MYELODYSPLASTIC SYNDROME (MDS)

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Hematology

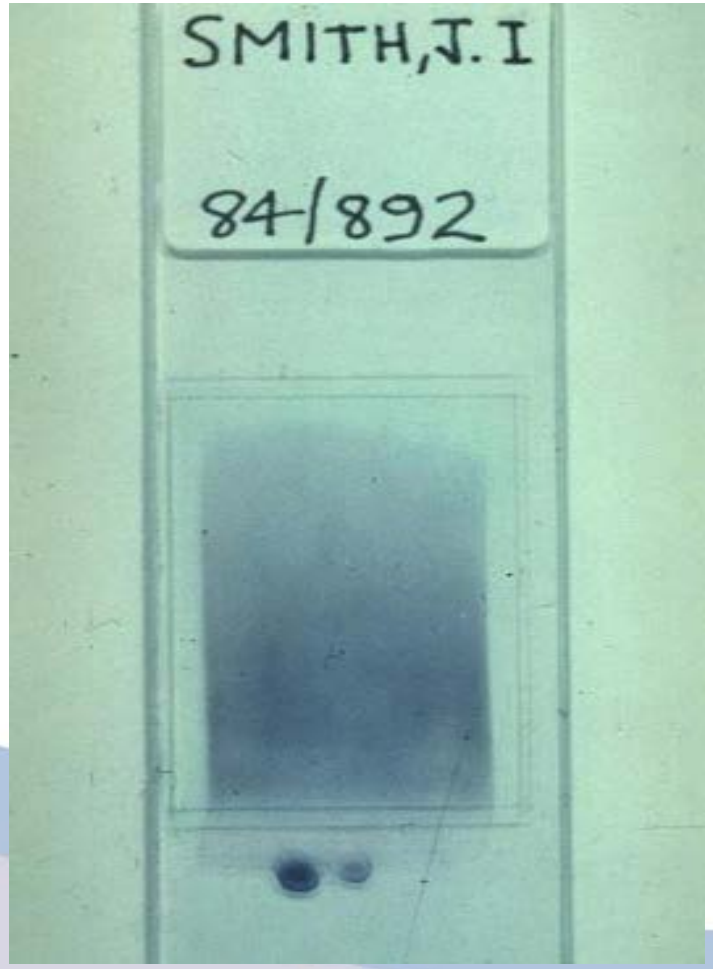
General Perspective

Diagnosis

- History & Physical exam, blood work (CBC, differential, chemistry)
- BM aspiration and biopsies (H & E Stain, Immunochemistry)
- Flow cytometry
- Cytogenetic studies, FISH, Molecular studies

