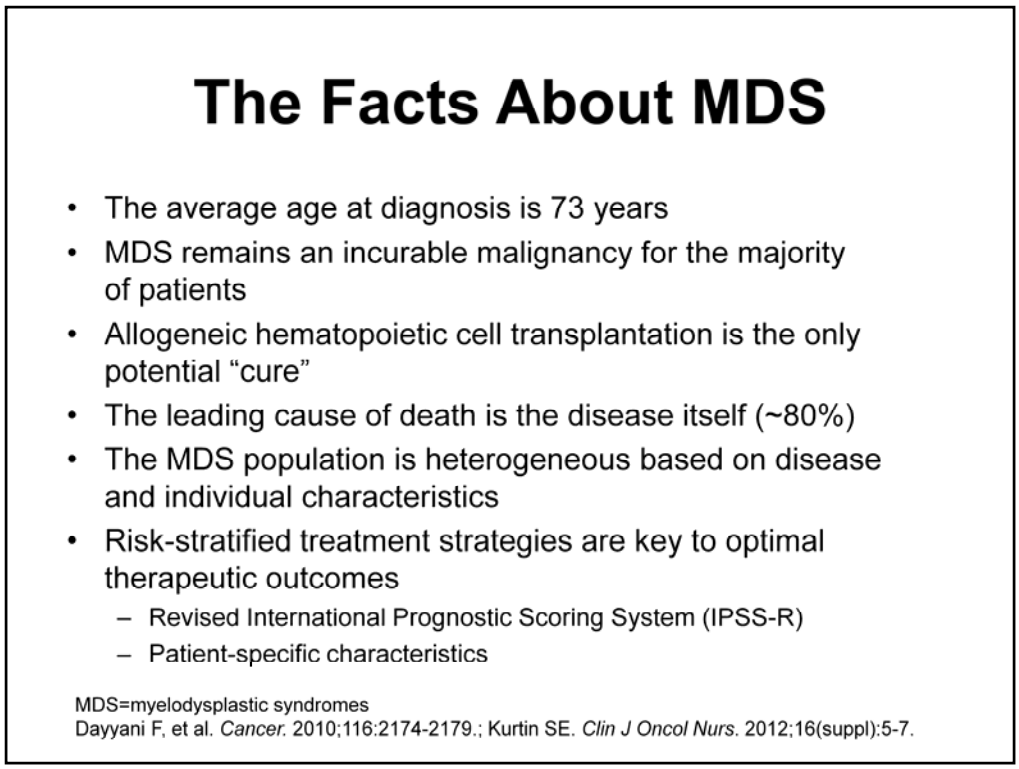
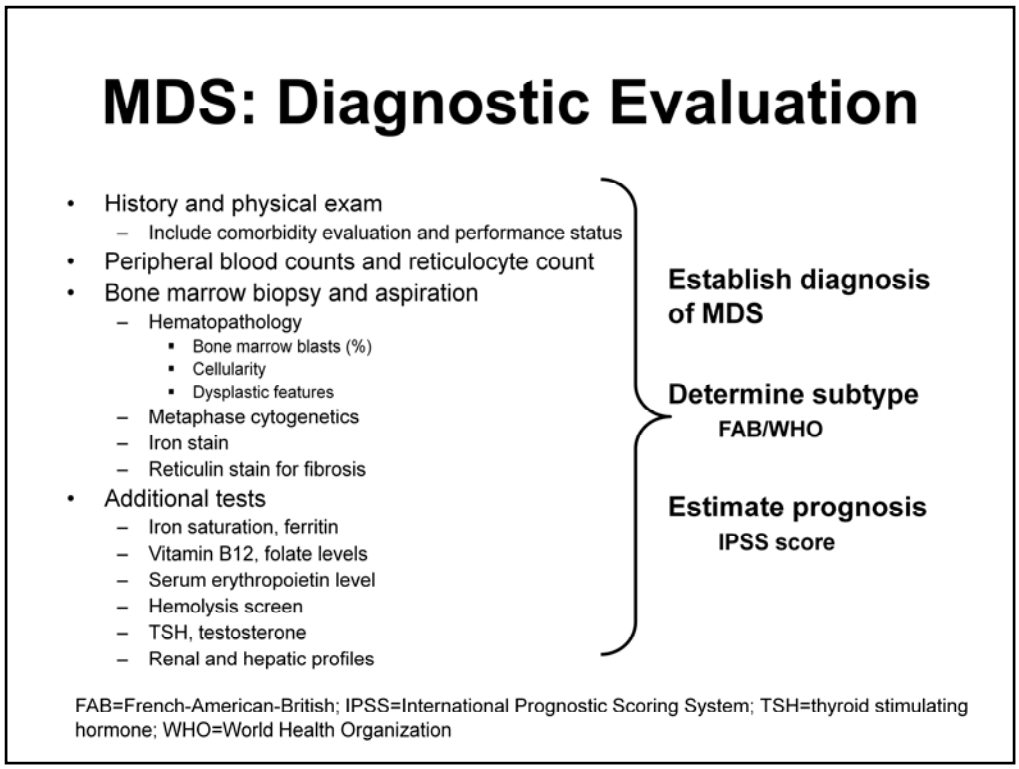
Hello, my name is Sandy Kurtin. I am a nurse practitioner at the University of Arizona Cancer Center in Tucson, Arizona, and I would like to take a minute to talk to you about practical tools for managing myelodysplastic syndromes including symptom management.



First, let's talk a little bit about MDS as a disease. We know that the average age at diagnosis is 73 years, so this is an older population. We know that this disease remains incurable in the absence of an allogeneic stem cell transplant, which is not an option for most of these patients based on age and common comorbidities. We know that the leading cause of death is the disease itself in roughly 80% of the patients diagnosed. MDS is a heterogeneous disease, and we really need to consider individual risk factors, and we do this by risk stratification using established diagnostic tools such as the International Prognostic Scoring System. We also need to take into consideration individual patient characteristics.



Perhaps, the most important part of MDS is getting an accurate diagnosis and putting people into one of these risk categories. We do this by evaluating cytopenias, common causes, as well as the possibility of an MDS diagnosis. An MDS diagnosis requires a bone marrow biopsy and aspiration. This is in a sense the tissue diagnosis, and we must include cytogenetic evaluation to accurately stage and risk-stratify these patients. We also want to look at things like a serum erythropoietin level which become important when considering erythropoietin-stimulating agents for treatment. Most patients with MDS have adequate stores of erythropoietin, and giving them additional erythropoietin-stimulating proteins is not terribly effective. We can then use this information to establish the diagnosis, define the subtype, and estimate the prognosis using the International Prognostic Scoring System.

