Practical Tools for Management of Myelodysplastic Syndromes

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Welcome to *Managing MDS*. My name is Sandy Kurtin. I am a nurse practitioner at the University of Arizona Cancer Center in Tucson, Arizona. We are going to talk today about the practical tools for the management of myelodysplastic syndrome.

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Definition

- The myelodysplastic syndromes (MDS) represent a spectrum of clonal, hematologic stem cell malignancies that are characterized by
  - Dysplastic and ineffective hematopoiesis
  - Peripheral cytopenias
  - Variable risk for leukemic transformation
- In general, as the disease progresses, bone marrow function declines
- The average age at diagnosis is 73 years

Kurtin SE. *Clin J Oncol Nurs*. 2006;10:197-208.; List AF, et al. In: Lee CR, et al, eds. *Wintrobe's Clinical Hematology*. 11th ed. 2004:2207-2234.; Steensma DP, Bennett JM. *Mayo Clin Proc*. 2006;81:104-130.

First just review a little bit about the definition of MDS, this is a group of heterogenous myeloid stem cell disorders that are characterized by dysplastic and ineffective hematopoiesis, peripheral cytopenias, and a variable risk for leukemic transformation. In general, as the disease progresses, bone marrow function declines, and it is important to keep in mind that the majority of these patients are in their 70s and 80s, the average age at diagnosis being 73 years of age.

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Key Principles of Therapy in MDS Risk-Adapted Treatment Selection

- Allogeneic bone marrow transplant remains the only potentially curative therapy
- Risk-adapted treatment selection is recommended
  - IPSS-R/WPSS risk category
  - Disease-specific attributes
  - Individual patient characteristics
    - Comorbidities
    - Performance status
    - Lifestyle
    - Quality of life
    - Financial considerations

IPSS-R/WPSS=Revised International Prognostic Scoring System/World Health Organization (WHO) classification-based Prognostic Scoring System.
Kurtin S. *J Adv Pract Oncol*. 2010;1:119-129.; Kurtin SE, Demakos EP. *Clin J Oncol Nurs*. 2010;14:E29-E44.

A few of the key principles of therapy in MDS in terms of risk-adapted treatment selection is that allogeneic bone marrow stem cell transplant remains the only potential cure, and for the majority of these patients, that is not an option based on both their age and the other situations such as comorbid conditions. So, we look at their IPSS risk category, and we are going to talk about that in more detail in just a moment, disease-specific attributes, and then perhaps most importantly in this population of patients is the other things that play a role in how well they can tolerate treatment. So, things like comorbidities, performance status, lifestyle, their quality of life, and certainly financial considerations.

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Functional Status and Fit vs. Frail

- Functional status: Measured by ECOG and KPS
  - Activities of daily living (ADLs):
    - Ability to bathe, dress, toilet and maintain continence, transfer, and eat independently
  - Independent ADLs (IADLs):
    - Finances, shopping, housekeeping, transportation, and self-medication
- Frailty:
  - Weight loss, weakness, poor nutritional intake, cognitive impairment and poor endurance ("withering")
  - Cardiovascular health study (n=5,317): frailty associated with hospitalization, falls, declining ADLs including diminished mobility, and death ($P<.001$)

ECOG=Eastern Cooperative Oncology Group; KPS=Karnofsky performance score
Pal SK, et al. *CA Cancer J Clin*. 2010;60:120-132.; Balducci L, Extermann M. *Oncologist*. 2000;5:224-237.

So, I first like to just take a minute to talk about functional status. This is something that we are used to looking at when we are doing clinical trials certainly, and we use Karnofsky's or ECOG performance status. This is a subjective estimate, at best. We do not have the opportunity to monitor patients over long periods of time, and we really count on them to tell us how they are doing throughout the day. We estimate this by how they tell us they are doing with activities of daily living and independent activities of daily living. More recently, there has been a lot of work looking at the concept of frailty, and I would like to talk of this sort of withering syndrome, the patients that you see that are coming back to see you and at each visit they look a little weaker, they are able to do less and less. So, some of those clues would include weight loss, weakness, poor nutritional intake, so these are the patients who are gradually losing weight, cognitive impairment, and poor endurance. Importantly, a lot of this work is modeled after the cardiovascular health study. You can see here a very large study, over 5,000 patients, where they found that frailty was associated with hospitalizations, falls, a further decline in activity of daily living, impaired mobility, and even death.

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Comorbidities and MDS

- 600 consecutive patients evaluated at MD Anderson using adult comorbidity evaluation-27 (ACE-27)
- Median overall survival
  - Overall: 18.6 months (*P*<.001 for all)
  - No comorbidities: 31.8 months
  - Mild: 16.8 months (HR 1.3)
  - Moderate: 15.2 months (HR 1.6)
  - Severe: 9.7 months (HR 2.3)
- Patients with severe comorbidities have a 50% decrease in median survival independent of age or IPSS risk group
  - Low-risk: 43 months
  - Intermediate-risk: 23 months
  - High-risk: 9 months

HR=hazard ratio
Naqvi K, et al. *J Clin Oncol*. 2011;29(16):2240-2246.

