Myelodysplastic Syndrome (MDS) Nurse Education Session

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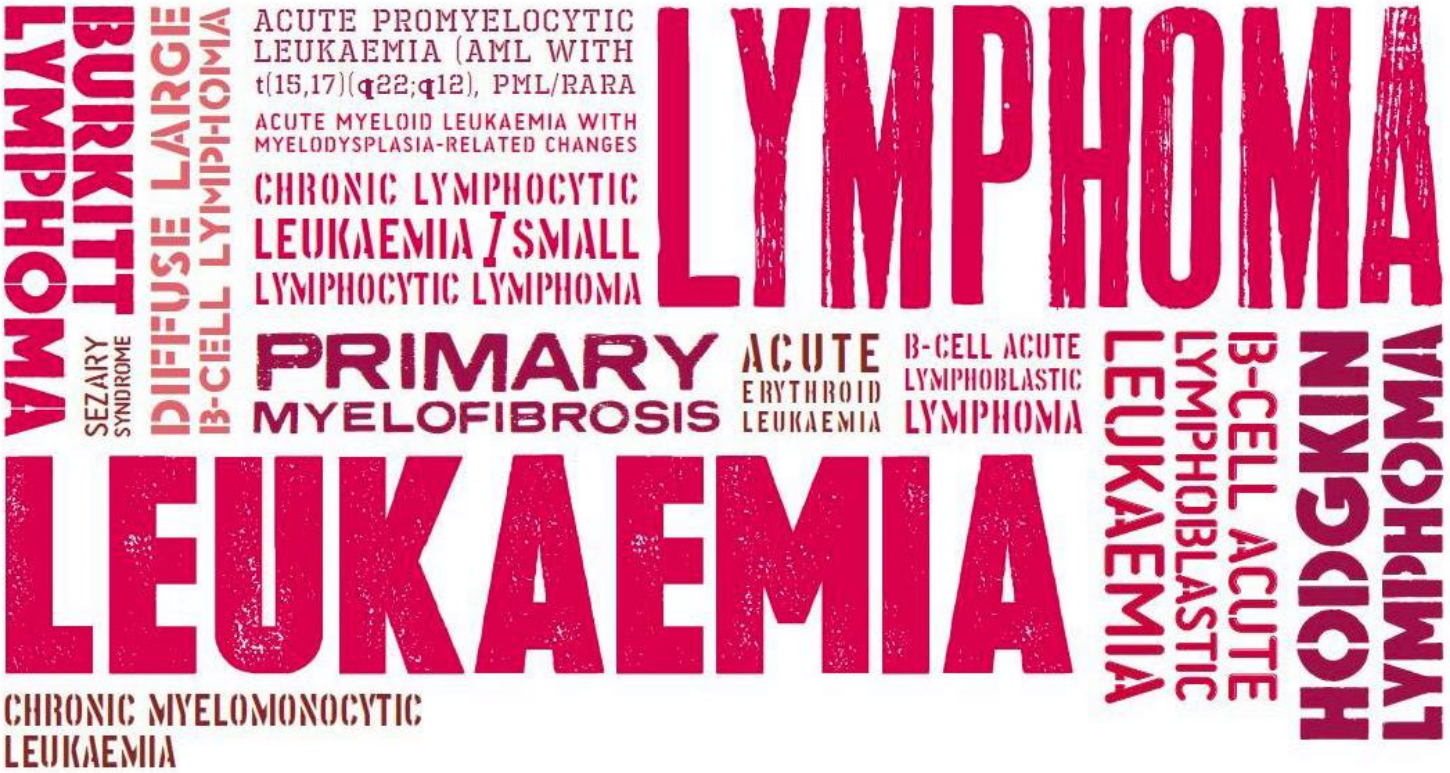
When you drive by the hospital on your day off

It's Blood Cancer Awareness Month



Discussion Objectives

- Disease Overview
- Discuss the pathophysiology and classification of MDS
- Discuss strategies to assist patients in achieving optimal outcomes
- Review commonly used drugs and supportive therapy in the management of MDS

What is MDS

Definition:

- "A *group* of disorders characterized by abnormal differentiation and maturation (dysplasia) of the hematopoietic stem cells, notably the myeloid cell lines" (Murray et. al., 2012, p.222).

Leads to:

- bone marrow failure
- ineffective hematopoiesis
- peripheral cytopenias: anemia, thrombocytopenia, and neutropenia
- Non-specific symptoms related to cytopenias e.g. fatigue, infection, bleeding

What is MDS

Classification:

- Asymptomatic in early stages
- Diagnosis often incidental

Prognosis, risk, management based on IPSS:

- number of cytopenias (RBC, PLT, WBC)
- blast percentage in marrow
- Marrow chromosome analysis (good, intermediate, poor)