IPSS Risk Categories

Variable/score	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	< 5	5–10	–	11-20	21–30*
Karyotype	Good	Intermediate	Poor	–	–
Cytopenias	0/1	2/3	–	–	–

Risk category	Numeric score	Patient distribution	Median survival†	Evolution to AML
Low	0	31%	5.7 years	9.4
Int-1	0.5–1.0	39%	3.5 years	3.3
Int-2	1.5–2.0	22%	1.2 years	1.1
High	≥ 2.5	8%	0.4 years	0.2

Life expectancy at 75 years US	**11.2 years**
Life expectancy at 65 years US	**17.7 years**

* >20% blasts denotes acute myeloid leukemia (AML); †Data generated prior to active therapies
AML=acute myeloid leukemia
US Social Security Administration, 2009.; Greenberg P, et al. *Blood*. 1997;89:2079-2088 [published correction in *Blood*. 1998;91:1100].

Now, traditionally, we have used the IPSS risk categories. This has been updated more recently, but I would like to spend a little bit of time just talking about the IPSS risk categories, the original staging criteria. Basically, this tool looks at bone marrow blast percentage, the karyotype, and the number of cytopenias or how many cell lines were involved, and as the blast count goes up, the score goes up as more worrisome karyotype such as complex karyotypes carry a poor prognosis that carries a higher score. If you consider a patient with let's say less than 5% blasts, only anemia and a favorable karyotype, their score is 0, and they are considered to have low-risk disease, and you can see that the median survival without treatment is 5.7 years, and the evolution to AML for 25% of these patients is 9.4 years. So, these patients basically do not die of leukemic transformation. On the other hand, if you have a patient with 20% blast, maybe complex cytogenetics and two different cytopenias, they are going to have very high-risk disease, and you can see that their life expectancy is very short, and they do die of leukemic transformation. So, if you have both of these patients presenting at the same time and you are trying to consider treatment, the high-risk patient need treatment immediately and the low-risk treatment may be able to be monitored. Now, we just talked about the average age at diagnosis being 73 years of age, and I think it is important to understand in this older population that life expectancy at 75 years in the United States is 11.2 years, and at the age of 65, it is 17.7 years. So, if you have an older patient who is diagnosed with high-risk disease, age alone should not exclude treatment because the disease will kill them quickly, and they may otherwise have a very good life expectancy if their disease can be controlled.

IPSS-R Cytogenetic Risk Groups

Cytogenetic risk grouping	Cytogenetic types	Estimated survival
Very good	del(11q), -Y	60.8 mo
Good	Normal, del(20q), del(5q) alone and double, del(12p)	48.5 mo
Intermediate	+8, 7q-, i(17q), +19, +21, any other single or double, independent clones	24 mo
Poor	del(3)q21/q26, -7, double including 7q-, complex (3 abnormalities)	14 mo
Very poor	Complex (> 3 abnormalities)	5.7 mo

IPSS-R=IPSS-Revised; mo=months

Now, more recently, the IPSS has been revised, so we have the IPSS-R, and what this does is it further risk-stratifies the patients by cytogenetic subgroups, and these are presented for you here. I will not go into great detail because I know this is provided in other series, but you can see that cytogenetics alone vary widely when you look at estimated survival. So, again, complex abnormality, greater than three abnormalities is very poor prognosis with an average estimated survival of 5.7 months in the absence of treatment. Again, these people need to be treated quickly.

IPSS-R Risk Categories

Score/ Attribute	0	1	1.5	2.0	2.5	3.5	5
Cytogenetics	Very Good		Good		Int	Poor	Very Poor
Blasts	<5%			5-10%	11-30%		
Hemoglobin	≥10 g/dL			<10 g/dL			
Platelets	≥100,000		<100,000				
ANC	≥0.8	<0.8					

ANC=absolute neutrophil count

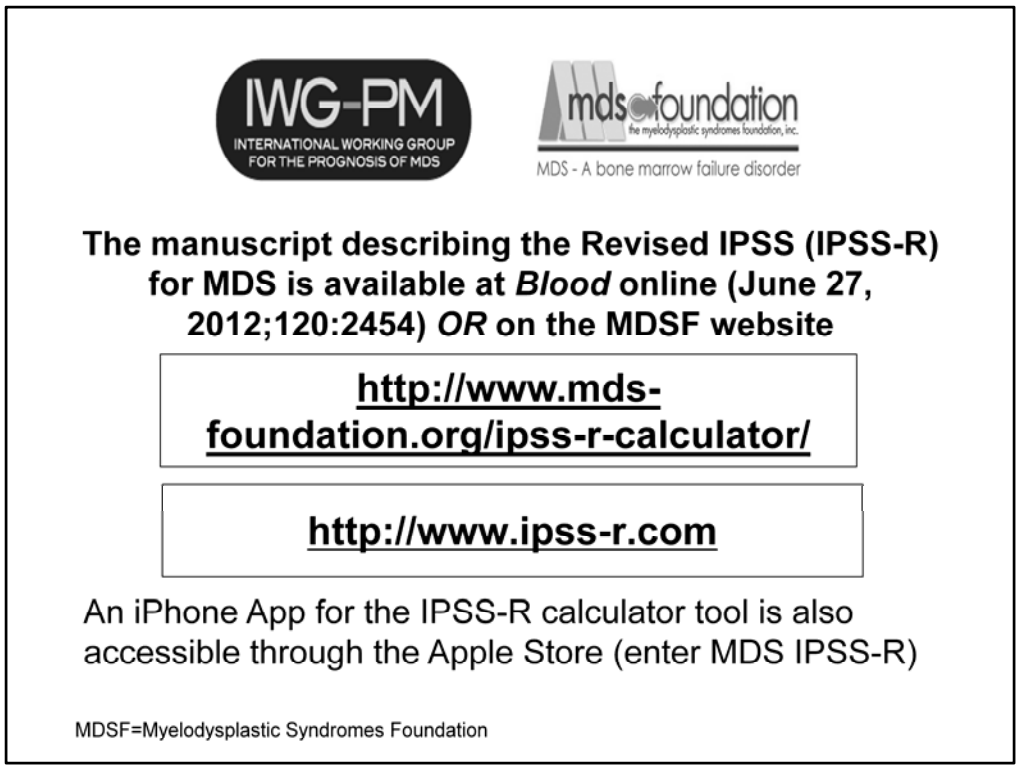
If we look down at the risk categories, the other thing that has been adapted is the depth of cytopenias. So, we really are looking at how low are the platelets, how low is the hemoglobin, how low is the ANC, and the scores are stratified according to that,

