

# Myelodysplastic Syndromes

- I. The term "dysmyelopoietic or myelodysplastic syndrome" refers to a qualitative and quantitative abnormality of hematopoietic cells, sometimes progressing to acute leukemia. Specifically excluded are dysmyelopoietic states with a well-understood, reversible basis such as B12 or folate deficiency.
- II. FAB classification - an attempt to systematize the recognition of preleukemic subtypes
  - A. History
    1. Before FAB, the term "preleukemia" was used to refer to a myeloproliferative disorder which preceded the development of acute leukemia. The definition excluded certain groups at high risk, such as Down's syndrome, irradiated patients, polycythemia vera, myelofibrosis, CML, etc.
    2. Since acute leukemia was not an inevitable development in those diagnosed with preleukemia, and since the term encompassed a wide clinical variation, it was necessary to refine our understanding of these diseases. Thus, the FAB classification.
  - B. FAB distinguishes two groups on the basis of marrow cellularity
    1. Normal to increased cellularity
      - a) Acquired idiopathic sideroblastic anemia
      - b) Refractory anemia with excess blasts
      - c) Refractory anemia with excess blasts in transition
      - d) Refractory anemia fitting no other classification
      - e) Chronic myelomonocytic leukemia
    2. Decreased marrow cellularity at some point in the course
      - a) Aplastic anemia
      - b) PNH
      - c) "Marrow failure with cellular marrow"
  - C. Common features of Group 1 patients
    1. Erythroid series
      - a) Ineffective erythropoiesis
      - b) Megaloblastosis, nuclear budding, karyorhexis, vacuolization, cytoplasmic and nuclear bridging
      - c) Ringed sideroblasts
      - d) Dimorphism
      - e) Modified surface antigens
        - (1) Lysis by anti-I
        - (2) Positive Ham's test
      - f) Decreased pyruvate kinase activity, among others
      - g) Increased content of hemoglobin F
    2. Granulocyte series
      - a) Poor or abnormal granulation
      - b) Decreased LAP score and peroxidase
      - c) Pseudo-Pelger-Huet anomaly, which most likely represents apoptotic neutrophils (Shetty)
      - d) Excess myeloblasts
      - e) Defective bactericidal activity

### 3. Platelets

- a) Anisocytosis with presence of giant and bizarre platelets
- b) Defective granules
- c) Abnormal microtubules, abnormal canalicular system
- d) Defective function - decreased aggregation, long bleeding time
- e) Presence of micromegakaryocytes

### D. Pathophysiology of MDS

1. MDS is a defect at the level of the hematopoietic stem cell. The abnormal clone has a competitive growth advantage, and over time occupies a significant fraction of active stem cell compartment. (90% of stem cells are quiescent and 10% are cycling at any given time).
2. Evidence favoring the role of cytokines in MDS
  - a) It is known that 15% - 20% of MDS patients give a history of infertility. This implies the existence of a longstanding abnormality affecting rapidly-dividing cells. Suppressive cytokines could produce this effect.
  - b) The active fraction of marrow cells is increased in MDS, leading to hypercellularity. Up to 90% of these cells are undergoing apoptosis at the same time. The property of simultaneous proliferation and apoptosis is termed Aantonomy.@
  - c) Stromal cells in MDS marrows are also apoptotic, implying that the cause is in the local environment, and not genetic. Cytokines would produce such an effect.
    - (1) Cytokines which cause apoptosis act by inducing a family of cysteine proteases (Acaspases@). These attack aspartate sites on proteins, cleaving and inactivating DNA-repairing enzymes.
  - d) TNF- $\alpha$  is present in increased amounts in the marrows of 3/4 of MDS patients. IL1- $\beta$  is another possible candidate cytokine.
    - (1) TNF- $\alpha$  has different effects on hematopoietic cells of differing maturity.
      - (a) Immature, CD34<sup>+</sup> cells are induced to proliferate
      - (b) Mature, CD34<sup>-</sup> cells undergo apoptosis
      - (c) This would explain the paradox of increased marrow cellularity and proliferative rate with simultaneous pancytopenia and apotosis.
  - e) Increased angiogenesis as a consequence of increased cytokine production is also found (Aguayo).