Diagnosis

Wright-Giemsa staining



Peripheral blood smear

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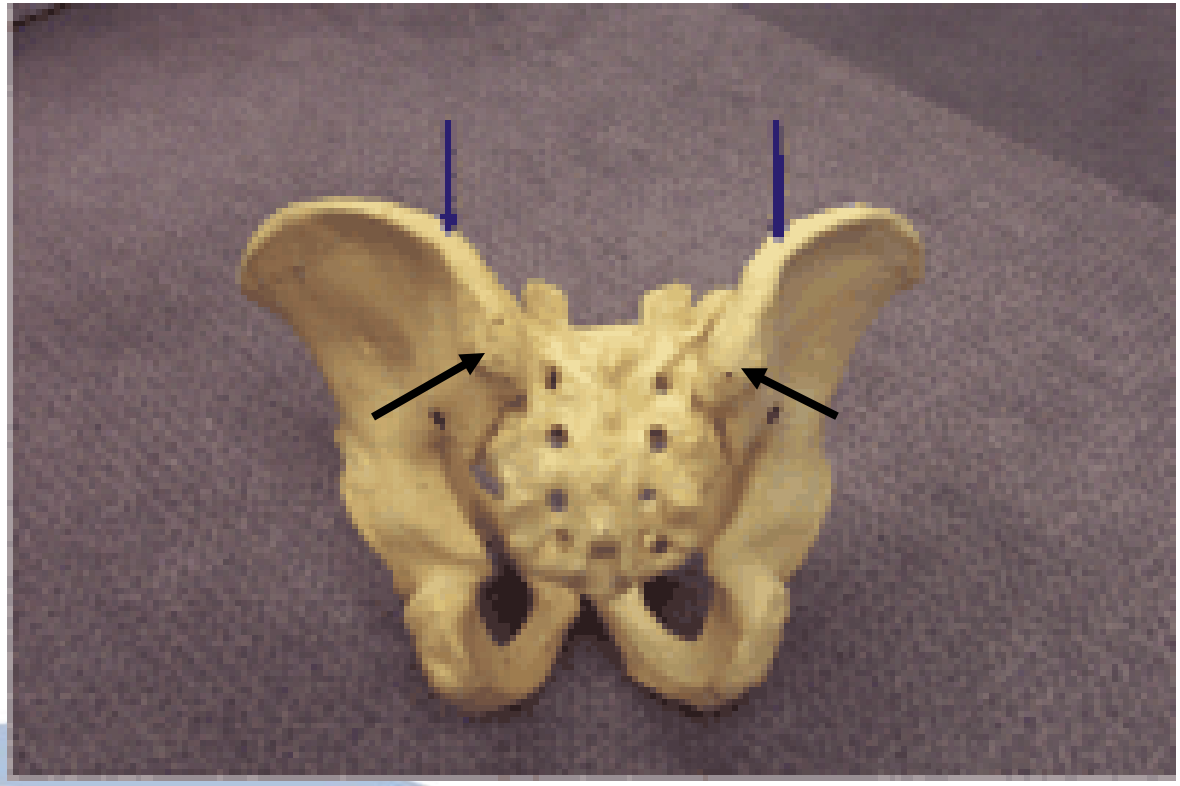
Bone marrow Aspiration and Biopsy



Posterior iliac crests

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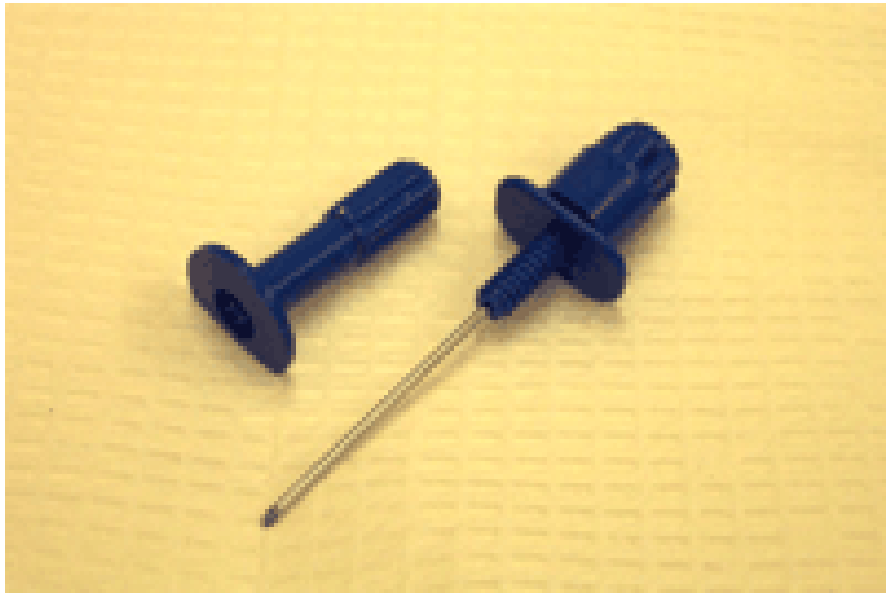
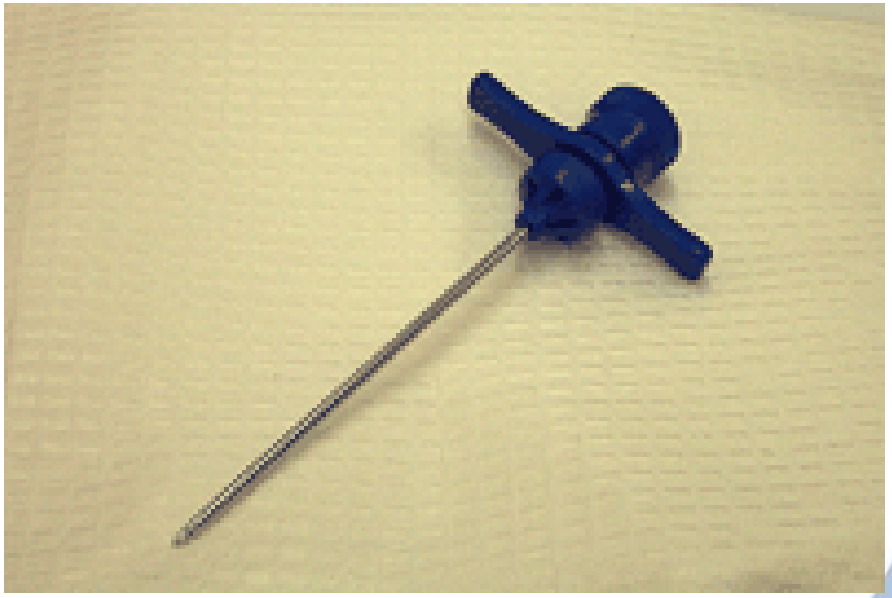
BM Aspiration Needle