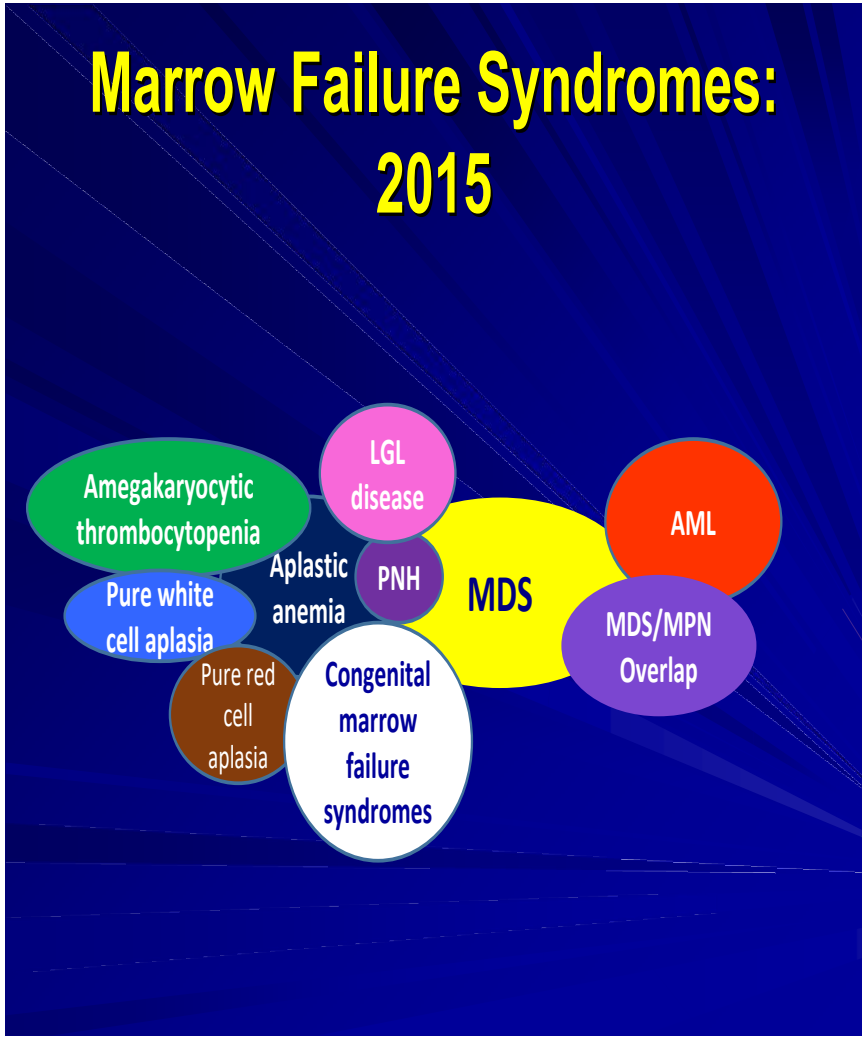
Higher IPSS scores:

- AML transformation
- transfusion dependence
- shorter survival

What is MDS

Malignant disease of blood & marrow:

- Often pancytopenia (all three RBC, PLTS, WBC)
- "Pre-leukemic," tendency to transform to AML (~50%)
- Familial, de novo (primary), or treatment-related (secondary)
- Mild or severe, slow-growing (anemia) or fast-growing (AML)
- Overlaps with other marrow failure syndromes
- Heterogeneous (diverse) disease with variable prognosis



MDS Epidemiology

- New cases: Incidence about 4 per 100,000
- Prevalence: 10,000-50,000 in people >65* REF
- Disease of the elderly: median age of diagnosis 65-70
- More common in males than woman

What causes MDS

Root causes:

- DNA damage to the bone marrow stem cells
- Epigenetic changes such as increased DNA methylation may occur
- Association with inactivation of p53 tumor suppressor gene for some