### E. Acquired idiopathic sideroblastic anemia

1. Most patients over age 50
2. No sex preponderance
3. Anemia, normochromic-normocytic
4. Very low retic count
5. Platelets and WBC usually normal

6. Marrow
    - a) Erythroid hyperplasia
    - b) Ringed sideroblasts are dominant feature (>15% of erythroblasts)
    - c) Decreased colony forming capacity
    - d) About 20% have karyotypic abnormalities
  7. Incidence of acute leukemia is 5% - 10%
  8. Poor response to therapy with pyridoxine
  9. Median survival 40-50 months
  10. Cazzola, et al reviewed 37 patients with diagnosis of AISA
    - a) 5 actually had RAEB
    - b) Median age 64
    - c) All were anemic, with mean hemoglobin 7.5 and MCV 103
    - d) Hypochromic RBCs seen in half of cases
    - e) Ringed sideroblasts averaged 63% of marrow erythroblasts
    - f) Abnormal chromosomes in 5/23. Sandberg reports a 12% incidence of chromosomal abnormalities.
    - g) Patients who would require transfusion could be predicted by
      - (1) Lower Hgb (6.9 vs 9.0)
      - (2) Lower neutrophil count (2.4 vs 3.3)
      - (3) Lower erythroid activity as measured by Fe turnover
      - (4) These patients also had increased risk of marrow failure or leukemic progression, and decreased survival.
    - h) Overall median survival was 72 months
- F. Refractory anemia with excess blasts
1. Relatively common, occurring in patients over 50 without sex preponderance
  2. Insidious onset of anemia, normochromic-normocytic to macrocytic
  3. Leukopenia and thrombocytopenia are common
  4. Bone marrow
    - a) Blasts are 5-20% in marrow and <5% in periphery
    - b) Auer rods absent
    - c) Colony forming units decreased
    - d) Dyserythropoiesis
    - e) Abnormal megakaryocytes
    - f) About 50% have chromosomal changes
  5. May remain clinically stable for months to years
  6. Chromosomal abnormalities in about 60%
  7. Acute leukemia develops in about 25%
  8. Median survival about 12 months
- G. Refractory anemia with excess blasts in transition
1. Features intermediate between RAEB and acute leukemia
  2. Marrow blasts 20-30%
  3. Chromosomal abnormalities in over 90%
  4. Two subgroups

- a) Young patients who look like they have acute nonlymphoblastic leukemia
    - (1) Organomegally
    - (2) Fairly low blast percentage
    - (3) Many Auer rods
    - (4) Respond to acute leukemia therapy
  - b) Older patients who look like they have RAEB
    - (1) No organomegally
    - (2) Poor response to antileukemic therapy
5. Approximately 60% transform to full-blown AML
  6. Median survival about 6 months
- H. Refractory anemia or cytopenia not included in the above
1. Bone marrow hypercellular or normocellular
  2. Dyserythropoiesis present
  3. Ringed sideroblasts <15%
  4. Blasts <5%
  5. Normal and abnormal megakaryocytes may be seen
  6. Abnormal karyotype in up to 50%
  7. Increased retic count reported (de Pree). I have observed this in patients with RAEB.
    - a) RBC survival is normal
    - b) This Apseudoreticulocytosis@ due to maturation delay in the erythroid series. RNA metabolism could be abnormal, or ribonuclease activity could be defective.
  8. Prognosis is somewhat better than that of RAEB, and certainly superior to that in RAEB-T, with median survival 35-50 months, and a 10% chance of developing AML.
- I. Chronic myelomonocytic leukemia (aka chronic myelomonocytic syndrome and subacute myelomonocytic leukemia)
1. No longer claimed by FAB group, which calls this a myeloproliferative disease rather than a dysmyelopoietic state
  2. Most patients over age 50
  3. Spleen sometimes palpable
  4. Gum infiltration absent
  5. Anemia and thrombocytopenia similar to RAEB
  6. Total WBC may be high, low, or normal, but monocyte count is >1000
  7. Monocytes may be cytologically bizarre
  8. Increased blasts in bone marrow
  9. Increased serum lysozyme levels
  10. Colony forming capacity is increased, and leukocytes of these patients have colony stimulating activity (unlike RAEB)
  11. Incidence of chromosomal abnormalities is 20% - 50%
  12. Chronic course with acute leukemia developing in 25% - 50% over 2-4 years