BM Aspiration and Biopsy Needle



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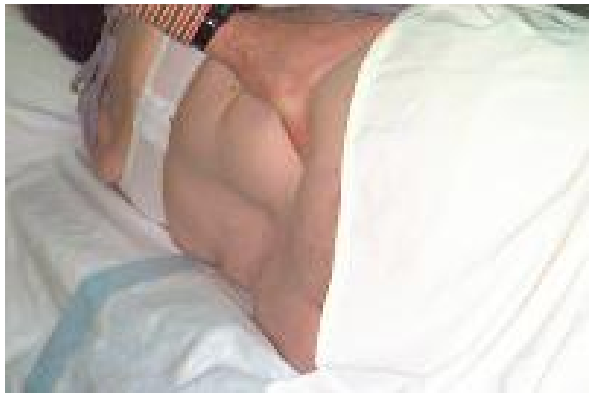
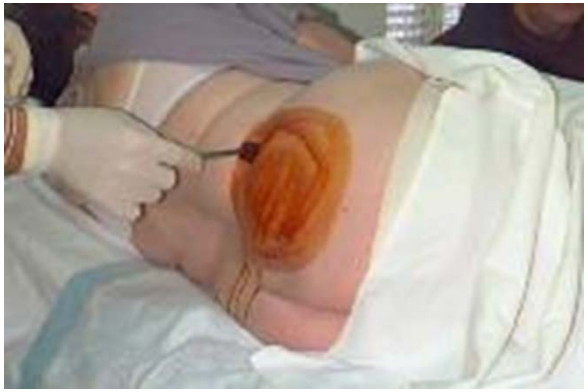
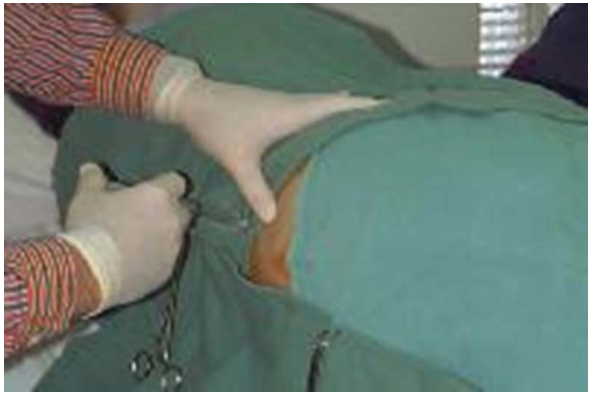
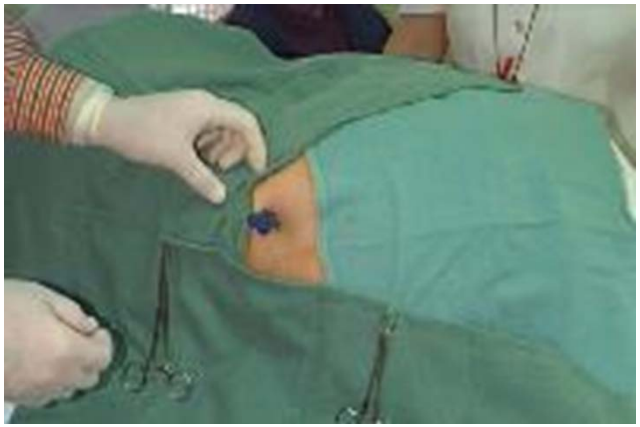
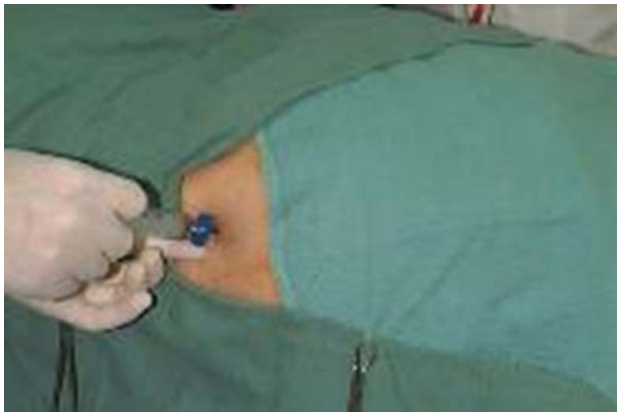