Interaction between neoplastic cells and the microenvironment

- Abnormal cytokine release/response and immune suppression

Bone marrow hyper-cellularity

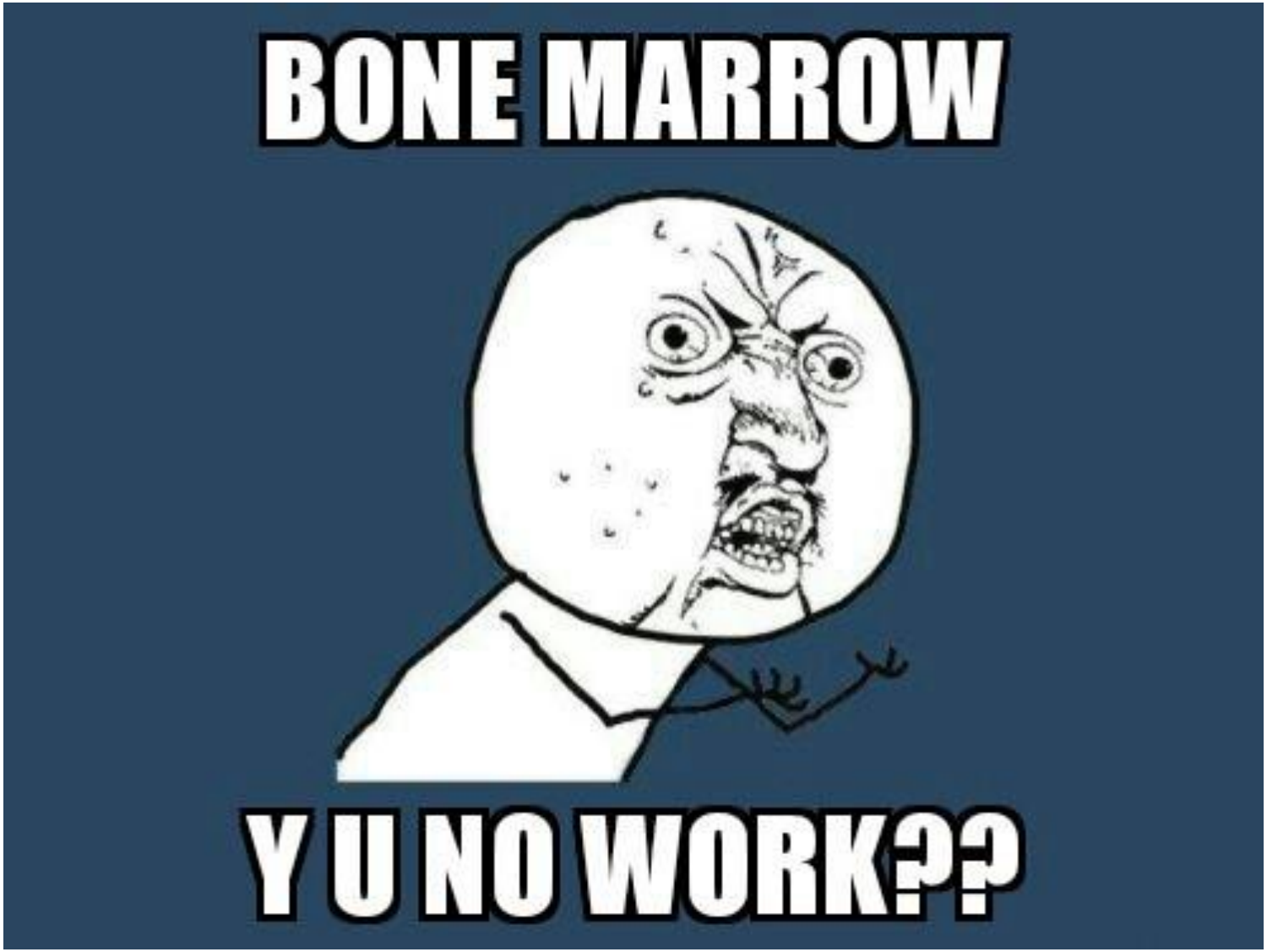
- Increased proliferation of neoplastic cells
- Increased or defective apoptosis
- 8 - 28% of patients have hypo-cellular marrows

Risk Factors of MDS

- Older age
- Male sex
- Immune dysfunction
- Rare inherited congenital abnormalities (e.g., fanconi anemia)
- Another blood disorder (e.g., aplastic anemia, PNH, polycythemia-vera, essential thrombocytosis)
- Some cases associated with exposure to:
  - Chemotherapy agents
  - Ionizing radiation
  - Industrial chemicals
  - Benzene

Therapy-related (tMDS)

Most often the cause is unknown


BONE MARROW
Y U NO WORK??

Other Facts About MDS

- Remains an incurable malignancy for the majority of patients
- Leading cause of death is the disease itself for most patients
- Allogeneic stem cell transplant is the only potential cure
  - Many complications
  - Not well tolerated if frail or have other illness
  - Even post transplant, the relapse rate can be relatively high
  - Most are not transplant eligible

Diagnosis of MDS

- Bone marrow biopsy and aspirate
- Cytogenetic testing (karyotype, FISH, flow cytometry, molecular)
- Basic lab tests (kidney, liver function)
- Erythropoietin level
- Iron studies (ferritin, TfSat)
- Exclusion of other causes of pancytopenia (viruses, meds / drug effect, nutritional / vitamin deficiencies, hematological disorders)

Not all dysplasia is Myelodysplasia

Prognostic Indicators For MDS

- FAB (French American British) Classification
- WHO-based Prognostic Scoring System (WPSS)
- MD Anderson
- International Prognostic Staging System (IPSS) or IPSS-R

IPSS

Score	0	0.5	1	1.5	2
Blasts %	< 5	5-10	---	11-20	20-30
Karotype Good risk: normal, isolated del(5q), -Y, isolated del(20q) Poor risk: complex abnormalities (>3), abnormalities of chromosome 7 Intermediate: all others	good	intermediate	poor		
Cytopenia (hemoglobin <100g/L, neutrophils <1500/μL, platelets <100	0-1	2-3			

- Marrow blast % (Note: >20%: AML, not MDS)
- Cytogenetics
- Number of cytopenias (hemoglobin, platelet, and neutrophil counts)