## J. Therapy

1. Has been disappointing
2. Since aggressive therapy is very toxic to these generally elderly patients and many may not progress to life threatening disease, it would be helpful to pick out a subgroup with poor prognosis and treat them.
3. Supportive therapy with transfusion as needed
4. Recombinant growth factors
  - a) GM-CSF
    - (1) Increases WBC in ~80% of cases
    - (2) Increases other cell lines to a lesser extent
    - (3) Risk of enhanced leukemia growth, especially in CMML and in those who already have marrow blast counts >14%
    - (4) Dose and mode of administration probably influence the results, but optimal regimen as yet unknown
  - b) G-CSF can increase the neutrophil count, with minimal effects on other cell lines. Maintenance therapy for up to 16 months has been shown to remain effective, although counts return to baseline within 2-4 weeks of discontinuing treatment.
    - (1) Thrombocytopenia develops in up to 30%
  - c) IL-3 also appears able to increase leukocyte counts in most or all patients. Less common are increases in platelet count, hemoglobin, or stimulation of disease progression.
  - d) Erythropoietin
    - (1) Least effective in those with sideroblastic anemia and those who have RBC transfusion requirement.
      - (a) There is a single case report (Bunworasate) of EPO causing transformation of sideroblastic anemia to acute monoblastic leukemia. The leukemia remitted with withdrawal of EPO therapy.
    - (2) Outside those groups, expect about a 50% response rate
    - (3) Patients with low endogenous EPO levels will respond better.
  - e) Combined G-CSF and EPO
    - (1) Rationale is *in vitro* synergy of G-CSF and EPO when applied to erythropoiesis
    - (2) Combination therapy (G-CSF + EPO) (Hellstrom-Lindberg, Negrin)
      - (a) Approximately 40% of patients achieve useful increase in hemoglobin, and a few become transfusion-independent
      - (b) Response is more likely in those with low EPO levels, but correlates weakly if at all with cytologic type of MDS.
      - (c) The combination has synergism over either agent used

- alone
- (3) Similar results found with GM-CSF and erythropoietin combination (Thompson).
- f) Sequential IL-3 then GM-CSF tried in 9 patients (Nand), but resulted in unacceptable toxicity.
- g) Interferon- $\alpha$  is preferentially cytotoxic against leukemia cell lines. Hematologic improvement has been noted in 30-50% of a small number of treated patients. Suppression of normal myelopoiesis is a problem, however.
5. "Differentiating agents"
- a) Low dose ARA-C, 20 mg/M<sup>2</sup> iv or sq for 14-21 days works best in the more overtly leukemic patients
- b) Retinoic acids
- (1) 13-cis-retinoic acid at 100 mg/M<sup>2</sup> per day may improve cytopenias after several weeks of therapy, but is fairly toxic. One 68-patient study (Koeffler) showed no benefit of treatment.
- (2) All-trans retinoic acid produces modest, transient responses, at best.
- c) Vitamin D<sub>3</sub> has activity in vitro, but shows no clinical benefit when given to patients at tolerable doses.
6. Low-dose etoposide appears promising
- a) Sustained clinical benefit in 7/10 patients with CMMoL, maintained on 50-100 mg po twice weekly or so (Oscier)
- b) 50 mg iv, 2 to 7 times/week, effectively palliated 4/10 patients with RAEB-t or secondary acute leukemia, yielding 1 complete remission and decreased transfusion requirement in the others (Ogata).
7. Danazol may be effective, especially in sensitized thrombocytopenic patients
8. Generally no response to B12, folate, iron, androgens, pyridoxine
9. Rare response to corticosteroids
10. Bone marrow transplantation
- a) Allogeneic transplantation is useful in younger patients with primary preleukemia and without increased blasts or significant marrow fibrosis. The 4-year survival rate post-transplant is about 40%, and the relapse rate over the same period is 45%. The mortality of the procedure is 25-45%.
- (1) Karyotype affects the prognosis for this procedure. Patients with an abnormality of chromosome 7 and/or complex abnormalities are 3x more likely to fail (Nevill)
- b) Allogeneic and syngeneic transplantation was studied in older (55 - 66) patients (Deeg).
- (1) Three-year survival ranged from 33% for RAEB-T to 46% for RAEB, to 59% for RA.