IPSS-R: Variable Survival/Prognosis and Risk of Leukemic Transformation

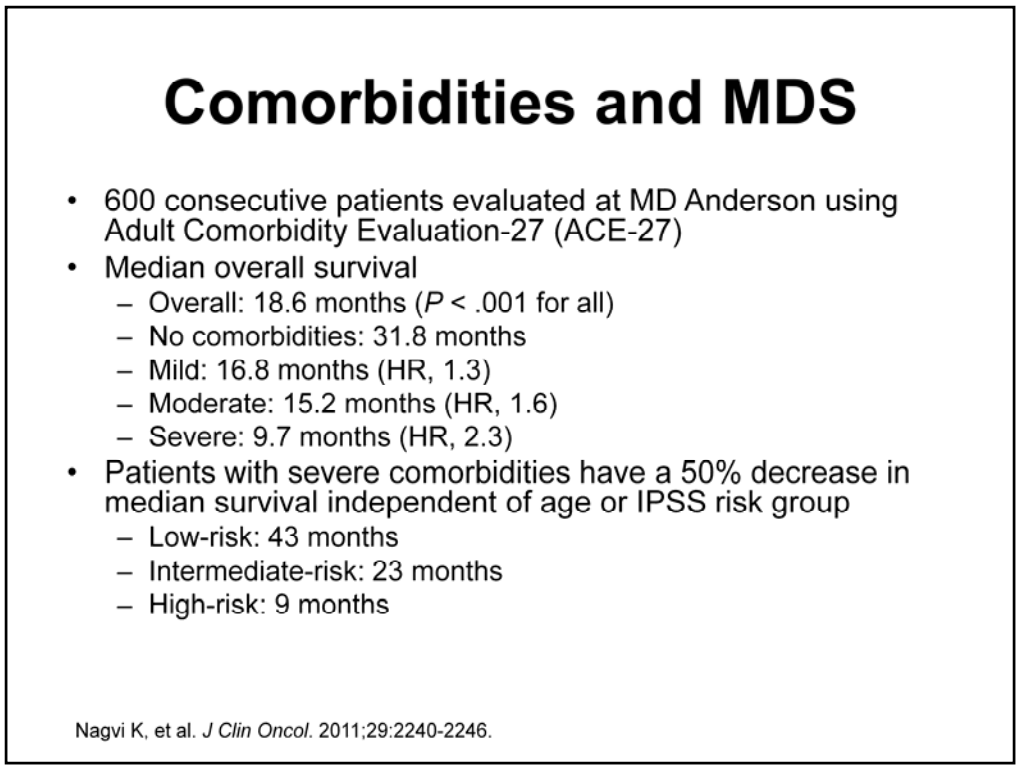
Score	1 Very Low	2 Good	3 Intermediate	4 Poor	5 Very High
Mean overall survival	8.7 years	5.3 years	3.0 years	1.6 years	0.8 years
Mean risk of AML in 25% of patients	Not reached	10.7 years	4.0 years	1.4 years	0.8 years

Greenberg PL, et al. *Blood*. 2012;120:2454-2465.

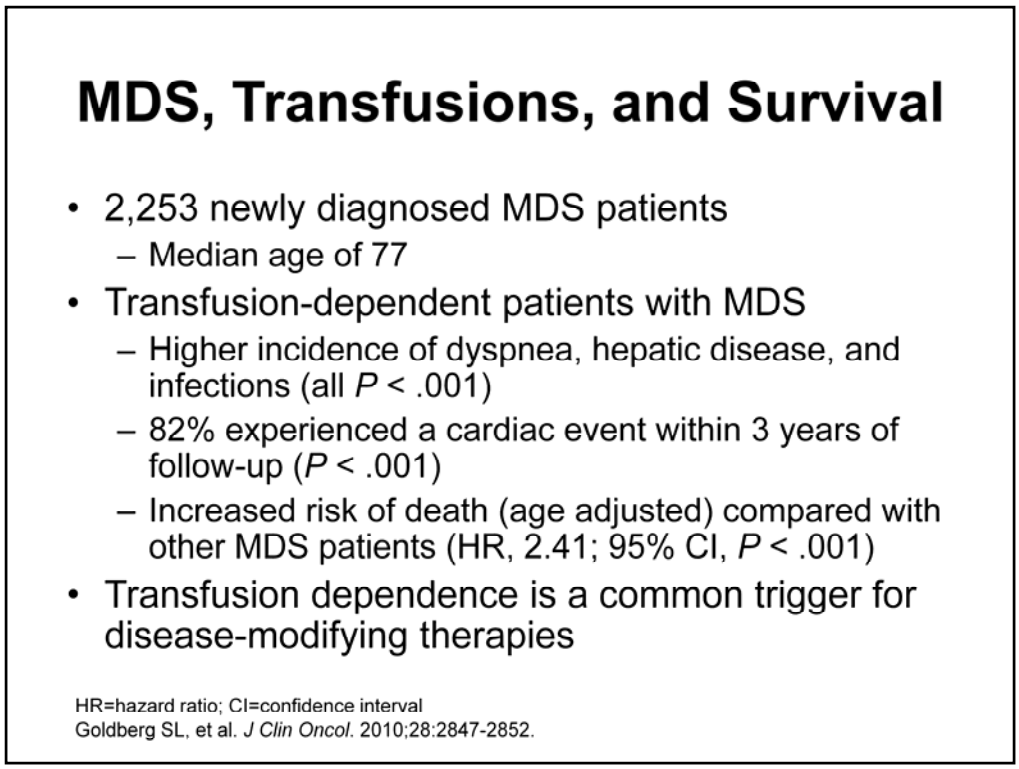
and then, if you look at those total scores, you will see variable survival and risk of leukemic transformation, again, depending on these risk categories. So, once again, getting an accurate diagnosis is critical to being able to really drive how we treat patients which then will determine symptom management as well.



