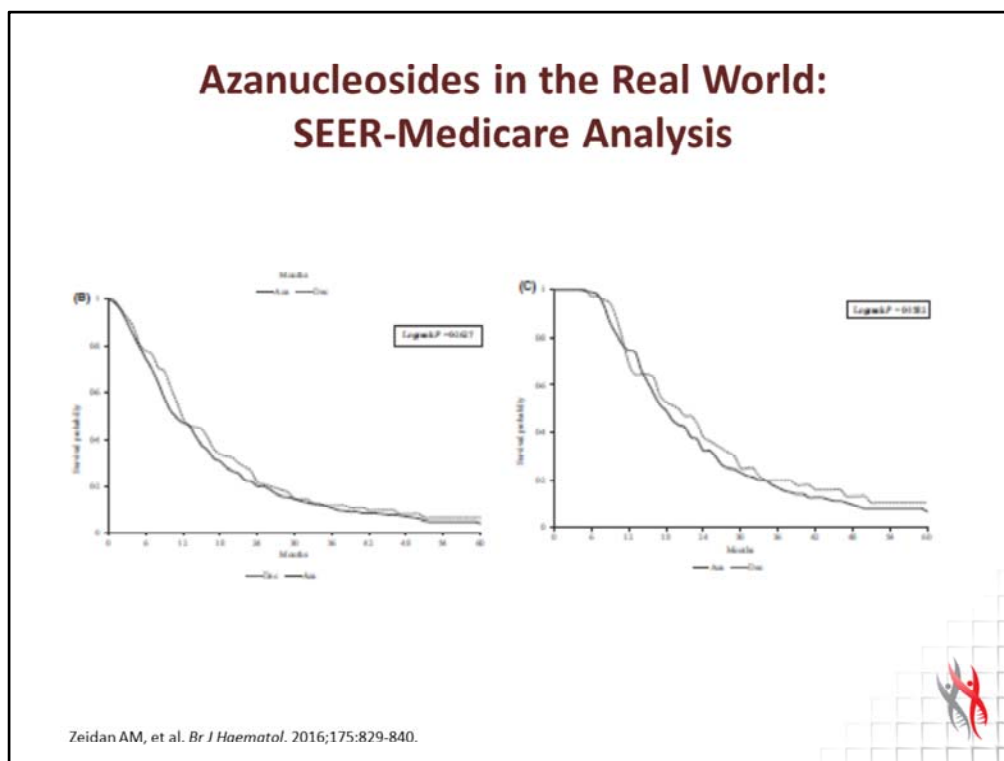
with MDS, even very neutropenic patients who are not being treated, in most patients who are receiving aza-nucleoside, where we are going to drop their neutrophils further and have gut toxicity potentially, I do. That will usually include a quinolone for antibacterial prophylaxis and an anti-mold azole, and I usually use voriconazole to prevent mold infections. Of course, one needs to give platelets. If patients become critically thrombocytopenic, I usually transfuse for 10,000, even for outpatients, if there is no bleeding. Others will choose 20,000 and of course we will need to mitigate the anemia with red cell transfusions. Appropriate discontinuation I think really has to do with whom do we know that the therapy is benefiting. We will talk more about that in a minute. What is the real-life experience with aza-nucleosides? Is it comparable to the AZA-001 study?

Monitoring and Managing Adverse Events in Older Adults with MDS

Survival of Patients with Stable Disease in Aza001

Stable disease (SD) as best response

Gore SD, et al. *Haematologica*. 2013;98(7):1067-1072.

We did a multivariate analysis of patients from the AZA-001 study. We did a landmark multivariate analysis to look at whether ongoing aza-nucleoside had a benefit to patients whose best response was stable disease. In the slide that you see before you right now, we took patients whose best response to azacitidine was stable disease at 6 months. We had to compare them to a comparable group in the conventional care regimen. We needed patients in the conventional care regimens who also had stable disease at 6 months. Now, that may be a selected group, we do not know. In multivariate analysis, when one looks at the people whose best response was stable in AZA versus whose best response was stable in the conventional care group, you can see there is absolutely no survival benefit. To me, if a patient is, at best, stable after 6 months of AZA, I think one can have a reasonable discussion with them about what is their tolerance to the drug, is it really worth it to continue the drug when we do not really know if it is improving their survival, and certainly it is not improving their counts by definition, if they are stable. Then I would usually encourage such patients to probably discontinue azacitidine especially if there is an interesting clinical trial for which they may be eligible.