- (2) Patients who were in better prognostic subgroups tended to be the survivors.
  - c) Autologous stem cell transplantation in young patients (median age 47) yields a 4-year disease free survival rate of 27% (de Witte).
11. Anticytokine therapy is an exciting new development
- a) The theory behind this therapy is that TNF- $\alpha$  acts as a growth factor for CD34+ progenitor cells belonging to the dysplastic clone, helping them to proliferate and take over the marrow. As they mature into CD34- myeloid precursors, TNF- $\alpha$  induces them to undergo apoptosis, producing marrow hypocellularity and cytopenia.
  - b) The combination of pentoxifylline, ciprofloxacin, and dexamethasone has anti cytokine activity.
    - (1) Pentoxifylline interrupts the production of intracellular diacylglycerol, a 2nd messenger produced in response to cytokine binding to cells
    - (2) Ciprofloxacin decreases the metabolic clearance of pentoxifylline
    - (3) Dexamethasone inhibits the translation of cytokine mRNA into protein
    - (4) 42% of MDS patients respond to this treatment, although it may take several months. Hematologic and/or cytogenetic improvement occur.
    - (5) There are no complete responses, because the underlying stem cell defect is not addressed. One area for study is the possibility of aggressive induction therapy following PCD treatment.
  - c) Other effective drugs
    - (1) Lysophylline is the active metabolite of pentoxifylline. It is much more effective, but must be given parenterally
    - (2) Amifostine (ethiol) is a chemoprotectant drug
      - (a) Dephosphorylated into its active form by alkaline phosphatase in normal cells. Many tumor cells lack this ability
      - (b) The active form contains a thiol group which binds platinum and scavenges free radicals. It also decreases apoptosis and stimulates normal hematopoietic cells.
      - (c) As a single agent, stimulates hematopoiesis in roughly 2 of patients with MDS (List).
      - (d) Up to 75% of patients respond when treated with PCD + amifostine (Raza)
    - (3) Thalidomide has anticytokine and antiangiogenic effects
      - (a) Sixteen of 83 (19%) MDS patients treated with thalidomide showed hematologic improvement (Raza)
      - (b) Ten became transfusion-independent

- (c) Lower blast counts and shorter duration of disease were markers for response to treatment.
- (4) One woman with rheumatoid arthritis had remission of her refractory anemia when treated with etanercept, an inhibitor of TNF- $\alpha$  (Birnbaum)
- 12. Topotecan produced a complete remission in 25% to 30% of patients with MDS or CMML in a preliminary study (Beran).
- 13. The National Comprehensive Cancer Network has published guidelines for the management of MDS (See figures below).
- K. Prognosis - several studies have employed multivariate analysis to distinguish prognostic subgroups of MDS (Mufti, Sanz)
  - 1. The International Prognostic Scoring System (IPSS) was devised using results from 816 previously-studied patients (Greenberg)
    - a) The bone marrow blast percentage, karyotype, and presence of cytopenias were highly predictive of survival in a multivariate analysis.
      - (1) Blast percentage
        - (a) Score 0 for < 5% blasts
        - (b) Score 0.5 for 5 - 10%
        - (c) Score 1.5 for 11 - 20%
        - (d) Score 2.0 for 21 - 30%
      - (2) Karyotype
        - (a) Score 0 for A good prognosis@ group (normal karyotype, -Y, del(5q), or del(20q))
        - (b) Score 1.0 for A poor prognosis@ group (three or more abnormalities or chromosome 7 abnormalities)
        - (c) Score 0.5 for A intermediate prognosis@ group (other chromosomal abnormalities)
      - (3) Define cytopenias as hemoglobin < 10g/dL, neutrophil count < 1000/ $\mu$ L, and platelet count < 100,000/ $\mu$ L
        - (a) Score 0 for 0 or 1 cytopenia
        - (b) Score 0.5 for 2 or 3 cytopenias
    - b) Four risk groups can then be distinguished, based on total point score
      - (1) Low: total score = 0
      - (2) Intermediate-1: total score 0.5 to 1.0
      - (3) Intermediate-2: total score 1.5 - 2.0
      - (4) Poor: total score 2.5 or above