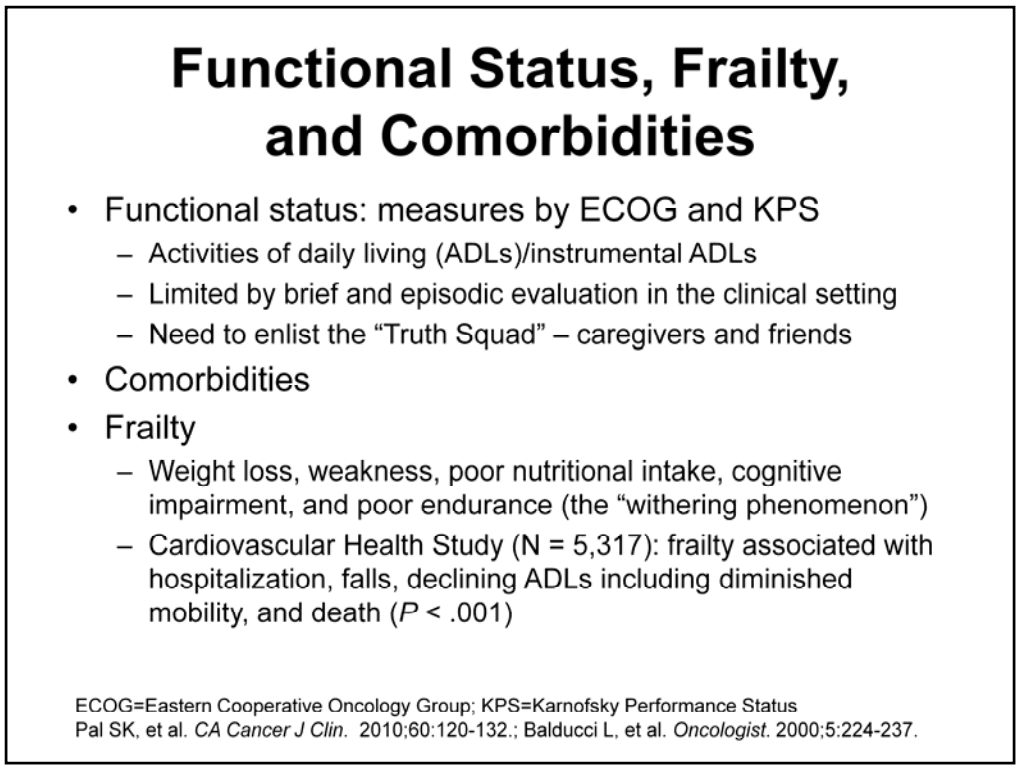
There is an app available for the IPSS-R. This was put together by the International Working Group for the Prognosis in MDS and sponsored by the MDS Foundation, and you can see the sites there to be able to go to those apps.



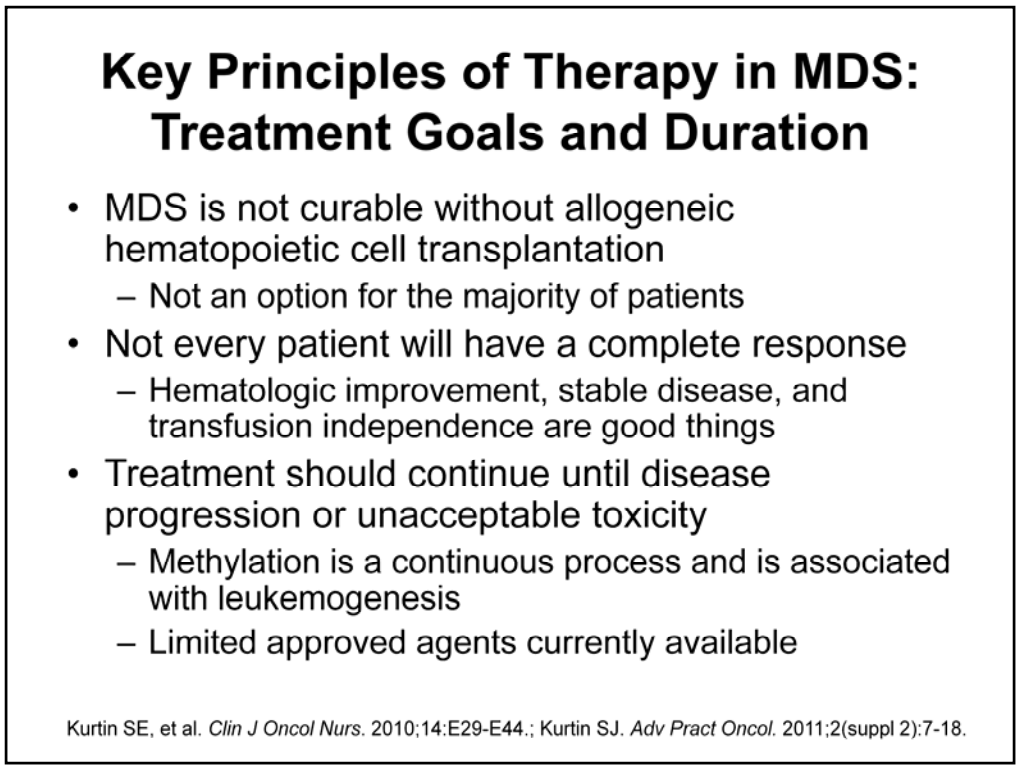
Now, let's take a little bit of time here to talk about comorbidities in MDS. So, we know these are older patients. Comorbidities are not uncommon. Some of them may be well controlled, but this is an important study conducted out of MD Anderson looking at 600 consecutive patients using the ACE-27 comorbidity evaluation tool, and just based on comorbidity alone, you can see that the median overall survival for all patients in this study was 18.6 months with a P value of 0.001, but when you look at severe comorbidities that life expectancy was measured at about half, 9.7 months. So, people with severe comorbidities had a 50% decrease in median survival independent of age or the IPSS risk group. So, we must really carefully evaluate comorbidities.