The second thing that we want to talk about are comorbidities. Now, these are older patients, we said the average age at diagnosis is 73. This is a study out of MD Anderson where they took 600 consecutive adult patients and they applied this Adult Comorbidity Evaluation-27 (ACE-27) to evaluate comorbidities, and looking at comorbidities alone, median overall survival was 18.6 months. In the no comorbidity group, it was 31.8 months, so almost double, mild comorbidities 16.8 months, moderate 15.2 months, and severe comorbidities 9.7 months. So a 50% reduction in median survival independent of age or IPSS risk group. So, the message here is that we really need to evaluate the patient beyond just their MDS diagnosis, but we need to look at what are the other things that are going on with that patient, who else do we need to get involved to help manage those comorbidities and try to make the patient as well as possible so that they are able to tolerate MDS treatment.

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IPSS-R Cytogenetic Risk Groups

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

Greenberg PL, et al. *Blood*. 2012;120:2454-2465.; Schanz J, et al. *J Clin Oncol*. 2012;30:820-829.

So, let's talk a little bit more about IPSS-R. This is the International Prognostic Scoring System, now revised. There is a yet enhanced version that is currently in the works. For right now, the IPSS-R is the most widely used risk stratification tool that we have for MDS. This is based on the number of cytopenias, cytogenetic abnormalities, and also the depth of those cytopenias now, which is something new, and how many cell lines are involved. So, this is just cytogenetics by themselves, and it is important to know that we used to have these just in three categories and now there are five, and you can see them here. So, -Y, very common in older patients, and deletion 11q are considered favorable, very good now. Good cytogenetics are normal, so normal it is not the best, but it is considered in the good category. Deletion 5q which we know is one of the most common cytogenetic abnormalities, and then there are a few others. You can see that when we look at poor and very poor, anything with 7 as I always say in MDS is not lucky, so -7, deletion 7q, or complex abnormalities, so this is up to three abnormalities, are considered poor, and when somebody has more than three cytogenetic abnormalities, that is considered to be very unfavorable or very poor.

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IPSS-R Prognostic Score Values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Inter-mediate	Poor	Very Poor
BM Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

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

We then look at the percentage of blasts in the bone marrow, the cytopenias as I mentioned, how many cell lines are involved, and depending on the degree of abnormality, they are assigned a score. So, you can see the cytogenetics playing out there where very good, that -Y or 11q, you get a score of 0, whereas, if you have greater than three abnormalities, you get a score of 4, and we are going to look at bone marrow blasts, and as those blasts increase, that person is moving toward that leukemic trajectory, and we now know that the new definition of acute myeloid leukemia is the presence of 20% or greater blasts in the bone marrow. So, when you get to greater than 10%, you are already considered to be poor because we know you are moving toward that leukemic transformation.

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IPSS-R Prognostic Risk Categories/Scores

RISK CATEGORY	RISK SCORE
Very Low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

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

Now we look at the depth of cytopenias and also the number of cytopenia, so it used to be that we would just give a single score here, but now, each of those is considered a criteria and you can see those described here. We take that aggregate score, so a total of all of those attributes and we are going to give them an overall risk score. So, let's say we have a person with only anemia and they have favorable cytogenetics, so maybe just -Y, and they have less than 5% blasts in their marrow, they are going to have a very low score, less than 1.5. On the other hand, you take somebody with greater than 10% blasts, maybe they have that paragraph of abnormalities in their cytogenetics, so greater than three chromosomal abnormalities, and they then are going to have a higher score greater than 6, very high. So why is this important? Because when you look at survival and the risk of leukemic transformation, which is what we see here, it is going to make a big difference in how we manage those patients at the time of diagnosis.

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IPSS-R Prognostic Risk Categories/Scores

N=7012	Very Low	Low	Intermediate	High	Very High
Patients (%)	19%	38%	20%	13%	10%
Median survival years	8.8	5.3	3.0	1.6	0.8
Median time to AML in 25% (years)	NR	10.8	3.2	1.4	0.7

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

So this is just showing you the percentage of people in each of those categories, thankfully the largest percent of patients have lower risk disease. So let's say we have these two patients we just discussed and they present in your clinic on the same day, that person with the less than 1.5 score who is in the very low category has 8.8 years median survival, and this is in the absence of active therapy, so again, these numbers apply to newly diagnosed previously untreated patients. And in the studies thus far, the median time to AML transformation has not been reported. So, for 25% of the patients in this grouping, this is not reported. On the other hand, if you take that high-risk patient, so that score was greater than 6, median survival can be measured in months, so 0.8 years, and the time to leukemic transformation is also very short. So the message here is these patients with very high risk disease generally die very quickly of leukemic transformation in the absence of treatment, where on the other hand, a very low risk patient, we might have time to monitor them and get a sense of the tempo of their disease and decide how best to proceed.