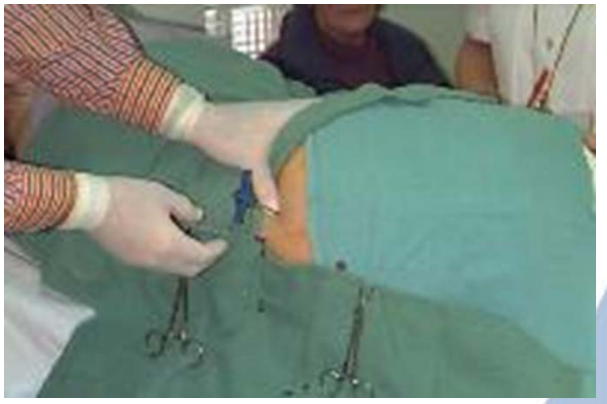
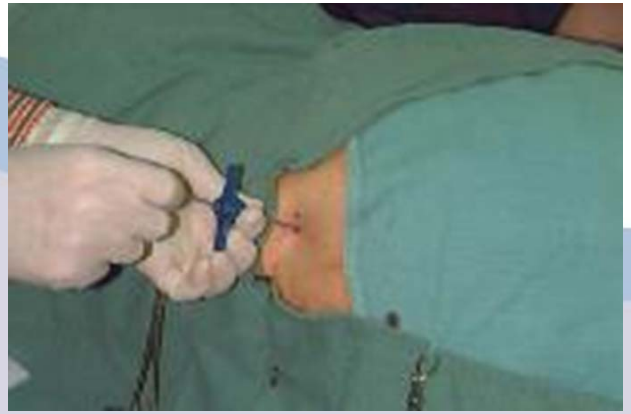
Bone marrow aspiration from posterior iliac crest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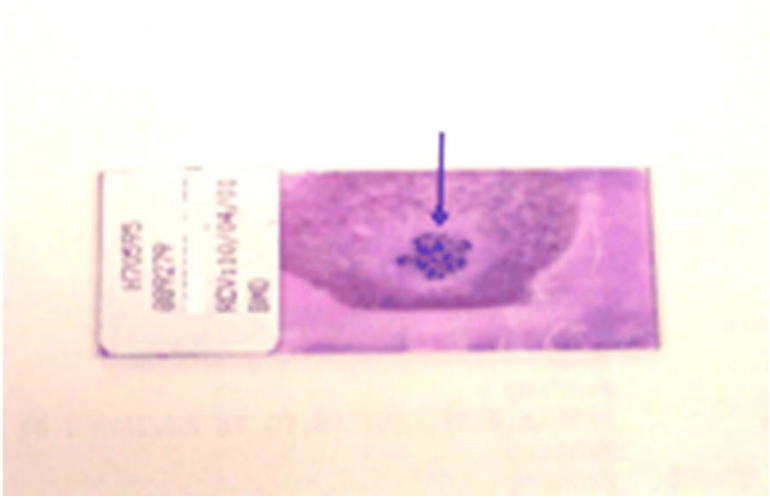
Bone marrow aspiration and biopsy specimens