Monitoring and Managing Adverse Events in Older Adults with MDS

Azanucleosides in the Real World: SEER-Medicare Analysis

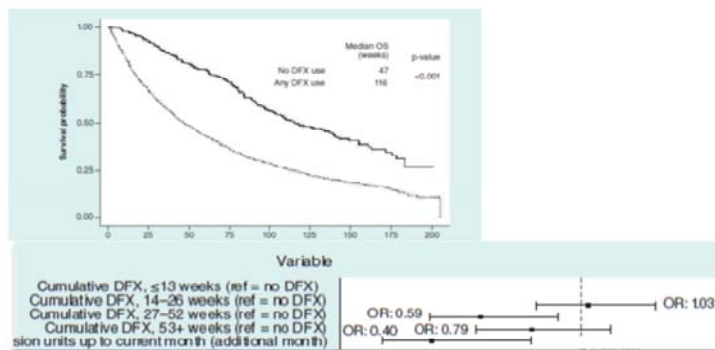Zeidan AM, et al. *Br J Haematol.* 2016;175:829-840.

Here is a very interesting and provocative study from our group, from my colleague Amer Zeidan residing here at Yale. This was a look at the impact of aza-nucleosides in the real world, if you will. The SEER Medicare is a database that links the NIH SEER Cancer Registry with Medicare claims. Dr. Zeidan and his team looked at the outcome of patients in the SEER Medicare database treated with azacitidine or decitabine and did a very careful survival analysis, to the extent that is possible, within essentially a retrospective large data observational study. First of all, you can see that, although we have no survival data which is positive in any of the randomized decitabine trials, in this real-world population, you can see that the survival of patients treated with azacitidine and decitabine essentially overlaps. You can also see that the median survival of patients treated with these aza-nucleosides is unfortunately inferior to that which was published in the AZA-001 survival study of azacitidine; this is disappointing. I think it is still probably better than the control group in the AZA-001 study. That is not to say that I am down on aza-nucleosides, I think they are certainly critically important, particularly for those patients who get the positive impact in their hemogram. As with many of our therapies, unfortunately the performance in an unselected real-world population is inferior to that which is achieved in a carefully controlled prospective clinical trial.

# Monitoring and Managing Adverse Events in Older Adults with MDS

Now, we come to the question of who should get iron chelation therapy? I am sure people have very strong opinions about this and we'll probably get lots of letters to the editor disagreeing with me, but the bottom line is and you cannot argue with this, that we do not really know based on controlled data. I think many of us believe that chelation is reasonable to consider in patients who have had a lifetime exposure of at least 20 units of transfused red cells and who are in an ongoing transfusion program, and usually whose serum ferritins exceed 1,000, again with an ongoing transfusion requirement. Dr. Zeidan led another study in the Medicare population where patients who met these criteria in MDS; they had a lifetime exposure to at least 20 units of red cells and were still getting transfused. And they looked at patients who either got deferasirox, or who did not, and did the best job they could in controlling for a variety of factors which might go into physician selection of such patients. In other words, you always worry that the patients who were selected for deferasirox were patients who were expected to live longer anyway, and given all the difficulties with large data sets and retrospective analysis, Dr. Zeidan did a very rigorous job of attempting to control for all that they could. You can see in the top curve looking at survival of patients chosen to get deferasirox or not, there was a survival benefit. More importantly, in this very complicated multivariate model, it was shown that for patients who had a cumulative deferasirox exposure of greater than 13 weeks, for every subsequent week of deferasirox, there was in fact survival benefit as you can see in the forest plot. This analysis has made me pretty much a believer that patients in an ongoing transfusion program who meet these criteria should be offered deferasirox.

