MDS Foundation's Educational Patient-Caregiver Forum

Stanford University Cancer Center
Saturday, October 28, 2017

The MDSs and their Treatments
Peter Greenberg, MD
Molecular Advances in Understanding MDS
Alex Aleshin, MD
Bone Marrow Transplants for MDS Patients
Lori Muffly, MD
Quality-of-Life Session with Open Discussion
Mary L. Thomas, RN, MS, CNS

The MDSs and their Treatments

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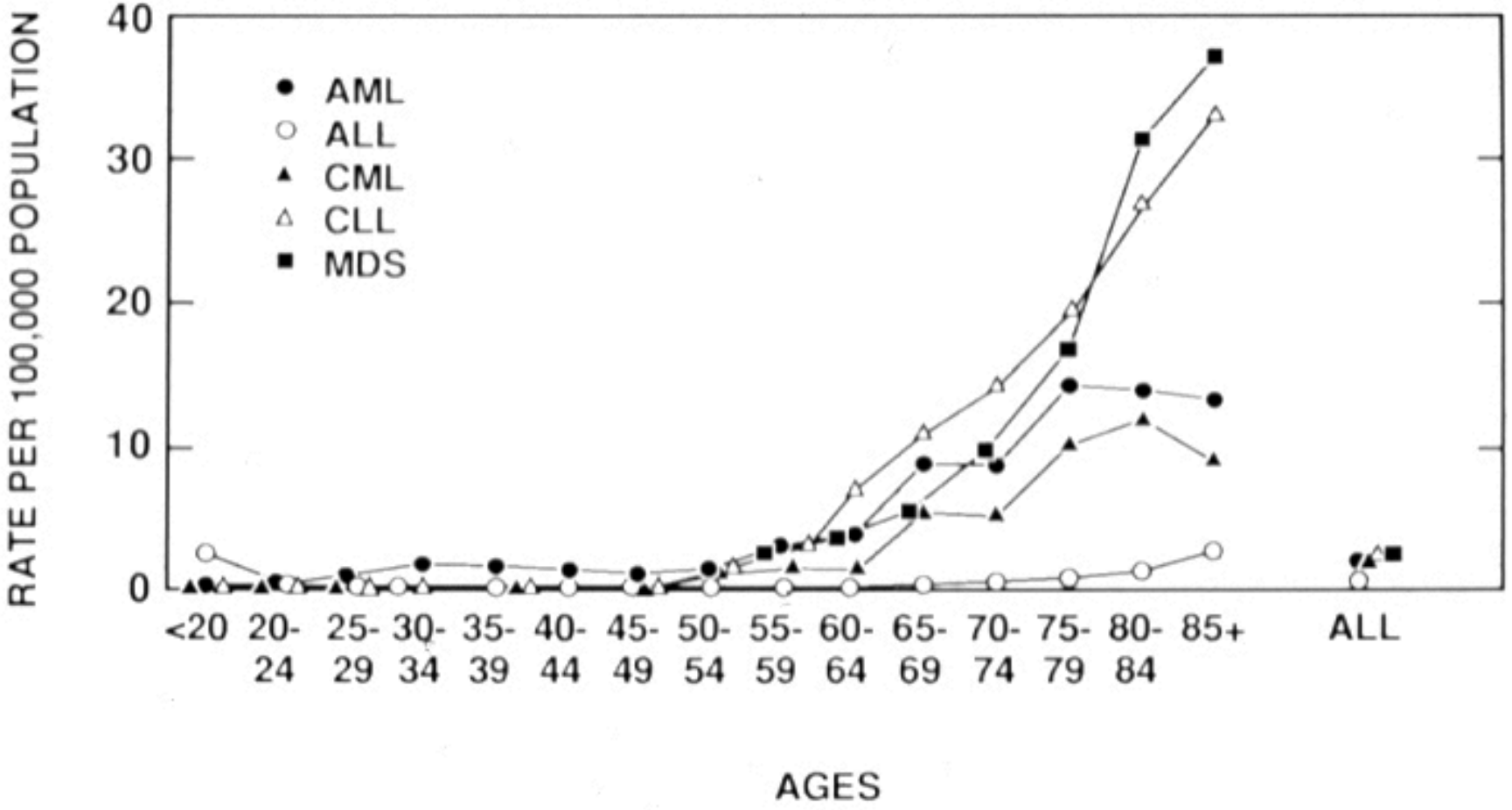
MDS: Questions