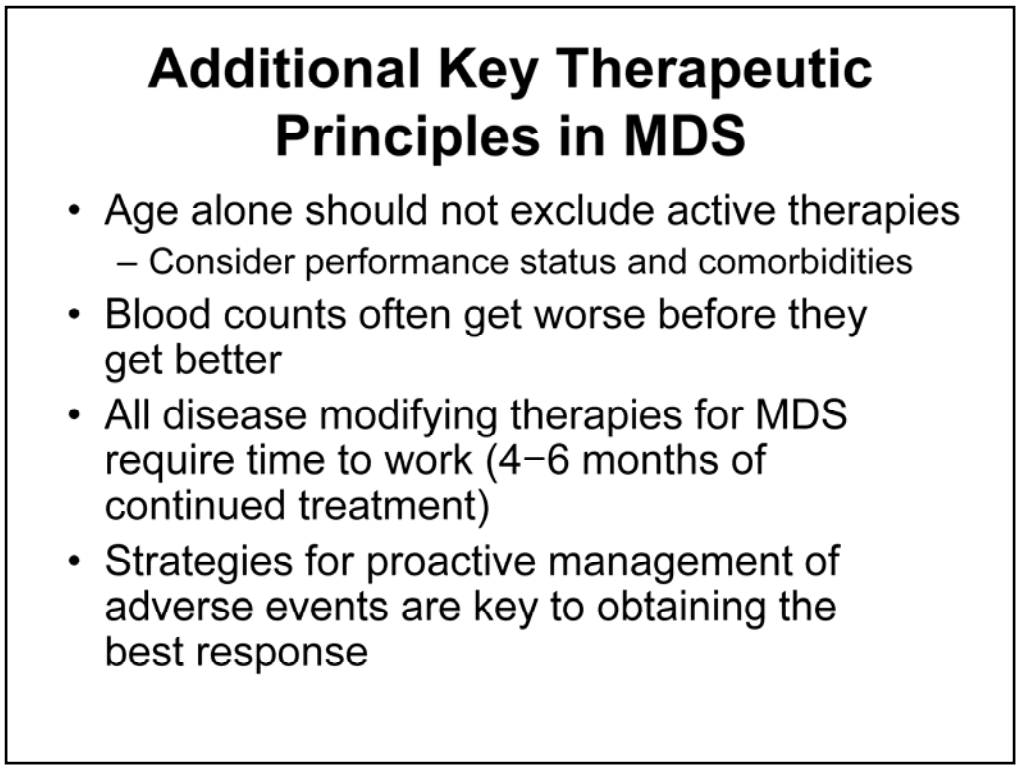
The next thing to consider is transfusion dependence. We know that transfusion dependence is inevitable in the majority of patients with MDS. Roughly, 90% of all patients at some point during their disease will require red blood cell transfusions. Some patients will also require platelets. In this evaluation, 2,253 newly diagnosed MDS patients with a median age of 77 were evaluated. These patients were transfusion dependent, and those that were transfusion dependent showed a higher incidence of dyspnea, hepatic disease, and infections. The 82% experienced a cardiac event within 3 years of followup, so very significant finding, and this also showed an increased risk of death, age-adjusted death, compared with other MDS patients. So again, transfusion dependence is a common trigger for instituting disease-modifying therapy.



The next thing to think about is functional status frailty and comorbidities. So, we talk a lot about performance status; however, this is very arbitrary. We are not with the patients for long periods of time. We see them in very brief encounters, usually in the clinic, and if they are in the hospital, it is not really a true representation of their performance status in their own home environment. So, we really need to think beyond traditional functional status. We have talked about comorbidities. The other thing that really is being explored is the concept of frailty, and frailty is usually found to represent a cluster of findings such as weight loss, weakness, poor nutritional intake, cognitive impairment, and poor endurance. I like to think if this is a withering phenomenon. The patients that you see that are withering as you see them over a course of several visits, and we worry about these patients. We know from the cardiovascular health study that frailty was associated with hospitalizations, falls, declining ADLs and including diminished mobility and death. So, again, we need to think beyond just the disease categories and really look at all of the different features of the individual patient.



So, let's then talk about key principles of therapy in MDS. We have talked about MDS not being curable without an allogenic stem cell transplant. This is not an option for most of these patients based on age and some of the comorbidities. Not every patient with MDS will have a complete response to therapy. So, our goals of therapy are often hematological improvement, stable disease, and transfusion independencies are felt to be good things. We know that treatment should continue until disease progression or unacceptable toxicity. In the case of patients on hypomethylating agents, we know that hypermethylation is a continuous process and is associated with leukemogenesis that we treat until disease progression or unacceptable toxicity. We also know we have a limited number of approved compounds, and we want to make the most of each one of those.



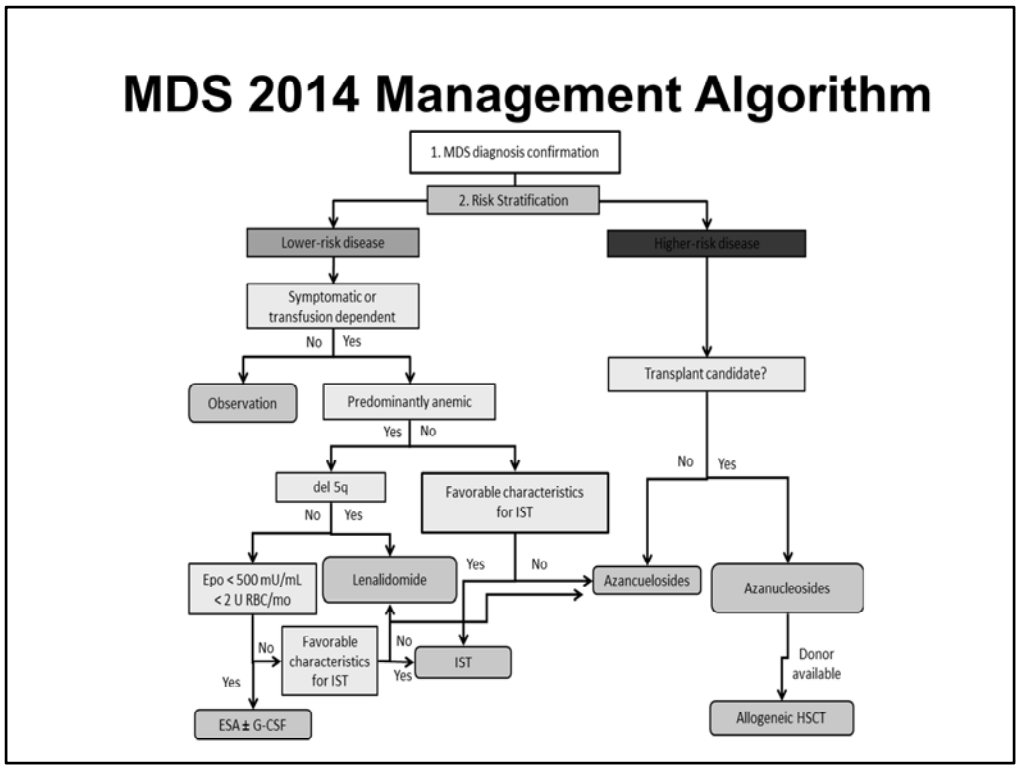
The next thing we want to really emphasize is that age alone should not exclude active therapies, and we talked a little bit about that in the beginning of this discussion. So, consider all of those other elements. We need to accept that when we initiate treatment in newly diagnosed patients, their blood counts are likely to get worse before they get better. This may require 4 to 6 months of continued treatment for them to really see a response. So, we really need to have strategies for proactive management of adverse events so that we can keep people on therapy long enough so they have the opportunity to have that response.