## c) Prognosis by risk category

Risk Category	Median Survival (yr)	AML Evolution (yr)*
Good	5.7	9.4
Intermediate-1	3.5	3.3
Intermediate-2	1.2	1.1
Poor	0.4	0.2

\* time until 25% of patients in the risk group develop AML

- d) FAB subclass and advanced age also influence prognosis.
- 2. Histology as a prognostic factor (Mangi)
  - a) Used immunohistochemical techniques, staining for chloroacetate esterase, CD15, CD68, HLA-DR, CD3, and lectin
  - b) Noted abnormally localized immature precursors (ALIP) in intertrabecular region of marrow
  - c) Distinguished 4 groups
    - (1) Group 1 with erythroid hyperplasia and no ALIP
    - (2) Group 2 with myeloid hyperplasia and (myeloid) ALIP
    - (3) Group 3 with marrow hypoplasia
    - (4) Group 4 with significant fibrosis
  - d) Group 2 patients had a significantly worse prognosis and were much more likely to transform to acute leukemia.
- 3. The presence of N-ras mutations, as detected by pcr, is associated with shortened survival and increased risk of leukemic transformation. It occurs in 9% - 10% of cases, and does not appear to correlate with cytologic subtype (Paquette).

## III. WHO Classification (1999)

- A. Excluded RAEB-T because it is too similar to acute leukemia, and CMML because it is too similar to myeloproliferative syndromes
- B. Refractory anemia (RA) similar to FAB definition, except that dysplastic features must be restricted to the erythroid line
- C. Refractory anemia with ringed sideroblasts (RARS) similar to FAB definition, except that dysplastic features must be restricted to the erythroid line
- D. Refractory anemia with excess blasts subdivided into two groups
  - 1. RAEB I marked by marrow blast percentage of 5% to 10%
  - 2. RAEB II marked by marrow blast percentage of 11% to 20%
- E. Refractory cytopenia with multilineage dysplasia (RC+Dys) includes RA and RARS with 2 or 3 dysplastic cell lines
- F. del 5q syndrome is characterized by erythroid dysplasia, thrombocytosis, hypolobulated micromegakaryocytic hyperplasia, and the 5q- chromosome deletion.
- G. Unclassifiable MDS - everything else

H. It is not clear that this reclassification has added any clarity or utility (Nösslinger).  
IV. Autoimmune myelodysplasia

A. Rare, 2% of cases

B. Morphologically resembles "refractory anemia not included in any other category"

1. Dyserythropoiesis

a) Erythroblastic synartesis (Cramer)

(1) Severe anemia and reticulocytopenia with marrow erythroblasts which clump together with tightly-bound Aglove finger@ invaginations between cells

(2) Mediated by an IgG autoantibody, probably directed against CD36

(3) Therapy directed at the autoimmune abnormality produced remission of the anemia in three described cases.

2. Dysmegakaryopoiesis

3. Bone marrow cellularity usually normal, but reported cases have had aplastic anemia or pure red cell aplasia at some point in their course.

C. Evidence for autoimmunity may be present

D. Responds to cyclosporin, corticosteroids, antithymocyte globulin

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## The FAB Classification of Myelodysplastic Syndromes

	<u>RA</u>	<u>RAEB</u>	<u>RAEB-T</u>	<u>AISA</u>	<u>CMML</u>
Blood blasts	<1%	< 5%	< 5%	< 1%	< 5%
Marrow blasts	< 5%	5 - 20%	20 - 30%	< 5%	1 - 20%
Ringed Sideroblasts	< 15%	< 15%	< 15%	\$15%	< 15%
Auer rods	-	-	+/-	-	-
Monocytes/ $\mu$ L	< 1000	< 1000	< 1000	< 1000	\$1000

NCCN Guidelines for management of MDS.