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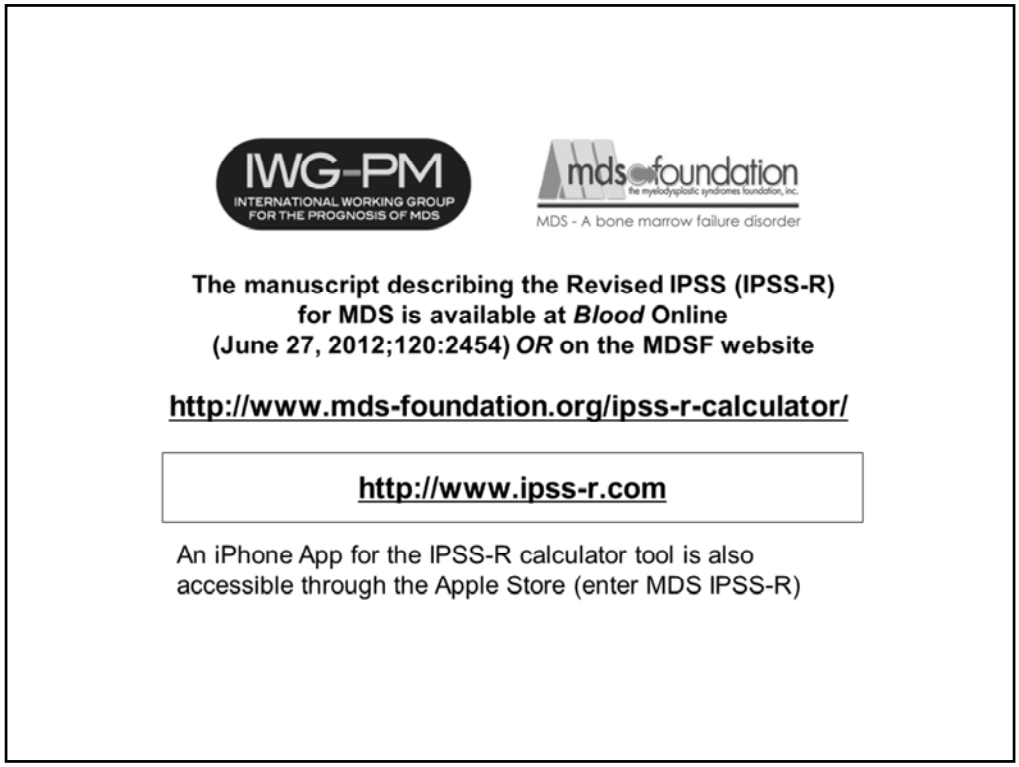

So, luckily, there is an app that is available through the MDS Foundation and the website is listed for you here that has the IPSS-R calculator on it, and this is something where you can plug in these attributes and it will generate a score for you including those cytogenetic abnormalities because that is difficult to commit to memory certainly.

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Treatment Triggers

- Transfusion dependence
- Progressive or symptomatic cytopenias
- Increasing blasts
- High-risk disease

Kurtin SE, Demakos EP. *Clin J Oncol Nurs*. 2010;14:E29-E44.

So, with that, let's say we now diagnosed our patients. We want to know who needs to be treated and how quickly. Our treatment triggers include transfusion dependence, and we will talk more about why that is important in a moment. If they have progressive or symptomatic cytopenias, and what that is telling is that bone marrow failure is moving along and they are going to need some disease-modifying therapy, if they have increase in blasts because again they are toward that leukemic end of the trajectory, and/or if they have very high-risk disease as we have just discussed. We will talk a little bit more about transfusions then. So, we know that transfusion dependance is inevitable in almost all patients with MDS. The red cell line, the erythroid lineage, is the most commonly dysplastic cell line in this disease, and anemia is one of the most common presenting cytopenias.

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MDS, Transfusions, and Survival

- 2,253 newly diagnosed MDS patients
  - Median age of 77
- Transfusion-dependent patients with MDS
  - Higher incidence of dyspnea, hepatic disease, and infections (all $P<.001$)
  - 82% experienced a cardiac event within 3 years of follow-up ($P<.001$)
  - Increased risk of death (age adjusted) compared with other MDS patients (HR 2.41, 95% CI, $P<.001$)

Goldberg SL, et al. *J Clin Oncol*. 2010;28:2847-2852.

So, this is a study of 2,200, almost 2,300 newly diagnosed patients, median age is 77, so very common, and these transfusion-dependent patients with MDS had a higher incidence of dyspnea, hepatic disease, and infections, all at a statistically significant level; 82% of them experienced cardiac events within 3 years of followup, so very significant. And they showed an increased risk of death, age adjusted, compared with other MDS patients, so very important that transfusions over time, whether you talk about iron overload or just the significance of intermittent anemia with hypoxia and all the other things that come with that, these people have inferior survival. So, transfusion dependence is often a criteria for enrollment in clinical trials, and it is a treatment trigger, it is a reason to consider disease-modifying therapy as opposed to just supportive care alone.

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FDA-Approved Agents for Active Treatment of MDS

Agent	FDA Approval Date	Mechanism of Action	Route of Administration
Azacitidine	May 2004	DNA methyltransferase inhibitor	Subcutaneous or IV Oral compound in clinical trials
Lenalidomide	December 2005	Immunomodulatory	Oral
Decitabine	May 2006	DNA methyltransferase inhibitor	IV or subcutaneous

Kurtin SE. *Oncology (Williston Park)*. 2007;21(11 Suppl Nurse Ed):41-48.

So, when we look at FDA-approved agents, what we consider to be active treatment or disease-modifying therapies, we current today still only have three FDA-approved agents. Two of these are in the same class of drugs. These are DNA methyltransferase inhibitors or what we call methyltransferase inhibitors, basically. Those are azacitidine and decitabine, and then we have a single immunomodulatory agent approved currently, which is lenalidomide, which is an oral agent. There are many drugs in clinical trials, but they have not yet been approved.