IPSS-R

Prognostic Category	IPSS-R Score Value						
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Int	Poor	Very Poor
BM Blasts%	≤2		>2-<5		5-10	>10	
Hemoglobin, g/dL	≥10		8-<10	<8			
Platelets, x10/L	≥100	50-<100	<50				
ANC, x10/L	≥0.8	<0.8					

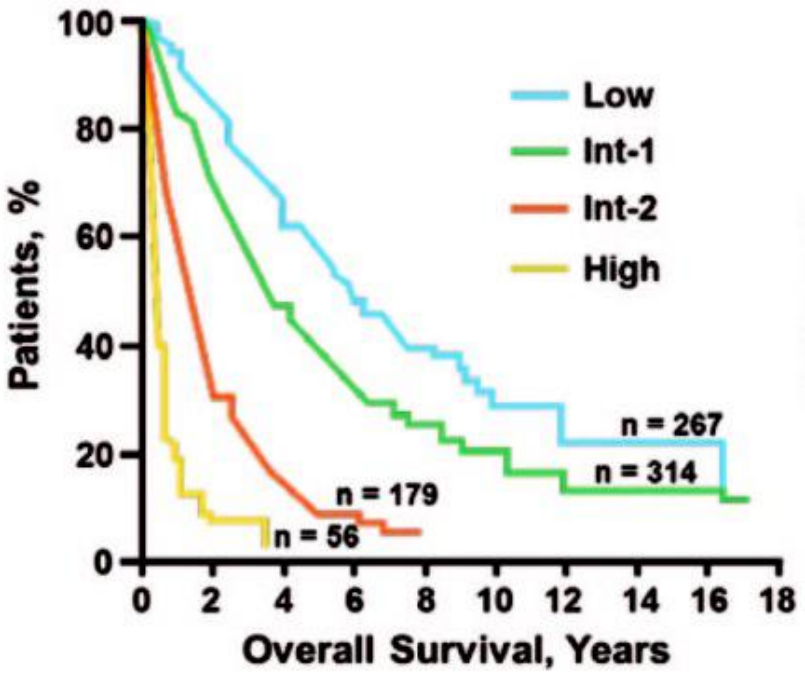
Cytogenetic groups

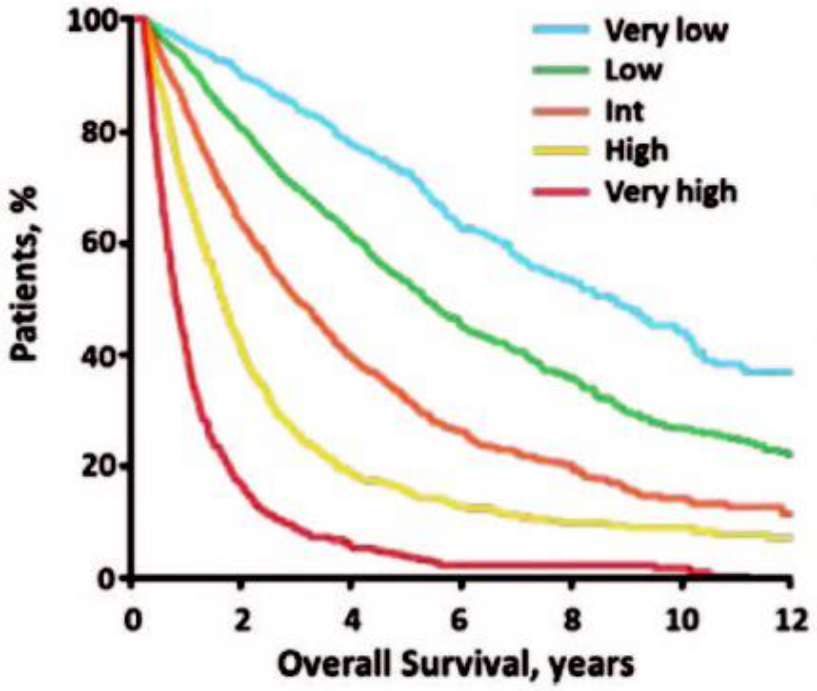
Very good: -Y, del(11q)
Good: normal: del(5q), del(12p), del(20q), del(5q) + 1 additional
Intermediate: del(7q), +8, +19, i(17q), other abnormalities not in other groups
Poor: -7, inv(3)/t(3q)/del(3q), -7/del(7q) +1 additional, complex (3 abnormalities)
Very poor: complex (>3 abnormalities)

Risk Category	Risk Score (for age 70)
Very Low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very High	>6