Risk-Adapted Treatment Selection

	Lower Risk	Higher Risk
Treatment Goal	Hematopoiesis	Survival
Clinical Endpoint	▪ Hematological Improvement ▪ QOL	▪ Alter Natural History ▪ Delay AML
Management Considerations	▪ Erythropoietin Stimulating Agents ▪ IMiD: Lenalidomide ▪ Immunosuppressive Therapy ▪ Azanucleosides: Azacitidine, Decitabine ▪Clinical Trial ▪Supportive Care	▪ Azanucleosides: Azacitidine, Decitabine ▪ AlloSCT ▪ Intensive Chemotherapy ▪Clinical Trial ▪Supportive Care

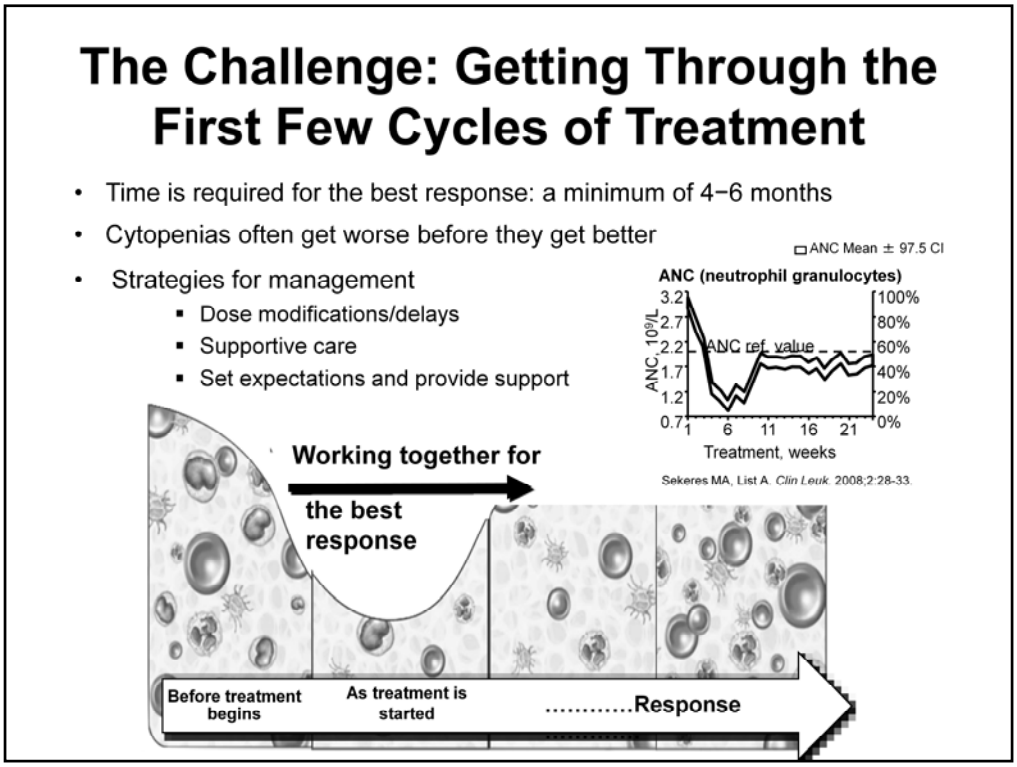
QOL=quality of life; IMiD=immunomodulatory drug; AlloSCT=allogeneic stem cell transplantation

Risk adaptive treatment selection, the goals of treatment then vary based on the risk category of the disease. In lower risk patients as we said, we have some time. Our goal is really to improve hematopoiesis and have them become transfusion independent. In higher risk patients, we really want to control that leukemic transformation, and our goal really is survival.

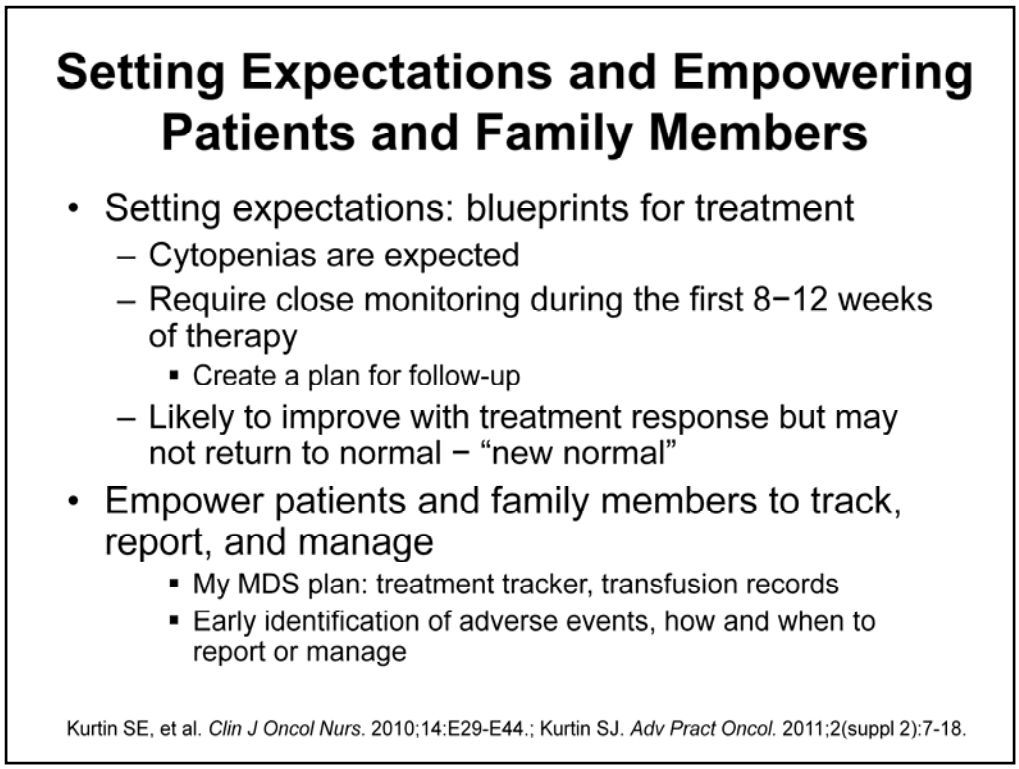


There are number of treatment decisions as you can see in this algorithm presented here. If the patient has a deletion of 5q, our drug of choice is going to be lenalidomide based on the trials that have been published to the MDS-001, the MDS-003, and MDS-005, and it can also be considered in non-del(5q) patients based on other trials as well. If they have a lower erythropoietin level and have a low transfusion burden, we may consider erythropoietin-stimulating agents, and if they have higher risk disease, we are going to favor the aza nucleosides or hypomethylating agents, azacitidine or decitabine. So, once treatment has been selected based on risk stratification, we are going to really need to focus on symptom management, again to get through that in initial of therapy in particular.

