





**Myelodysplastic Syndromes (MDS) Part 1:
Diagnosis, Prognosis,
Classification, Lower-Risk Treatments**

 **Aplastic Anemia & MDS International Foundation, Inc.**
Fighting Bone Marrow Failure Diseases Through Patient Support & Research Since 1983

National Patient and Family Meeting, Indianapolis, July 2009


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MDS Definition



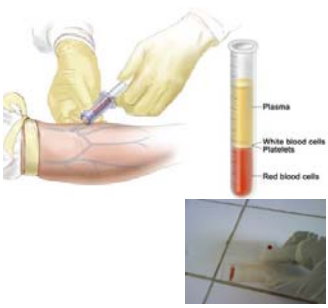
- A diverse group of bone marrow failure conditions characterized by 3 key features:
 - Inadequate production of healthy blood cells
 - “Ineffective hematopoiesis”
 - A tendency to progress to acute leukemia (which is defined by $\geq 20\%$ bone marrow blasts)
 - Abnormal appearing cells under the light microscope... and, in about half of cases, abnormal chromosomes

How Are Patients With MDS Discovered?



- “Incidental finding”
 - Blood count done during evaluation of another condition (not clear early diagnosis helps!)
- Symptoms
 - *Fatigue*
 - Anemia: shortness of breath, palpitations, pallor, chest pain, leg swelling etc.
 - Neutropenia: infection, mouth sores
 - Thrombocytopenia: easy bruising, bleeding, skin spots (“petechiae”)

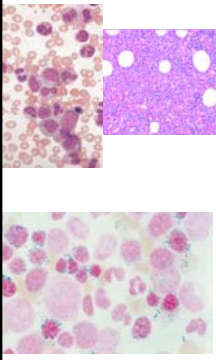
Key Peripheral Blood Findings



- **At diagnosis in MDS:**
 - Anemia
Hb <12 g/dL: >90%
Hb <10 g/dL: 54%
 - Neutropenia
ANC <1800 x 10⁹/L: 46%
 - Thrombocytopenia
Platelets <100 x 10⁹/L : 37%

Also: abnormal appearance of red cells, neutrophils, platelets
Implies *functional defects*

Typical MDS Bone Marrow Findings



- Marrow is normocellular or hypercellular (i.e., increased proportion of cells relative to fat)
- About 10% are hypocellular (low cellularity) and can be tough to distinguish from AA
- Cells look abnormal under the microscope ("dysplasia")
 - Wrong number of nuclei
 - Abnormal maturation
 - Missing essential granules
 - May involve red cells, white cells, megakaryocytes (make platelets), or some combination thereof
- Blasts may be increased
- Ring sideroblasts might be present (indicate abnormal iron metabolism)

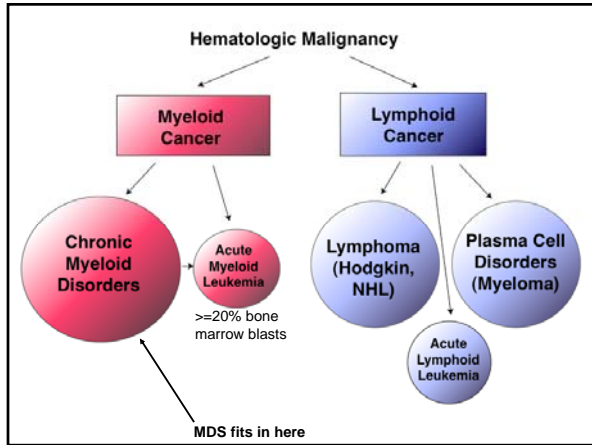
Newest Cytogenetic Prognostic Data in MDS

| Risk Group | Karyotypes (22 groups) | Median survival, months | Time until 25% of patients developed AML, months |
|-----------------------|---|-------------------------|--|
| Favorable | 5q-, 12p-, 20q-, +21, -Y, 11q-, t(11(q23)), normal, any 2 abnormalities including 5q- | 51 | 71.9 |
| Intermediate-1 | +1q, 3q21/q26 abnormalities, +8, t(7q), +19, -21, any other single abnormality, any double abnormality not including abnormalities of chromosomes 5q or 7 | 29 | 16 |
| Intermediate-2 | -X, -7 or 7q-, any double abnormality with -7 or 7q-, complex with 3 abnormalities | 15.6 | 6 |
| Unfavorable | Complex with >3 abnormalities | 5.9 | 2.8 |