- What is MDS?
- What does it mean for my life?
- Is there treatment for it?
- How should I be treated?
- When?
- Why?

Nature of MDS

- Chronic disease
- Heterogeneous disorders
- Symptomatic cytopenia(s)
- Generally elderly patients
- Co-Morbid conditions
- Potential progression to AML
- Multiple potential therapies
- Impact on quality of life

AGE SPECIFIC RATES OF LEUKEMIAS AND MYELODYSPLASTIC SYNDROMES



Prognostic Features in MDS

- Clinical
  - **CBC, marrow blasts, cytogenetics**
  - Age, PS, ferritin, LDH, β2M, marrow fibrosis
  - Treatment/Response
- Molecular
  - Specific mutations
  - Number of mutations

MDS Morphologic Classifications

Marrow Blasts	2008 WHO /NCCN	2016 WHO/NCCN
<5%	RARS	MDS-RSSLD
“	RCUD, MDS-U	MDS-SLD
“	del(5q)	MDS-del(5q)
“	RCMD	MDS-MLD
≥5-9%	RAEB-1	MDS-EB1
≥10-19%	RAEB-2	MDS-EB2
20-30%	AML-MRC/RAEB-T	AML-MRC/RAEB-T
>30%	AML/AML	AML/AML

IWG-PM/IPSS-R Prognostic Classification

11 Countries: 7012 patients

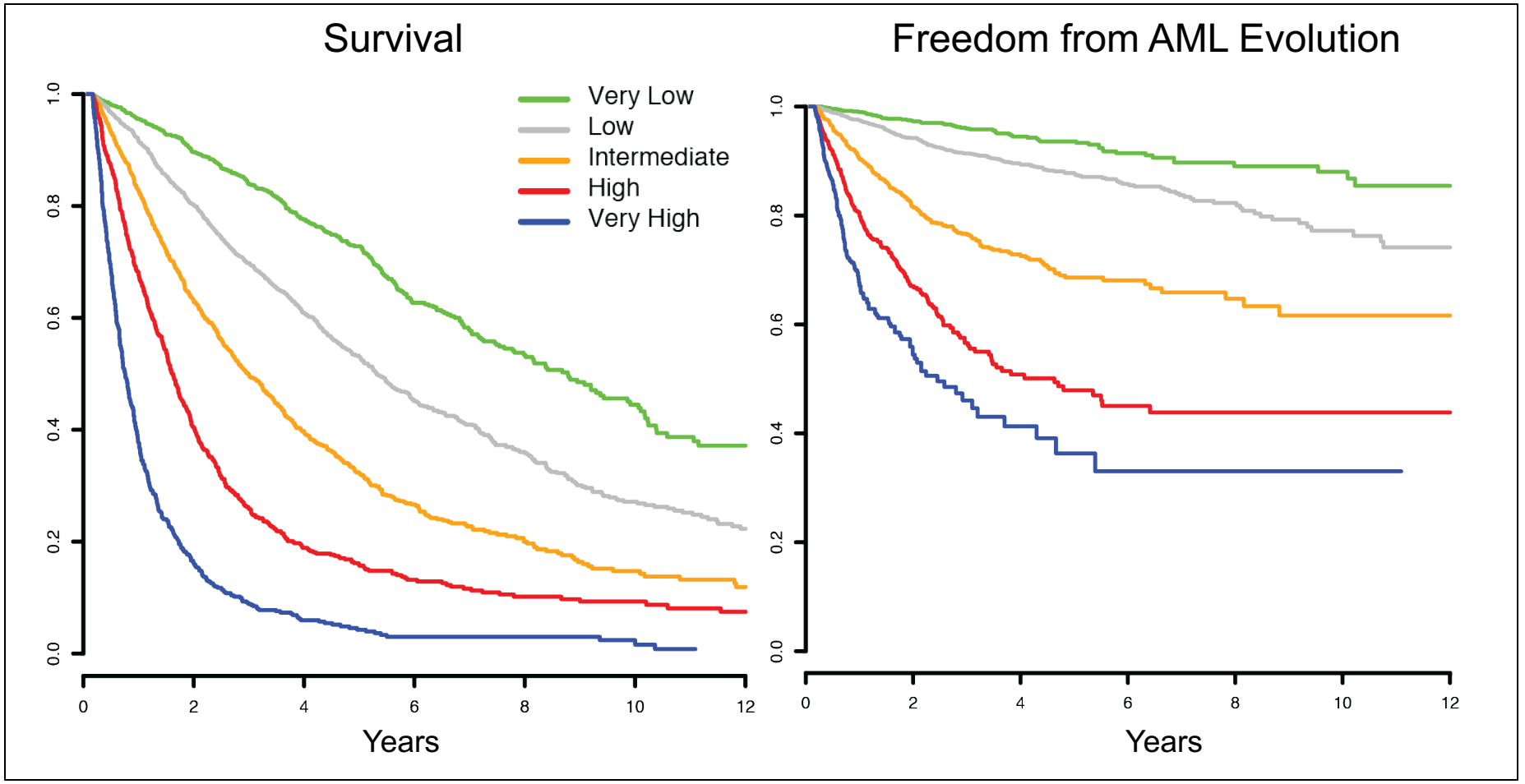
- Austria
- Brazil
- Czech Rep
- France
- Germany
- Italy
- Japan
- Netherlands
- Scotland
- Spain
- USA