Monitoring and Managing Adverse Events in Older Adults with MDS
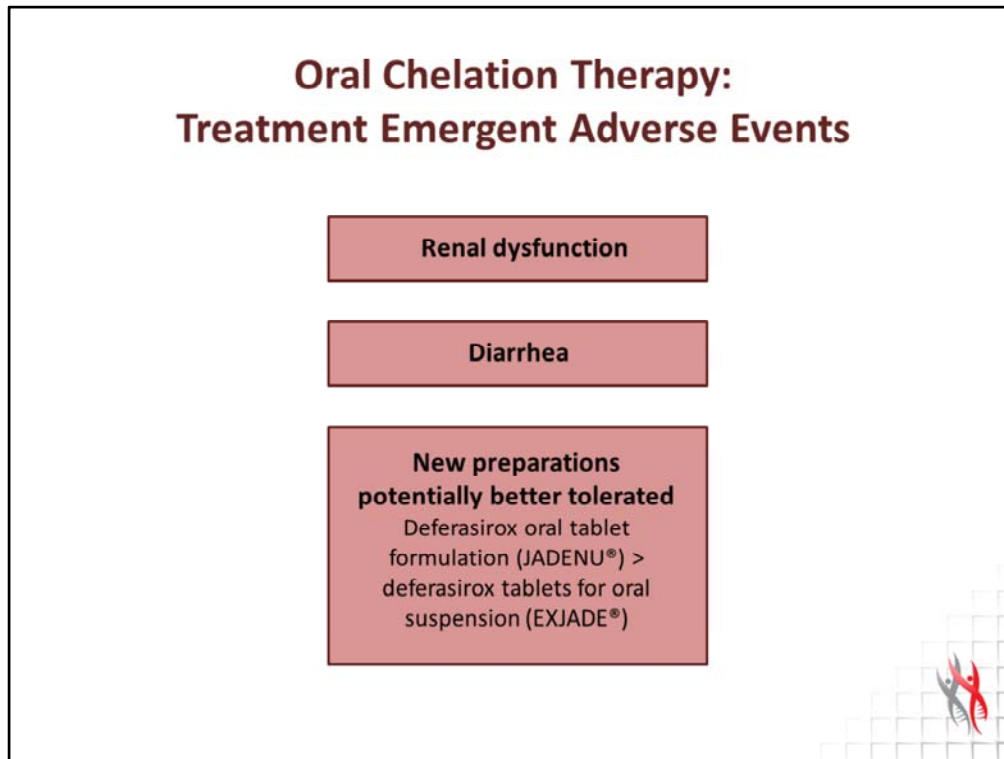
What about treatment-emergent adverse events for oral chelation therapy? While we worry about renal dysfunction and diarrhea in particular, those are things that I think make it most difficult for patients to tolerate these drugs. Again, it is my experience the Jadenu preparation (deferasirox oral tablet formulation) is better tolerated than the dissolving Exjade original formulation (deferasirox tablets for oral suspension).

Key Takeaway Points

- MDS is a disease of the elderly
- Most clinical trials have been performed in appropriate age brackets and reported AEs thus apply
- AE tolerance function proportionate to treatment goals

To conclude, I would like to leave you with a few take-away points. We know that myelodysplastic syndrome is a group of diseases in which the median age is older. These are diseases of the elderly. Most clinical trials have been performed in appropriate age brackets, and thus, the reported adverse events really do apply. That is why I have not mentioned any adverse events in this talk that are not really what you would see in the package label. We do emphasize, or I would like to emphasize, that the tolerance of the adverse events really should be proportionate to the treatment goals. In other words, if we are trying to get somebody to stem cell transplant, we are going to push the aza-nucleoside farther, and tolerate a few admissions potentially for neutropenic infection. However, if we are really sticking to just palliative goals, we may not want to do that. Again, if we are talking about lenalidomide and a non-del5q where it is strictly palliative and we do not have great expectations this is going to work, I am not going to let the platelet count drop that far. I just do not think it is worth the risk. I do think emerging data, for example combining lenalidomide with an ESA, is going to continue to improve our mitigations of some of the side effects. I think there is going to be emerging data coming out with eltrombopag to potentially mitigate some of the side effects, and I think this may make a difference for some of our patients. Thank you for viewing this activity.