Haase D et al, MDS Foundation Symposium, Patras, Greece 2009

MDS "Mimics"

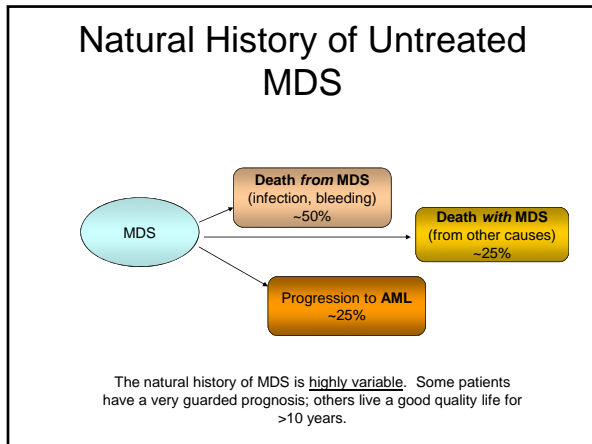
- Vitamin deficiencies, esp. B12 and folate
- Mineral deficiencies, esp. copper
- Congenital/inborn disorders, e.g. Fanconi anemia
- Infections, e.g. HIV
- Medications, esp. methotrexate, azathioprine, chemotherapeutics
- Hemolytic anemias
- Autoimmune conditions (immune thrombocytopenia, Felty syndrome etc)
- Alcohol abuse
- Other marrow disorders...
 - Aplastic anemia, leukemia, myeloproliferative, large granular lymphocyte disorders



World Health Organization MDS Categories (2008)

| Name | Abbrev. | Key Feature | Proportion of patients (%) |
|--|---------|--|----------------------------|
| Refractory cytopenia with unilineage dysplasia | RA | Anemia and erythroid dysplasia | 10 |
| | RN | Neutropenia and granulocytic dysplasia | <1% |
| | RT | Thrombocytopenia and megak. dysplasia | <1% |
| Refractory anemia with ring sideroblasts | RARS | >=15% ring sideroblasts | 5 |
| 5q- syndrome | Del(5q) | Isolated 5q31 deletion, anemia, hypolobated megakaryocytes | 5 |
| Refractory cytopenia with multilineage dysplasia | RCMD | Multilineage dysplasia with >1 cytopenia With or without ring sideroblasts | 20 |
| Refractory anemia with excess blasts, type 1 | RAEB-1 | 5-9% blasts | 20 |
| Refractory anemia with excess blasts, type 2 | RAEB-2 | 10-19% blasts; ±Auer rods | 20 |
| Unclassifiable | MDS-U | Does not fit other categories | 10 |
| Childhood MDS | RCC | Often hypocellular; pancytopenia | Rare |

WHO Tumour Classification 4th edition, IARC 2008.



International Prognostic Scoring System (IPSS) - 1997

| Prognostic Variable | Score | | | | |
|---------------------|--------|--------------|------|--------|-----------|
| | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| Marrow blasts (%) | <5% | 5-10% | -- | 11-20% | 21-30%*** |
| Karyotype class* | Good | Intermediate | Poor | -- | -- |
| # of cytopenias** | 0 or 1 | 2 or 3 | -- | -- | -- |

* **Karyotypes:** Good = normal, -Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes
 ** **Cytopenias:** Hb < 10 g/dL, ANC <1800/uL, platelets <100,000/uL
 *** 20% or more blasts now considered **AML**, but was still MDS at the time this system was developed
 From Greenberg P et al *Blood* 1997; 89:2079-2089 (correction 1998; 91:1100)