Bejar, R. ASH Education Book 2013

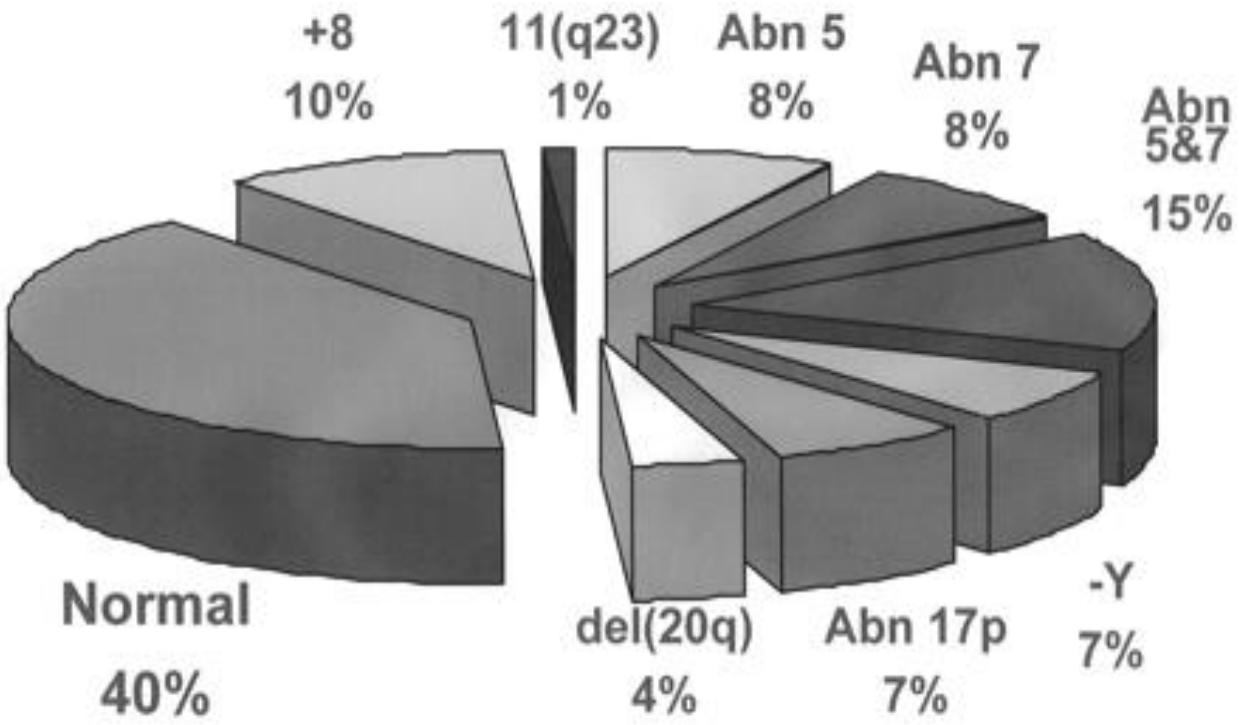
Survival Based on Prognostic Risk





Bejar, R. ASH Education Book 2013

MDS Cytogenetics



40-70% de novo MDS has karyotype abnormality
95% therapy-related MDS

ASH Education Book

Cytogenetic Abnormalities in MDS

Good risk:

- Del(5q)*
- Normal
- Isolated del(20q)
- -Y

Intermediate risk – all others

Poor risk:

- Abnormalities of chromosome 7
- Complex (3 abnormalities)

Very poor risk (IPSS-R)

- Very Complex (more than 3 abnormalities)


How can we help?

Goals Of Therapy For MDS

- Decrease disease-related complications (e.g., blood counts)
- Improve quality of life
- Change natural course of disease (increase survival; delay AML transformation; potential for cure)

**Goals per age, functional status, other medical conditions, IPSS risk*

Cheson et al., *Blood* 2006

Treatment Options For MDS

- Stem cell transplant for younger healthier patients
- Hypo-methylating agents
- Supportive Care

- Clinical Trials (e.g., Health Canada: hc-sc.gc.ca in inter /high risk)
- Growth factors (e.g., erythropoiesis-stimulating agents)
- Immunomodulating agents (e.g., lenolidamide in low risk Del(5q)
- Immunosuppressive therapy