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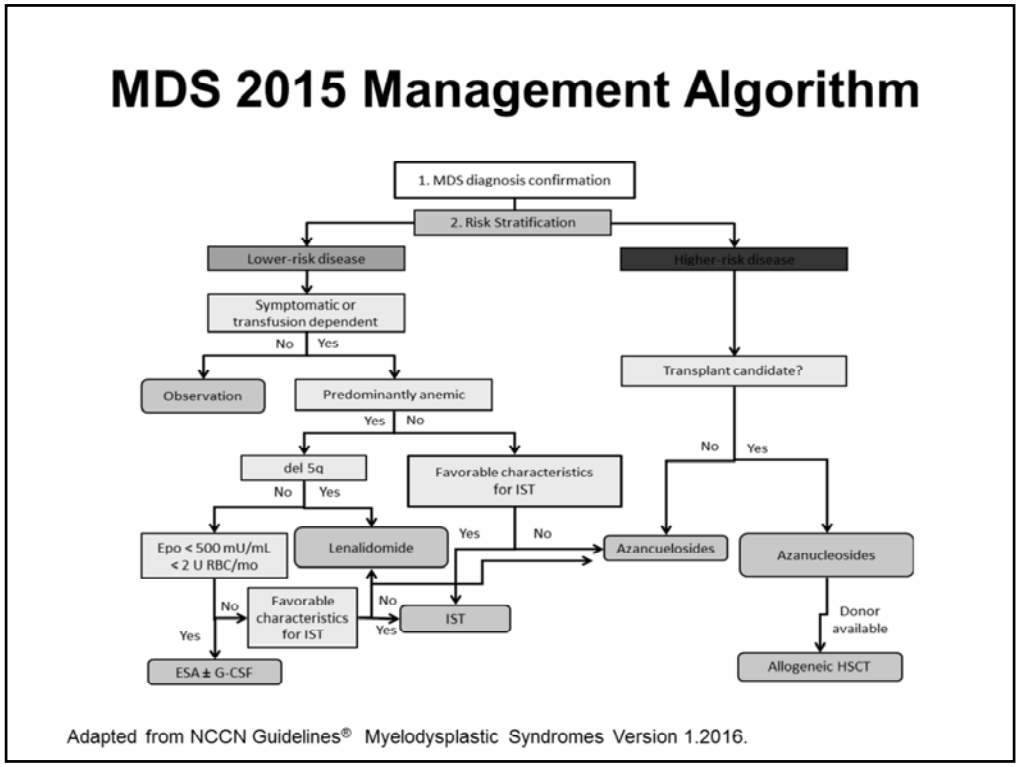

This is a general MDS treatment algorithm, and you can see here that we are going to differentiate these into the two groups of lower risk or higher risk disease, so they get risk stratified. We want to ask the question are they transplant eligible for those patients who do meet the criteria for transplant eligibility. Remember that is an allogeneic transplant not an auto transplant. We want to keep that in mind and move toward that goal early in the phase of treatment. We do not want to wait until they are very sick or in a crisis mode before considering that. So, really deciding that upfront is very, very critical. If they are not transplant eligible, we are going to use those DNA methyltransferase inhibitors or aza nucleotides as our first line of therapy. If on the other hand they have low risk disease, we are going to say are they are symptomatic, are there those treatment triggers, can we just watch them for a while, get a sense of a tempo of that disease. If we feel like they have treatment triggers, they are transfusion dependent for instance, it is very important to determine upfront what their cytogenetic profile looks like. If they have a deletion of 5q, we know that the data highly supports the introduction of lenalidomide. If they are 5q negative and they have a low EPO level and a low transfusion burden, they may benefit from erythropoietin-stimulating agents. Important to understand that in patients with adequate EPO levels, these drugs will not really be helpful, and again, our supportive care, they do not change the underlying disease. We should always consider a clinical trial because as we see there are only three currently available drugs, two of which are in the same category, so we are always striving to get people enrolled in clinical trials so that we have the option of finding additional therapies.

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Key Principles of Therapy in MDS: Treatment Goals and Duration

- MDS is not curable without allogeneic HCT
  - Not an option for the majority of patients
  - Not every patient will have a complete response
  - Hematologic improvement, stable disease, and transfusion independence are good things
- Treatment should continue until disease progression or unacceptable toxicity
  - Limited FDA-approved agents currently available
  - Methylation is a continuous process and is associated with leukemogenesis
  - Prognosis after failure of hypomethylating agents is extremely poor

HCT=hematopoietic cell transplantation
Kurtin SE, Demakos EP. *Clin J Oncol Nurs*. 2010;14:E29-E44.; Kurtin SE. *J Adv Pract Oncol*. 2011;2(Suppl 2):7-18.

So then, let's talk about some of the principles once we have decided to move forward with treatment. Keeping in mind that MDS is not curable without allogeneic transplant, as we said, the majority of these patients will not qualify for an [allogeneic] transplant. So, we are really looking at ways to control the disease. We may not ever achieve a complete response or the absence of disease, but if we have improved quality of life and people have stable disease and have achieved transfusion independence, those are all very good things. We know that we need to continue treatment until the disease has progressed or there is unacceptable toxicity because we know we have not eradicated this malignant clone, and in the absence of treatment, that clone will re-emerge and in many cases may be more aggressive. We know that methylation, for instance, these hypomethylating agents that we use, these DNA methyltransferase inhibitors (DNMTIs), we know that methylation is a continuous process and it is associated with leukemogenesis. So, if you remove that inhibiting agent, that process will re-emerge as I mentioned. Furthermore, prognosis after failure of one of these hypomethylating agents is extremely poor, generally estimated to be somewhere between 6 and 9 months.