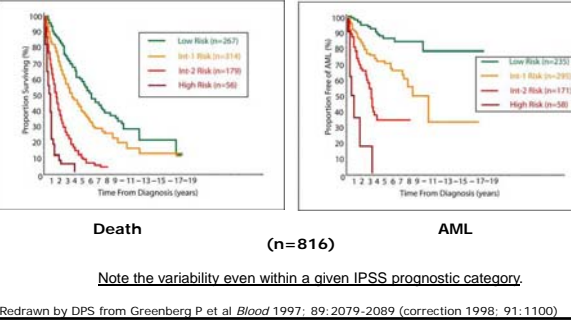
IPSS Risk Categories: Patient Distribution And Outcomes

| Score sum | IPSS Risk Category | Median survival (years) | Time until 25% get AML (years) |
|-----------|--------------------|-------------------------|--------------------------------|
| 0 | Low | 5.7 | 9.4 |
| 0.5-1.0 | Int-1 | 3.5 | 3.3 |
| 1.5-2.0 | Int-2 | 1.2 | 1.1 |
| >=2.5 | High | 0.4 | 0.2 |

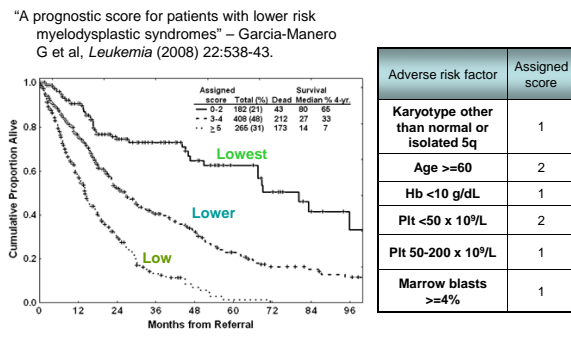
Patient Distribution

From Greenberg P et al *Blood* 1997; 89:2079-2089 (correction 1998; 91:1100)

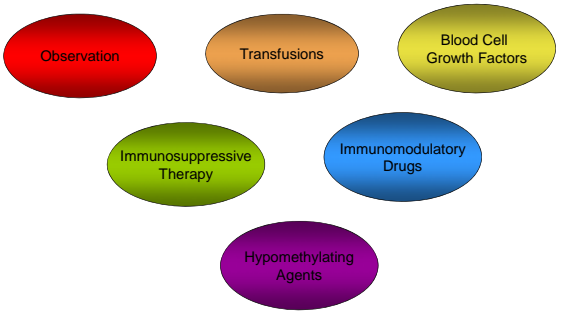
IPSS Predicts Overall Survival and AML Evolution In *De Novo* MDS



What Constitutes “Low-Risk MDS”?



A “Rainbow” Of Treatment Options For Lower-Risk Patients With MDS



Observation

No clear benefit from early treatment of MDS, unlike "solid tumors"

"Watchful waiting" appropriate for mild blood count abnormalities

Transfusions

RBC transfusion

*Generally used if Hb <8 g/dL, but regional variation in practice
Some people need Hb kept higher to avoid symptoms
Each unit of RBCs has 200-250 mg elemental iron*

Platelet transfusion

*Generally used if platelet count below $10 \times 10^9/L$, or for bleeding or need for a procedure
"Alloimmunization" is a risk – patients stop responding to transfusions*

Blood Cell Growth Factors

Red cell growth factors
*Medicare only pays for these if Hb <10 g/dL
Safety concerns in solid tumors, not (yet) in MDS*

- Epoetin alfa (Procrit™)
- Darbepoetin alfa (Aranesp™)


White cell growth factors
*No survival benefit but may help decrease infx.
Sometimes combined with red cell factors*

- Filgrastim, G-CSF (Neupogen™)
- Pegfilgrastim (Neulasta™)