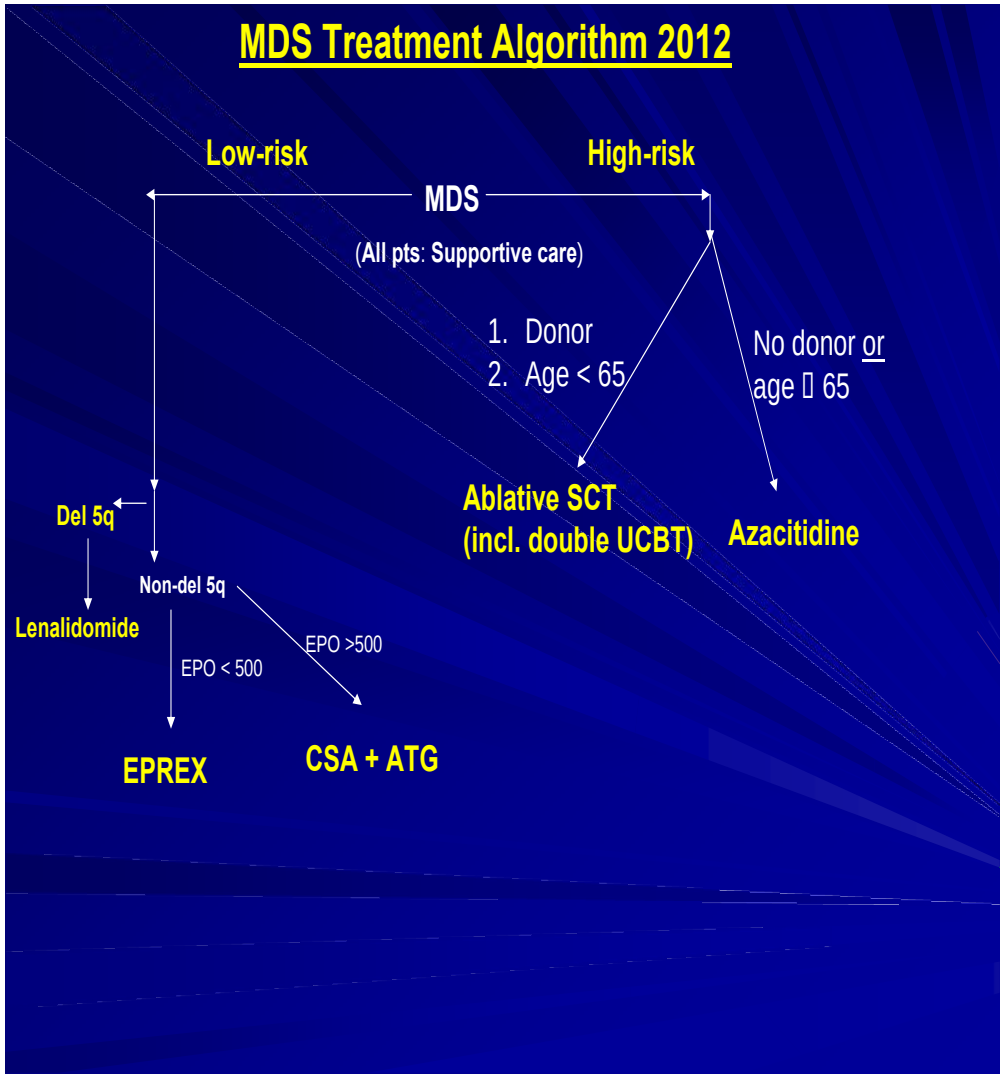
Management Of MDS (VGH)

Low-risk MDS:

- Supportive care + enhance hematopoiesis
- E.g., blood transfusions, growth factors, immunosupression

High-risk MDS:

- Supportive care + modify the disease
- E.g., HPSCT, azacitidine



Source: T. Nevill, Myelodysplastic Syndrome: Primary Care Perspective Webcast, 2015

Providing Supportive Care In MDS

- Psychosocial support
- Packed Red Blood Cell transfusions (irradiated blood if SCT)
- Platelet transfusions (+/- use of antifibrinolytic agents (Tranexamic acid) active bleeding or profound thrombocytopenia)
- Iron chelation (e.g. Desferal® or Exjade® in the event of evidence for iron overload (higher ferritin))

NCCN Guidelines Version 1.2015

Hypomethylating Agents

Azacitidine (Vidaza®) in Canada:

- Transplant ineligible patients with high-risk MDS
- AML patients with 20-30% blasts + multi-lineage dysplasia

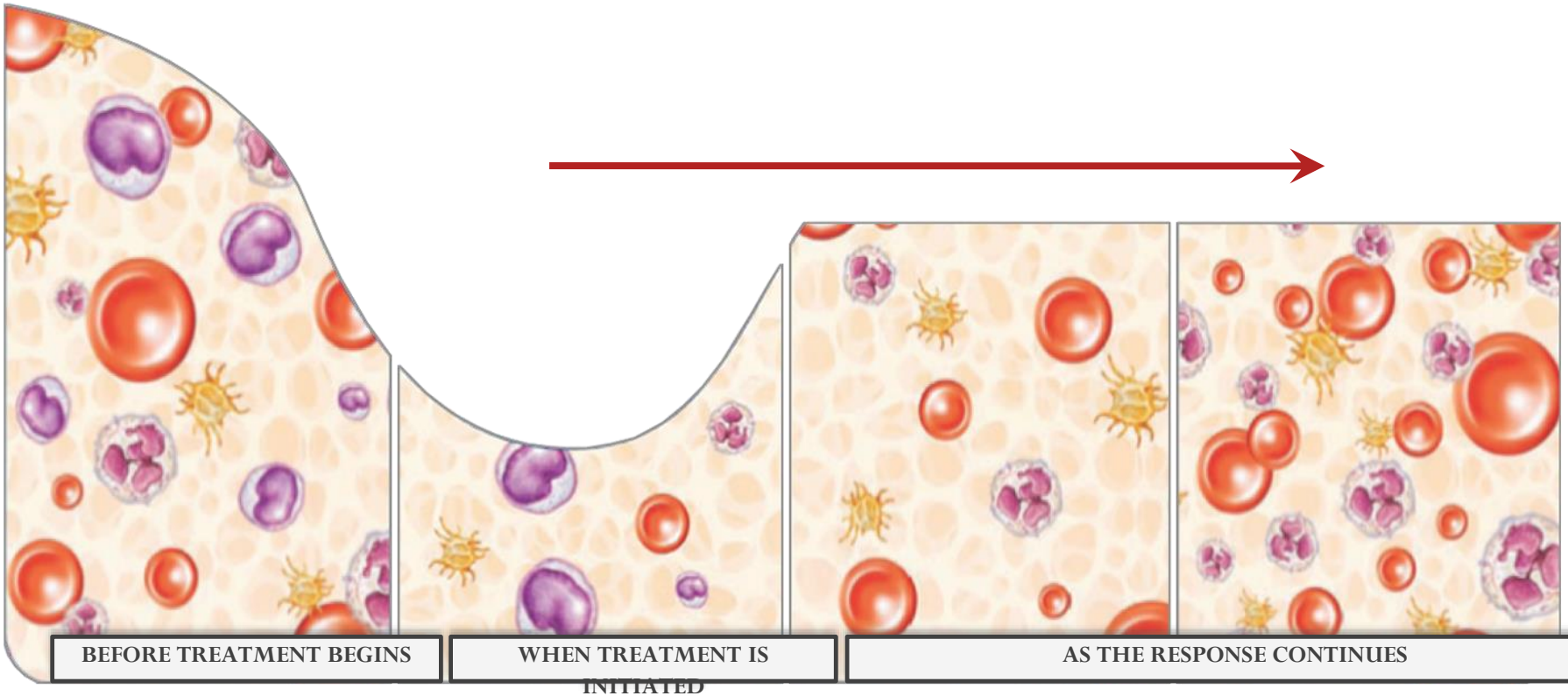
Azacitidine mechanisms of action:

- Suppresses DNA hypermethylation (constant process of in MDS)
- 28 day cycle: s/c injection 7 consecutive days, 21 day rest
- Minimum 6 cycles recommended
- Cytopenias may worsen during first few cycles (supportive care)
- Continue as long as beneficial or until disease progression

STAYING OPTIMISTIC WHILE GETTING THROUGH THE FIRST FEW CYCLES OF AZACITIDINE

Working together for the best response

EARLY TOXICITIES ARE USUALLY TRANSIENT AND MANAGEABLE



Source: C. Murray, A case-based orientation to the azacitidine nursing standard, 2013

Managing MDS: Azacitidine

Azacitidine:

- DNA hypo-methylating or de-methylating agent
- Capacity to alter the disease course
- Improved survival (in ALL patients)
- Higher transfusion independence
- Delayed disease progression
- ~50% patients = hematological improvement, 10-15% patients = CR
- BC began funding for azacitidine through BCCA in January 2010

**Significant improvements in QOL, including fatigue, physical functioning, dyspnea, general well being*

Source: T. Nevill, Myelodysplastic Syndrome: Primary Care Perspective Webcast, 2015

Nursing Implications

- Importance of managing AE:
  - To allow patients to continue on therapy
  - To achieve optimal therapeutic outcomes
- Manage AE:
  - Injection site reactions (erythema, bruising, pigment changes)
  - Cytopenias (anemia, thrombocytopenia, neutropenia)
  - Gastrointestinal effects (nausea, constipation)
- Counsel patients:
  - Expectations for therapy (QOL)

"Counselling And Adverse Event Management For Patients With Myelodysplastic Syndromes Undergoing Azacitidine Therapy: A Practice Standard For Canadian Nurses"

By Murray, C., Wereley, A., Nixon, S., Hua-Yung, C., von Riedemann, S., Kurtin, S., & Canadian Nurses Working Group on Azacitidine in MDS.

Why Use A Nursing Standard

Rationale:

- Fill a *gap* in literature on AE management & patient counselling in azacitidine therapy
- Provide *consensus*-based guidelines that reflect *best practices* of nursing experts

Focus:

- Strategies to assist with the predictable and manageable *adverse drug reactions* associated with azacitidine use in MDS
- Strategies to assist in *counselling patients* with MDS and setting expectations for therapy, in order to achieve the best QOL and patient outcomes

Application: Content Of Standard Part One - Patient Counselling

- Informed consent:

  -Discuss patient understanding of their condition and its management

  -E.g., concept & import of continued treatment; not a cure; why use aza

- Schedule & administration:

  -Help navigate appointments & tests

  -E.g., printed materials (calendar, diary); what to expect at visits (process, time)

- Support:

  -Focus on patient needs to manage after clinic visits

  -E.g., assess living circumstances; identify education / logistical needs

- Follow-up:

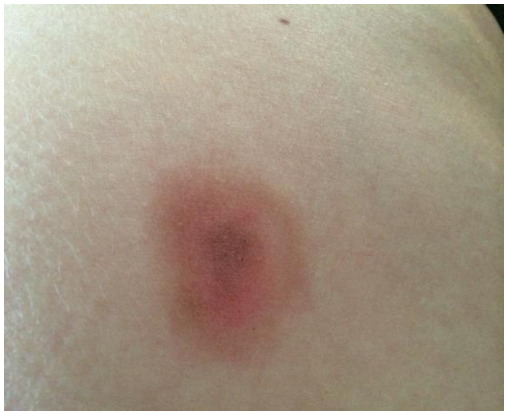
  -Guide patient education on AE to reduce risk