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Strategies to Minimize Adverse Events

- Set expectations
- Plan supportive care strategies
- Engage and empower patients and caregivers

Kurtin SE, Demakos EP. *Clin J Oncol Nurs*. 2010;14:E29-E44.; Kurtin S. *J Adv Pract Oncol*. 2011;2(Suppl 2):7-18.

So, some of the other things we want to do, we want to minimize adverse events. We really want to adequately prepare the patient and their caregivers for this treatment, the expectations. So, we need to set expectations, plan our supportive care strategies, and really engage the patient and caregiver in working with us on getting through their treatment.

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Key Principles of Therapy in MDS: Treatment Duration

- A minimum of 4-6 months of treatment is required to evaluate initial response
  - Best response may not be evident until 9 months of therapy
- Myelosuppression is the most common toxicity in all types of active therapy for MDS
  - Cytopenias will often get worse before they get better
  - Moderate asymptomatic cytopenias may persist for months or years in patients responding to treatment

Kurtin SE, Demakos EP. *Clin J Oncol Nurs*. 2010;14:E29-E44.; Kurtin SE. *JADPRO*. Submitted for publication, June 2011.

And some of the biggest challenges in MDS, which are different than some other diseases that we see, is it may take up to 4 to 6 months of treatment before you really begin to see even an initial response, and in some cases, the best response may not be evident for up to 9 months. The next thing that we have to deal with is that myelosuppression is the most common toxicity in any of the disease-modifying therapies for this disease. So, we have patients with cytopenias, and we expect those cytopenias to get worse before they get better. So, you have older patients with cytopenias, sometimes significant cytopenias, what I call moderate but asymptomatic cytopenias, and these may persist for several months before the patient responds. That can create a sense of uncertainty and fear in some cases, both in the patients and in providers, and getting familiar with those is really important to keeping people on the therapy long enough to actually achieve a response.

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Key Principles of Therapy in MDS: Setting Expectations and Empowering the Patient and Family

- Setting expectations
  - Cytopenias are expected
  - Require close monitoring during the first 8-12 weeks of therapy
    - Create a plan for follow-up
  - Likely to improve with treatment response but may not return to normal — "new normal"
- Empower the patient and family to track, report, and manage
    - My MDS Manager™
    - www.buildingblocksofhope.com
    - Early identification of AEs, how and when to report or manage

Kurtin SE, Demakos EP. *Clin J Oncol Nurs*. 2010;14:E29-E44.

We really want to say these cytopenias are expected, it is not a surprise. We expect this in almost every patient. As a result, we need a plan and that plan means that we are going to monitor these patients very closely in the early phases of treatment, the first 8 to 12 weeks, sometimes beyond that, and we really to need to create a plan for followup. So, for instance, if you have patients getting their labs weekly, I say do not do it on Friday because you may not get those results and not hear about it until Monday or Tuesday and in that time the patient may have needed some kind of supportive therapy and you want to avoid having them end up in the emergency room. We need to understand that the patient will likely improve on treatment, but they may never reach counts that are normal. So, what we call the new normal. So, they may always have some level of thrombocytopenia, some level of neutropenia or leukopenia, and in some cases their hemoglobin or their anemia may not completely normalize. We need the patients to understand this, and there are some tools that we suggest to help them track, report, and manage their own counts and kind of keep an eye on how they are doing. There is a new app that is in the process of development called 'My MDS Manager.' It is not currently available. We expect this in the next few months. There is a project that I worked on called the 'Building Blocks of Hope.' The website is here. It is an interactive online digital educational tool with embedded videos and all kinds of good information for the patients, and we really want to encourage patients and their caregivers to learn what to look for, learn what to report, and who to report it to so that we can intervene with any side effects early.

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Strategies to Minimize Adverse Events

- Supportive care is essential for all patients with MDS to improve quality of life
  - Transfusion support, growth factors, management of infections, management of comorbidities, chelation therapy, referrals to supportive services
- Minimize AEs in patients on active therapies
  - Dose adjustment, drug holidays, or administration of growth factors to allow safe continuation of therapy
  - Clear guidelines to the patient and family for early reporting of AEs or strategies for independent management

Kurtin SE, Demakos EP. *Clin J Oncol Nurs*. 2010;14:E29-E44.; Kurtin S. *J Adv Pract Oncol*. 2011;2(suppl 2):7-18.

Supportive care is essential in all of these patients, that may include transfusion support, certainly in the early months of therapy. In patients who are transfusion dependent, they may actually need transfusions more frequently initially until they respond than they had, and that is important for them to understand. Growth factors can be used. White blood cell growth factors, we do not generally do that preventively, but in the presence of an infection we can certainly use these agents, aggressive management and prevention of infection, the comorbidities as I discussed, it is really important for these patients to stay connected to their primary care providers and other sub-specialists so that we keep all of those disease states in the best balance possible. In patients who have iron overload in low-risk disease, we consider chelation therapy to remove that excess iron which we know is detrimental, and then certainly referral to supportive services. Minimizing adverse events with treatment. Really looking at individual drug profiles, there are very good guidelines for dose adjustments. These are very commonly needed in the patients with MDS or drug holidays certainly. In lenalidomide therapy, this is a mainstay, we expect patients to require dose modification over the course of the treatment. In many patients, they may require more than one dose adjustment. So, very important to be familiar with each of the drugs and how to implement those dose modifications so that you can minimize adverse events.