Platelet growth factors
*Brand new; risks unknown in MDS
Reports of increased blasts in a few patients
Only approved for immune thrombocytopenia*

- Romiplostim (NPLate™)
- Eltrombopag (Promacta™)

Immunosuppressive Therapy



Anti-Thymocyte Globulin, ATG (ATGam™)



Cyclosporine, CSA (ATGam™)


*Made from horse, rabbit, goat
Serum sickness is main issue
Patient selection?*

*Widely used to prevent graft
rejection in transplant
patients*

Treatment Options For Lower-Risk Patients


Immunomodulatory Drugs

Lenalidomide (Revlimid™)




*Works best in patients with del5q (2/3 respond)
Can cause neutropenia, thrombocytopenia
Effect lasts an average of about 2-3 years
Cost issues*

*Used mostly for higher-risk patients, but some physicians use in lower-risk setting, especially if patient is transfusion-requiring
Optimal dose/schedule not defined
Can cause low blood counts
Interest in combining these with other drugs
Azacitidine shown to improve survival in higher-risk patients*

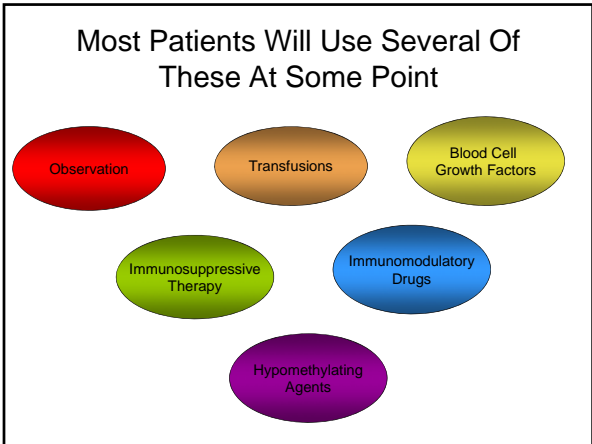


Azacitidine (Vidaza™)




Decitabine (Dacogen™)

Hypomethylating Agents

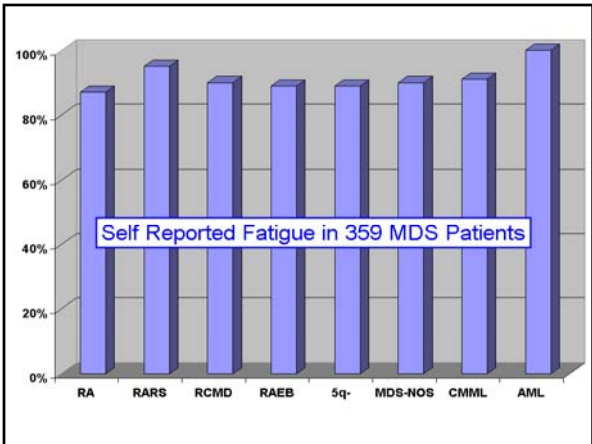


What Do We Mean by "Quality of Life" (QOL)?



- While QOL is to large extent in the eye of the beholder, it is generally considered to have several domains:

| | |
|---------------------------------------|---------------|
| Presence and Severity of Symptoms | Physical |
| Ability to Function | Social |
| Quality of Interpersonal Interactions | Psychological |
| Sense of Well-Being | Emotional |
| Transcendence | Intellectual |
| | Spiritual |



Internet Based Quality of Life Study in 359 MDS Patients

Results

- Most MDS patients have a reduced QOL and a significant symptom burden
- >90% of survey respondents complained of "excessive" fatigue
- QOL worse than published controls for both validated instruments (P<0.0001)

•Does Fatigue Correlate With Anemia?

- Fatigue levels were independent of:
 - Hemoglobin levels
 - Transfusion Dependence
 - Not explained by co-morbidities

QOL Research

- Most treatment trials in MDS focus on the "objective" measures of disease activity, and not QOL.
 - If the disease improves, QOL is assumed to follow
 - This may or may not be true!

Questions