IPSS-R: Prognostic Features for Disease Status

Greenberg et al, IWG-PM, Blood 9/12, n=7012

- **Bone marrow blasts: ≤ or >10%**
- **Cytogenetic groups: 5 groups**
- **Depth of abnormal blood counts**
  - hemoglobin, neutrophils, platelets
- **Age**
- Other predictors
  - performance status, serum tests (ferritin, LDH)

IPSS-R prognostic risk-based categories: Survival and risk of AML evolution



Greenberg et al, IWG-PM, Blood 9/2012; www.ipss-r.com

MDS: Incidence of Recurrent Mutations

NCCN Practice Guidelines, Version 1.2018

- >20%: ***ASXL1,*** *TET2, SF3B1**
- 10-20%: ***RUNX1,*** *DNMT3A, SRSF2*
- 5-10%: ***TP53***, ***EZH2***, *U2AF1, NRAS, ZRSR2*
- <5%: ***CBL***, ***ETV6***, *SETBP1, IDH1/2, JAK2,…*

Bold = Poor risk

**= Good risk*

FDA Drug Approvals

- Epo 1993; Darbepoetin 2002
  - for chemotherapy-induced anemias
- GCSF 1996 (‘90 SUH); Peg-GCSF 2002
  - for infection (‘93 w/ Epo SUH)
- Azacytidine 2004
- Lenalidomide 2005 for (del)5q MDS
- Decitabine 2006
  - 2010: 5 day outpatient regimen
- Deferasirox 2005/2015; Deferiprone 2011
  - for iron chelation
- (Romiplostim, Eltrombopag 2017)