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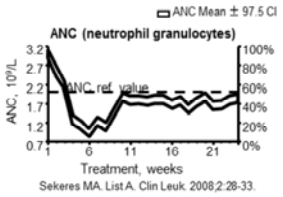
The Challenge: Getting Through the First Few Cycles of Treatment

- Time is required for the best response: a minimum of 4–6 months
- Cytopenias often get worse before they get better
- Strategies for management
  - Dose modifications/delays
  - Supportive care
  - Set expectations and provide support



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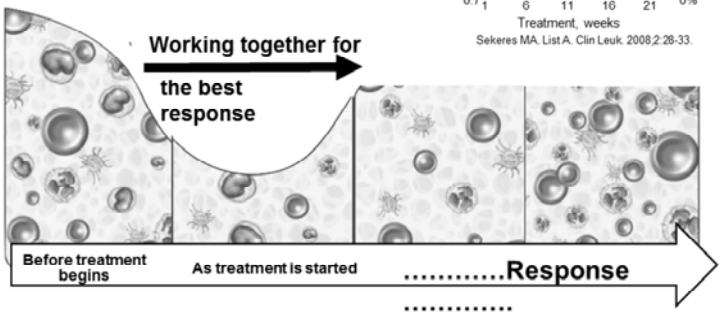

This is one of my favorite slides, it really shows the trajectory of the disease where you start with the very packed marrow, and then, you reach this, what I call, the ravine, this dip in the patients' counts. Again, we expect it, it is not a surprise. We are going to use dose modifications, supportive care, and really setting expectations for the patients and their caregivers to get across that ravine, if you will. This is where I bring this back out to the patients and I say remember we talked about this, it was expected, we knew these counts were going to drop. We need to give you the therapy long enough, that 4 to 6 months to actually get to the other side of that ravine and hopefully have a response. In patients who get only one or two cycles of therapy and then we stop, basically all we have done is really expose them to toxicity without the potential for benefit. So, we really need to commit to that full 4 to 6 months of therapy before we abandon treatment, with the exception of patients who really just simply do not tolerate it for whatever reason, their comorbidities or other problems.

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Common Adverse Events

- All agents
  - Myelosuppression (may also be disease related)
    - Anemia, neutropenia, thrombocytopenia
  - Nausea and vomiting
  - Constipation
  - Renal and hepatic toxicities
- Drug-specific adverse events
  - Azacitidine: injection-site reactions
  - Lenalidomide: rash, pruritus, diarrhea, safety program for lenalidomide
- Iron overload
  - Chelation therapy may be associated with cytopenias, renal and hepatic toxicities

Kurtin SE, Demakos EP. *Clin J Oncol Nurs*. 2010;14:E29-E44.; Scott BL, Deeg HJ. *Annu Rev Med*. 2010;61:345-358.; Kurtin SE. *Oncology (Williston Park)*. 2007;21(11 Suppl Nurse Ed):41-48.

Common adverse events with the drugs. Myelosuppression in all of them. We have talked about that. We can see nausea and vomiting. This is primarily in the hypomethylating agents. Constipation is very common in the hypomethylating agents. A lot of people want to blame this on the antiemetics, but I can tell you even without them people have a problem. These are older patients. If they have thrombocytopenia, we do not want them straining, so we really do need to have a bowel regimen in place and make sure that they understand how to use that. You can see renal or hepatic toxicities with all of these drugs, and it is important to familiarize yourself with each one of them and make sure that you are monitoring that closely along with their CBC. Drug-specific adverse events, azacitidine can be given either IV or subcutaneous (sub-Q). In the patients getting sub-Q injections, there can be some local reactions. There is a technique that I call the “Air Sandwich” that myself and Erin Demakos, who is a colleague, developed this tool.

We now use it in other disease states as well, and you can refer to that in the literature to get guidelines for that, but it can significantly reduce the incidence of local reactions. In lenalidomide, we can see a rash. This can be transient, patchy, it is not considered a true allergic drug reaction. It is something that is thought to occur as a result of the effect on these lymphocytes that are embedded in the tissue. So, it is an immunomodulatory agent and this rash can be a result to that. There are people who can have allergic reactions or true drug rashes, and that will need to be treated in a different way, but often you can treat these symptomatically and continue therapy. We can also see some diarrhea, as you know the immunomodulatory agents require a safety program for prescribing, the REMS Program, so you would need to check with that. You cannot prescribe it without being registered for the REMS Program. We talked a little bit about iron overload, but the important thing here is that if people are on chelation therapy, these drugs can cause cytopenias themselves, and renal hepatic toxicity. So, you do not want to just automatically blame the anti-MDS therapy, the disease-modifying therapy. You need to really assess whether the iron chelation therapy may be contributing to any of these side effects, and in my practice, we adjust that first before we abandon the disease-modifying therapy.