Very important to set expectations for the patients and their caregivers, plan supportive care strategies and really empower the patient and caregivers to be involved in their care.

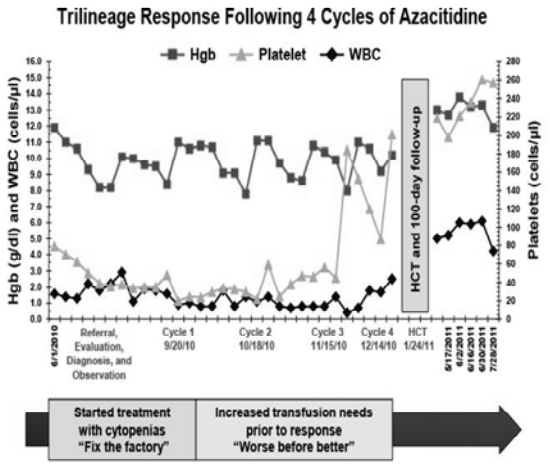


Now, the next slide shows you what I call the ravine slide really looking at these expected cytopenias. So, we expect this. It is not a surprise. We need to institute frequent blood counts in the initial weeks of treatment, generally weekly for the first 8 weeks of therapy. We have opportunities for dose modifications or delays in instituting the next cycle of therapy for unresolved cytopenias. We can use supportive care in a way of transfusion support as well as growth factors in some cases, but we really need to emphasize that it will get worse before it gets better, and we need to get through that initial 4 to 6 months of therapy so that patients have the opportunity for response.



Now, setting these expectations for patients is very important. Giving them a blueprint and showing them this picture of the ravine really emphasizing that it is expected. It is not a surprise. We really need them to know that they need the frequent monitoring for the first 8 weeks at least and in some case 12 weeks. So, they need a plan for followup. Where are they going to have their labs drawn, who do they talk to after they have been drawn, how are you going to treat that in the presence of cytopenias, and what are the thresholds for transfusions for individual patients based on symptoms? We also want to encourage them to keep track of their own counts which will help them become more engaged in their care.

Trilineage Response to Azacitidine



Kurtin SE, et al. *Clin J Oncol Nurs*. 2012;16(suppl):23-25.

Now, the next slide shows you an example of a patient. This is a 39-year-old patient with high-risk MDS, started on a hypomethylating agent, azacitidine, and you can see here that at the time of treatment, this patient's platelet count was 32,000. It is not going to get better if we wait. The only way to make that better is to treat the underlying disease and that can be done safely with supportive care and monitoring. You can see that this patient required transfusions intermittently of red blood cells. There is the pink line, and you can see the transfusions denoted by the quick tick up and similarly would require a few platelet transfusions as well, but after 4 cycles of therapy, you can see trilineage response. This patient was lucky enough to have a sister who was a complete match and went on to have an allogenic stem cell transplant, but this example just shows you that you need to commit to that full course of therapy before you consider a treatment failure.

Subgroup Analysis of the AZA-001: Elderly Patients >75 Years With High-Risk Disease

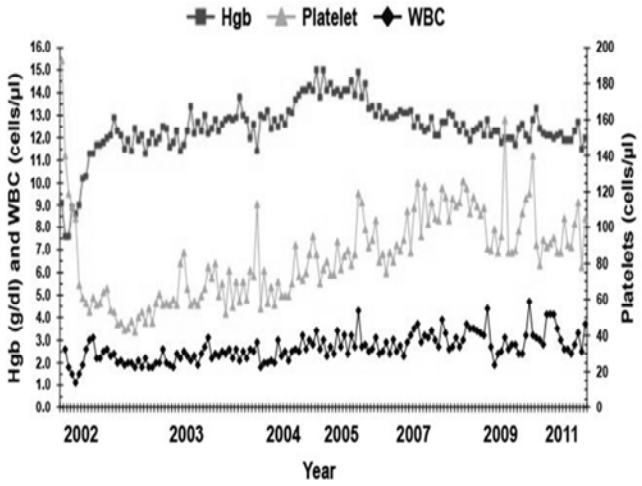
- 87 elderly patients > 75 years
- High-risk disease: IPSS: Int-2 or high
- Azacitidine (AZA) significantly improved overall survival (OS) compared with best supportive care (BSC)
  - Two-year OS rates: 55% vs 15% ($P < .001$)
- AZA generally well tolerated
  - Adverse events (AEs) most common in the first 2 cycles

AE (grade 3/4)	Cycle 1–2		Cycle 3–4		Cycle 5–6	
	AZA	BSC	AZA	BSC	AZA	BSC
Anemia (%)	2	1	0	1	2	0
Neutropenia (%)	15	6	8	3	7	2
Thrombocytopenia (%)	14	10	8	2	5	0
Fatigue (%)	0	0	1	1	1	0
Pyrexia (%)	0	0	1	1	1	0

Seymour JF, et al. *Crit Rev Oncol Hematol*. 2010;76:218-227.

Now, the next slide shows the AZA-001 trial which looked at older patients. So, there was a subgroup analysis of patients over the age of 75; 87 of these patients with high-risk disease which showed a significantly improved overall survival compared to best supportive care in this subgroup analysis, and generally, this was well tolerated, and you can see that the cytopenias were less of a problem over time as the patient responded. So, again, age alone should not exclude treatment, and if you plan appropriately for the initial phases of therapy with frequent monitoring of counts and supportive care as needed, patients can go on to do well in many cases.

Sustained Response to Lenalidomide: 10 Years Transfusion Independent



Kurtin SE, et al. *Clin J Oncol Nurs*. 2012;16(suppl):23-25.