APPROACHES FOR TREATMENT OF MDS

- **Clinically Relevant Cytopenia(s)**
- **Age: > <60 years old**
- **Performance Status: Excellent, Good, Poor**
- **Prognostic Risk Category:** IPSS/IPSS-R
  - Lower risk: Hematologic improvement
  - Higher risk: Alter disease natural history
- **Stem Cell Transplant candidate?**
  - Risk category, Age, Performance status, Donor

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www.nccn.org

ESA Responses in MDS

Santini et al, Blood 122: 2286, 2013; n=456, 29% RBC TD

ESA Response Score:

Serum epo	>200	1
Serum ferritin	>350	1
IPSS-R:	Very Low	0
	Low	1
	Int	2
	High	3

Score	0	1	2	3	4
Response	**85%**	**80%**	**64%**	**40%**	**20%**
IPSS-R	Very Low	Low	Intermediate	High	
Response	**85%**	**68%**	**48%**	**31%**	

MDS:Molecular Subgroup Treatments

Subgroup	Features	Treatment
SF3B1	**Good risk, ring sideroblasts**	**Luspatercept***
Other splice genes	**Categorizes MDS ontogeny**	**Splice gene modulators*** **(H3B-8800)**
TP53	**Poor risk**	**+/- Decitabine** **HDACis*** **p53 modulator PRIMA1/APR-246***
IDH2	**Distinct mutant subgroup, T-LGL association**	**Enasidenib**
Del(5q)	**Mainly good risk**	**Lenalidomide**

*Clinical trials

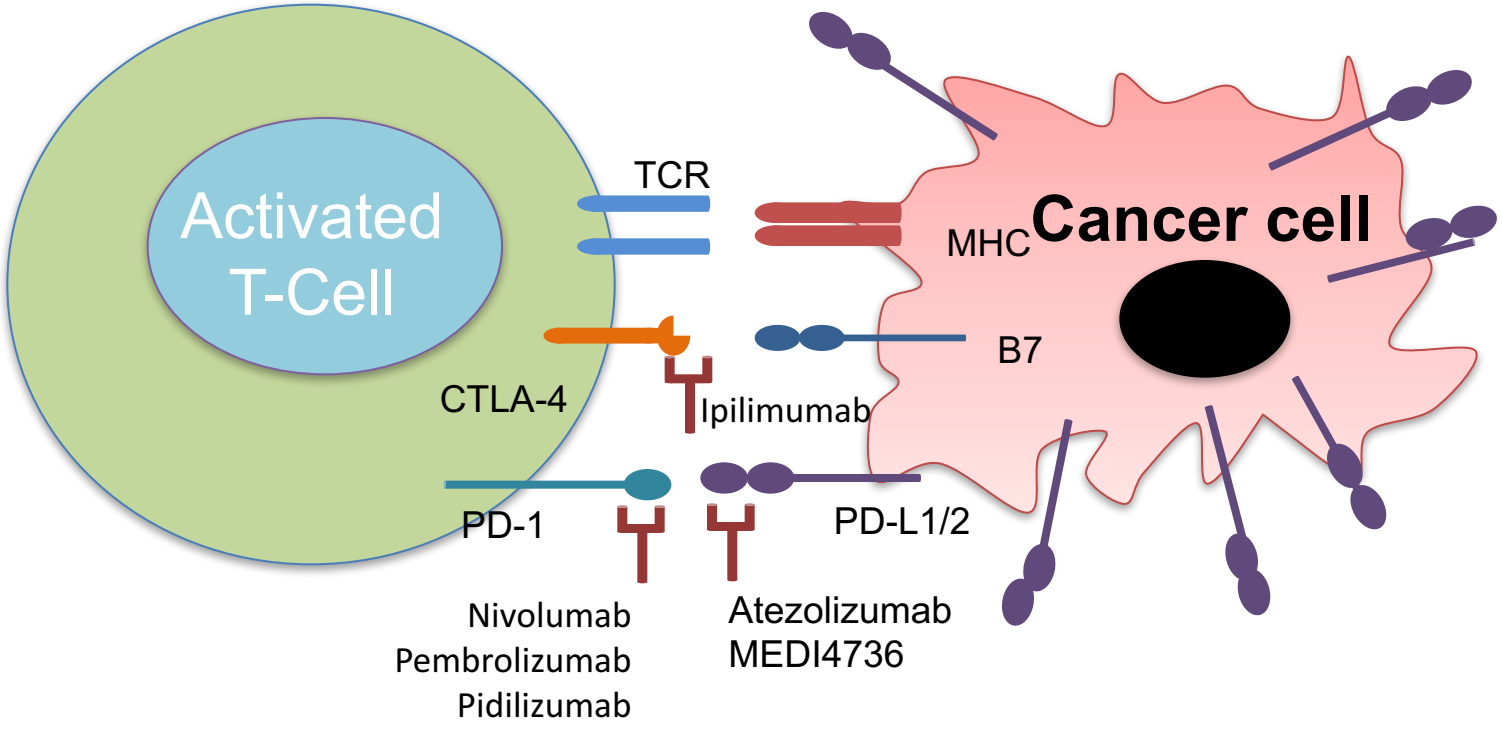
Potential Indications for Iron Chelation