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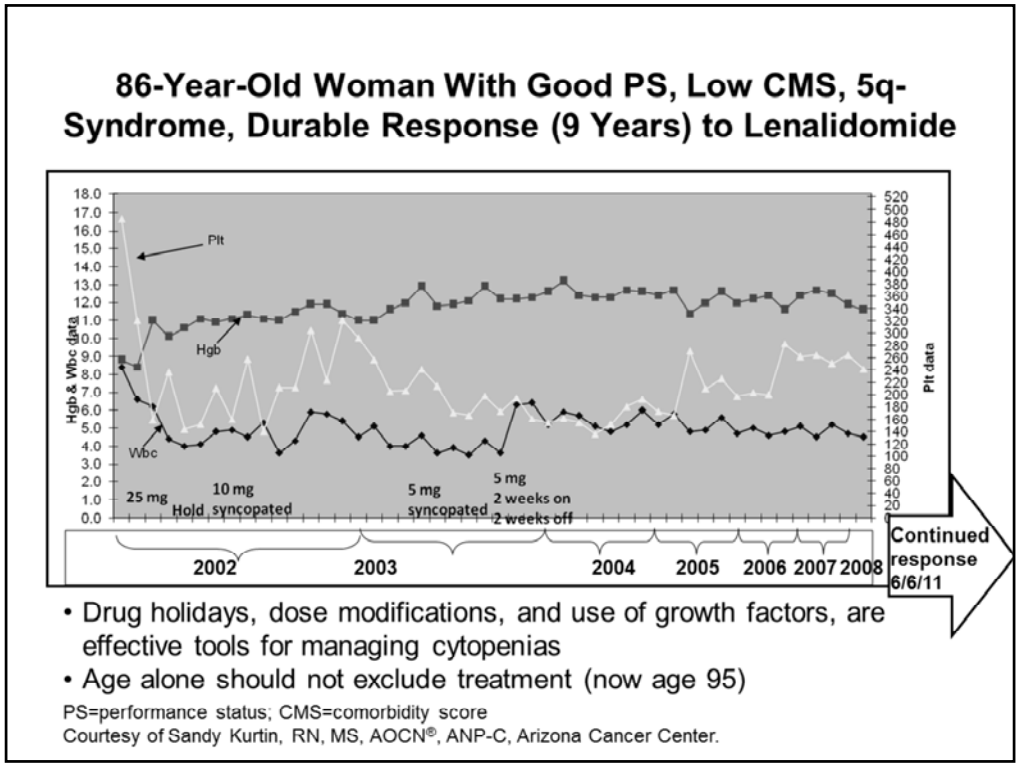

I will end with just a couple of cases here to illustrate some of these different trends that we see and the effects that we see in terms of cytopenias and response. So, the first case, here is an 86-year-old woman with a good performance status, low comorbidity scores, otherwise very healthy, had 5q- syndrome which is the cluster of findings with the sole cytogenetic abnormality of the deletion of 5q. She was actually on one of the original lenalidomide trials, and she had a durable response for over 9 years, but I will draw your attention here to the left side of the graph where you see the platelet count being very high. It is little confusing because the numbers for the platelets are on the right axis but the arrow starts on the left, and in 5q- syndrome, people can actually have thrombocytosis. So, they actually have a high platelet count many times, but you can see very, very quickly early in the course of treatment, she had a drop in her platelet count. She also had a drop in the white count and her hemoglobin got worse before it got better. You can see then that she sort of recalibrates and for a long time has moderate leukopenia and neutropenia but asymptomatic, and her hemoglobin continued to respond. So, very important to institute those early blood counts, dose modification as indicated, and you can see here this patient started on the clinical trial which is 25 mg of lenalidomide, that is too much in MDS. So, we know that the starting dose here is 10 mg, and she required a number of dose modifications over the course of her illness.

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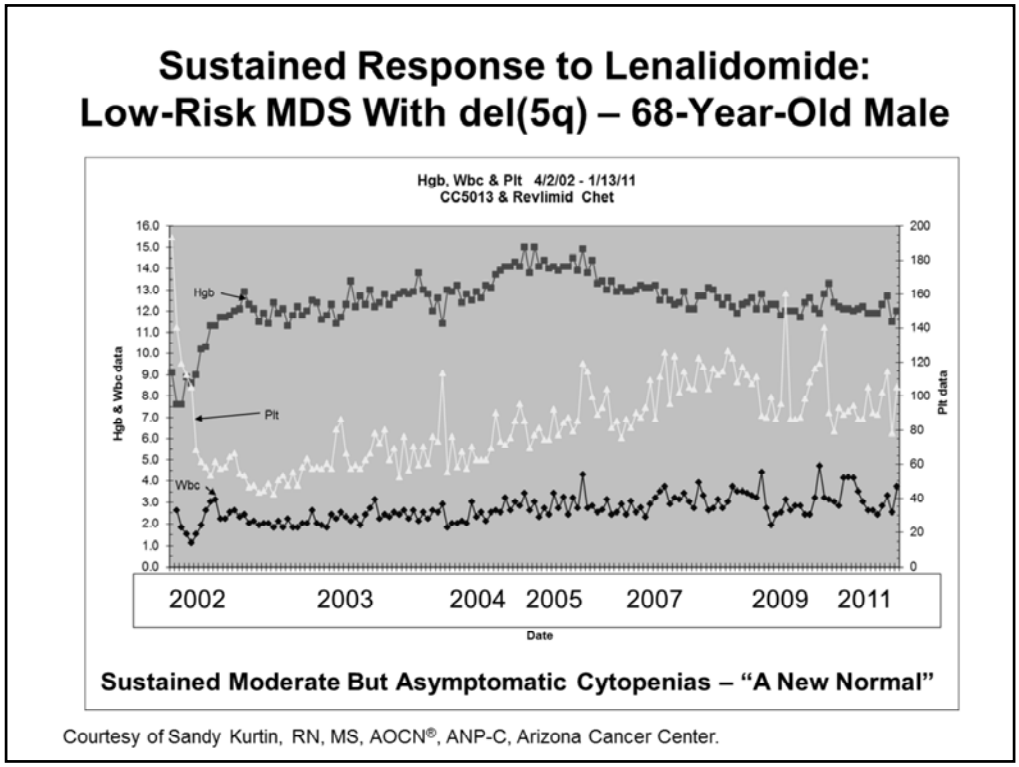