  -E.g., what to watch for, how to manage AE

Application: Content Of Standard Part Two - AE Management

Injection-site reactions (ISR) - *most common AE:

- Erythema 40% patients
- Hematoma / bruising 10% patients
- Pain 20% patients
- Pigment changes



Patient education:

- Set expectations /describe common reactions, tips to minimize reactions; severity; tips to take care of injection site

Application: Content Of Standard Part Two - AE Management

Cytopenias - *blood counts below below the normal range

- Thrombocytopenia 70% patients
- Neutropenia 66% patients
- Anemia 51% patients

Patient education:

- Reassure counts are an expected consequence & may drop at first
- Counsel patients of SS (when to report, how to decrease complications)
- Reinforce value of regular blood work & follow-up
- Neutropenia, thrombocytopenia, anemia precautions

Application: Content Of Standard Part Two - AE Management

Gastrointestinal events – *moderate emetogenic

- Nausea ~50% patients
- Vomiting ~25% patients
- Constipation ~50% patients

Practical tips:

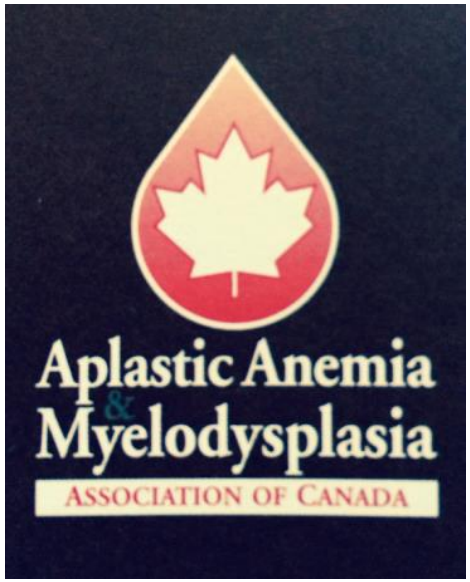
- Premed with anti-emetics
- Be aware anti-emetics may contribute to constipation
- Refer to general guidelines for cancer care (e.g., BCCA, NCCN)


"NO!
Try not!
DO or DO NOT,
There is no try."

AAMAC

http://www.aamac.ca/

- Telephone and e-mail patient-to-patient support
- Educational material on Aplastic Anemia, MDS & PNH
- Quarterly newsletter
- Patient Tracker
- Local support group meetings
- Grants for medical research and education
- Website, Facebook, Marrow forums



Other Resources

- Clinical practice guidelines
- MDS Clear Path
- Blood® Journal (e.g. How I Treat)
- Nursing Standard: "Counselling and adverse event management for patients with myelodysplastic syndromes undergoing azacitidine therapy: A practice standard for Canadian nurses."

Discussion

References

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2) WHO Classification

WHO Classification	% Blasts BM	% Blasts PB
RA/RARS*	< 5	None/rare
Refractory cytopenia with multi-lineage dysplasia (RCMD)/RCMD-RS* (bilineage or trilineage dysplasia)	< 5	None/rare
RAEB-1	< 5	5-9
RAEB-2	5-19	10-19
MDS- unclassified	< 5	None/rare
MDS with isolated del(5q) Female predominance, transfusion-dependant anemia; normal or increased platelet counts with hypolobulated micromegakaryocytes in the hyperplastic marrow; low incidence of transformation into acute leukemia	< 5	< 5

*Ringed sideroblasts ≥15% of nucleated marrow erythroid cells

Suplementry slides

Del(5q) Syndrome

- Hematologic features (10-15% of MDS)
  - Refractory macrocytic anemia
  - Mild leukopenia
  - Mononucleated megakaryocytes, normal to elevated platelets
  - Normal blast count
  - Transfusion dependence

Isolated 5q deletion in MDS carries a relatively favorable prognosis

Low Risk Disease

IPSS: low/intermediate-1

IPSS-R: very low/low/intermediate-1

Treatment Options:

- Supportive Care
- Growth factors
- Immunomodulating agents
- Immunosuppressive therapy
- Hypomethylating agents (consider with Int-1 with cytopenias)
- Clinical Trial

Immunomodulatory Agents

- Lenalidomide
  - Dose: 10 mg/d 21-28 days per month
  - Indicated for patients with a del(5q) abnormality
  - Novel immunomodulatory agent
- Approved for use in patients with lower risk MDS with del(5q) where it is very effective
- Not approved for other lower risk MDS patients where it shows some efficacy, but not as much as with the del(5q) population

Int-2/High Risk Disease

IPSS: intermediate-2/high

IPSS-R: intermediate-2/high/very high

Treatment Options:

- Hypomethylating agents
- Clinical trial
- HSCT