The next case is an example of lenalidomide in a patient with deletion 5q, and this is a gentleman who was on the original MDS-01 trial, and you can see in the far left of the graph here that there is a very rapid decline in blood counts initially. So, again, we need that frequent monitoring in the early weeks of treatment, and then he went on to become transfusion independent and actually was transfusion independent for 12.5 years. He recently died of coronary artery disease in October of 2014 but still had his MDS under control. The other thing you see here is that this patient had two normal platelet counts after his initial diagnosis and once he started treatment on lenalidomide. So, this is what we call moderate asymptomatic cytopenias. He was never hospitalized during this time until he had his cardiac disease, and so, we need to learn to tolerate these moderate but asymptomatic cytopenias. It is not a reason to stop therapy. He did very well over a long period of time. The other thing that you will see here is a relatively low white blood cell count, somewhere between usually 2.7 and 3 total, and an ANC running between 700 and 1,000, but again not admitted to the hospital. He was subjected to have periodic sinus infections for which he got treated with antibiotics and a single dose of Neupogen (filgrastim), and again did very well. Even though he had these longstanding cytopenias, he was relatively asymptomatic.

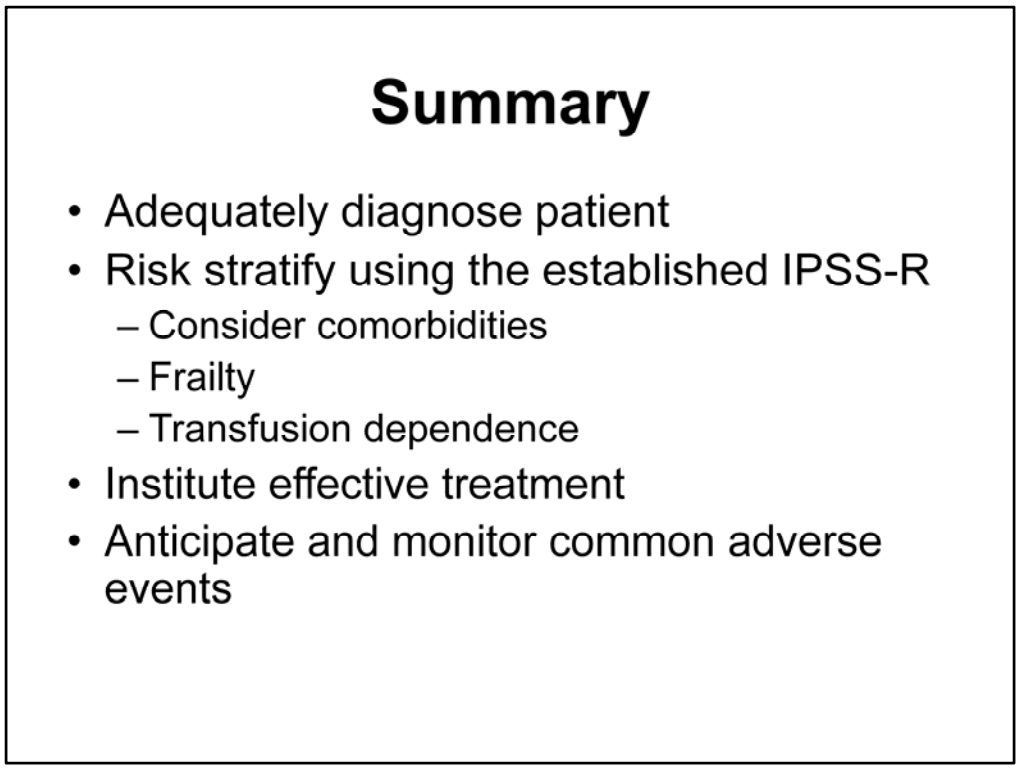
So, common adverse events then for all agents are myelosuppression, and we have talked about how to anticipate that and how to effectively monitor and treat that. Nausea and vomiting can be seen in any of these compounds. Constipation is a problem, primarily for the hypomethylating agents, but in some patients receiving lenalidomide they may experience constipation, very important to institute a bowel regimen, particularly in the presence of thrombocytopenia because you do not want them straining. There can be renal and hepatic toxicity with any of these drugs. We need to know baseline, and then we need to know how they are doing over time. So, this requires continued monitoring. Drug-specific adverse events then: azacitidine can be associated with the injection site reactions. Lenalidomide, you may see drug-associated rash. You may see pruritus. Patients can experience diarrhea, and this drug is under a REMS program requiring specific safety monitoring and prescription practices so that is something to check with your local representative for how to get registered in order to prescribe this agent. Iron overload is something that we worry about in transfusion-dependent patients. There is a short clip in one of these series to discuss that in more detail, but basically, we will consider chelation therapy. In some patients who have lower risk disease, a longer life expectancy, and have elevated ferritin levels, the de-escalation agents can also be associated with cytopenias and renal and hepatic abnormalities.

MDS Patients Who Are Likely to Benefit Most From Management Iron Overload

Characteristic	NCCN[1]	MDS Foundation[2]
Transfusion status	▪ Received > 20 RBC transfusions ▪ Continuing transfusions	▪ Transfusion dependent, requiring 2 units/mo for > 1 year
Serum ferritin level	▪ > 2500 µg/L	▪ 1000 µg/L
MDS risk	▪ IPSS: low or intermediate 1 risk	▪ IPSS: low- or int 1 ▪ WHO: RA, RARS and 5q-
Patient profile	▪ Candidates for allografts	▪ Life expectancy > 1 year and no comorbidities that limit progress ▪ A need to preserve organ function ▪ Candidates for allografts

RBC=red blood cell; RA=refractory anemia; RARS= refractory anemia with ringed sideroblasts
[1]NCCN. Clinical practice guidelines in oncology. MDS. v2.2013. [2]Bennett JM. *J Hematol*. 2008;83:858-861.

In terms of who would benefit from iron chelation therapy, the guidelines vary internationally, but you can see here that after roughly 20 red blood cell transfusions, patients are going to be more prone to having an elevated ferritin level, and the level is anywhere from 1,000 to 2,500. Again, we are going to institute this in lower risk patients because iron chelation requires months to years to effectively remove all of the tissue-bound iron.



So, by adequately diagnosing a patient and risk-stratifying them using the established IPSS-R risk stratification considering comorbidities frailty and transfusion dependence, and then really looking at how we can effectively institute treatment while we simultaneously anticipate and monitor common adverse events, we can effectively treat many of these MDS patients, and some of them can do well over a long period of time.