The second patient is a 68-year-old patient, also deletion 5q, receiving lenalidomide, and this again is a person who responded to treatment for almost 12 years. He just recently died almost a year ago of heart disease, not of MDS. So, a couple of very important points here, very early drop in blood counts got worse, then got better, and if you trend his platelets over the course of his illness, he had two normal platelet counts for the entire time, but he was not bleeding, he was asymptomatic, and there was no reason to intervene or to change his dosing. Similarly, neutropenia was something he had over a long period of time but never really was hospitalized until he developed heart disease and he needed coronary stents. So, very important to kind of readjust to this concept of moderate asymptomatic cytopenias in these patients who can do actually quite well and not require intervention, hospitalization, and such. We need to get used to those and allow for continued treatment.

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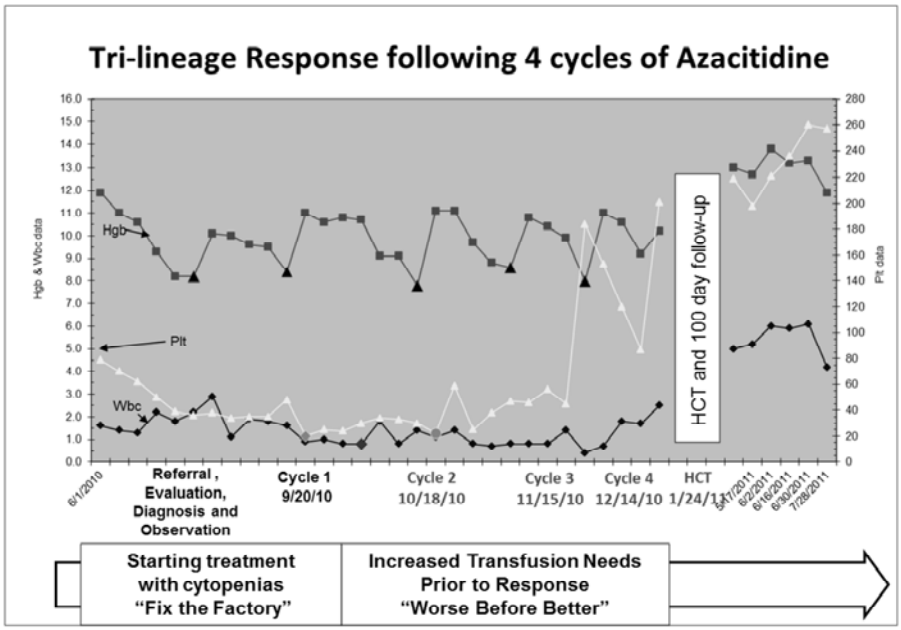

Courtesy of Sandy Kurtin, RN, MS, AOCN®, ANP-C, Arizona Cancer Center.

This is another patient, a very young patient, who was originally diagnosed after having her second child, became very, very fatigued. They thought she had postpartum depression, and you can see that her count started to drop before we actually instituted treatment. So, she was referred and worked up, and when we actually started her therapy, you can see there cycle one of therapy, her platelet count was 32,000. This is because of her disease and that is not going to get better by monitoring, so you kind of need the bite the bullet, support with supportive care, and institute therapy. And you can see these big triangles here which all imply red blood cell transfusions, and then similarly indications of platelet transfusions, and that it was not until cycle four of therapy, after cycle four of therapy, that we saw trilineage response, so all of her counts improved. Luckily, she was young. She had a sister who was a match, and she went on to have an allogeneic stem cell transplant. So a lot of the patients are not that young, but in those patients who are, it is an option that is important to consider and consider early so that we are planning as we go.

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Conclusions

- MDS is primarily a disease of the elderly
- Currently, three FDA-approved agents
- Clinical trials are necessary to find new treatment options
- Understand principles of risk-adaptive therapy using IPSS calculator
- Set expectations and support patients through therapy
- Minimum 4 to 6 months of treatment necessary to experience a response

So, in closing, it is important to understand that MDS is a disease primarily of older patients. We only have three currently available FDA-approved agents and we need to have patients included in clinical trials to try to find newer options for treatment, understanding the principles of risk-adaptive therapy using the IPSS calculator, setting expectations and supporting patients through that therapy, and really committing to a minimum of 4 to 6 months of treatment before we abandon disease-modifying therapy for patients to hopefully be able to experience a response.

I want to thank you for viewing this activity, and for additional resources, please view other educational activities on *ManagingMDS.com*. Thank you.

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