- **RBC transfusions: ≥20-40**
- **Symptomatic anemia/Further RBC txn need**
  -- mainly Low, Intermediate-1 IPSS or BMT candidate
- **Evidence of organ dysfunction**
  -- cardiac, hepatic, endocrine
- **Serum ferritin >2500**→1000; ↑ Liver iron content
- **Rx**: Deferasirox orally or Deferrioxamine SQ

Future MDS Molecular Classifications

- **Diagnostic**/Additive to Clinical Features
  - Specificity vs Non-clonal cytopenias ('mimics')/Biomarkers
  - Polymorphisms α disease susceptibility
- **Prognostic**/Additive to Clinical Features
  - Specific mutations & number of abnormalities
  - Predictive of treatment response
  - IWG-PM/Molecular global project
- **Pathogenetic**
  - Driver vs passenger mutations
  - Gene expression, signaling pathways, epigenetic Δ
- **Therapeutic**
  - Identify & target biospecific driver lesions EARLY

Immune Checkpoint Inhibitors' Sites of Action



Rivera et al, Leuk Lymph 57:995, 2016

Frequency of Splicing Gene Mutations in Myeloid Malignancies

- **MDS:** ***20-30%*** *SF3B1, SRSF2, U2AF1, ZRSR2*
- **MDS with ring sideroblasts:** ***70-90%*** *SF3B1*
- **AML:** ***40-60%*** *SF3B1, SRSF2, U2AF1, ZRSR2*
- **CMML:** ***50%*** *SRSF2*

Stanford MDS Center: Biologically Focused Clinical Trials

- **Lower risk**:
  IPSS-R
  VL, Low, Int

- **Higher risk**:
  IPSS-R
  High, Very High

***Central personnel**:*
Savita Kamble
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- **Deferasirox** vs Placebo*
- **Luspatercept** (*TGFβ inhibitor*)*
- **Splice gene modulator** (*H*3)

- **AzaC & PD-L1 inhibitor** (*atezolizumab*)
- **Splice gene modulator** (*H3*)

*Completed 10/17

MDS Information Resources

- MDS Foundation
- Aplastic Anemia and MDS Foundation
- Leukemia and Lymphoma Society
- National Comprehensive Cancer Network (NCCN)
- Stanford MDS Center

MDS: Directions

- **Clinical**
  - **Re-structure classification & treatment**
    - IWG-PM Molecular mutational characterization
    - Biospecifically targeted treatment approaches
    - Timing/type of Stem Cell Transplantation
    - Include QOL in treatment evaluations
- **Biologic**: Abnormal stem cells/mutations
- **Economic**
  - Broad-based forums to evaluate cost effectiveness & potentially decrease costs