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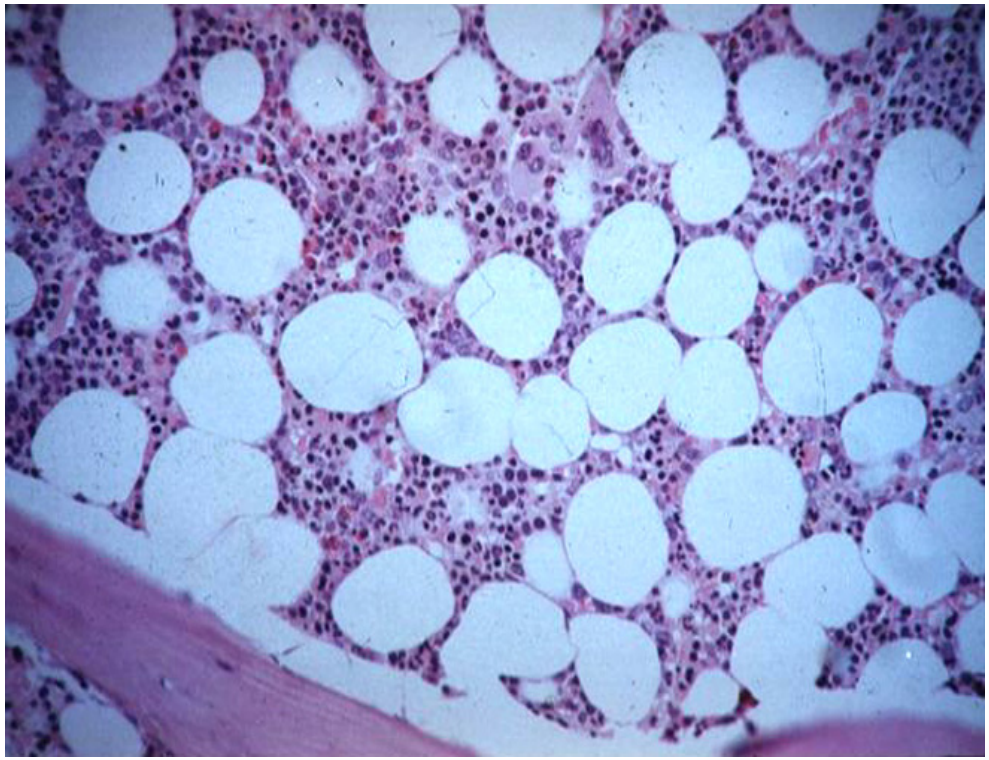
Normocellular normal bone marrow
Core Biopsy - Low power view (x10)

	BM cellularity
Newborn	90-100%
Childhood	60-70%
Adulthood	50%
Elderly	40%



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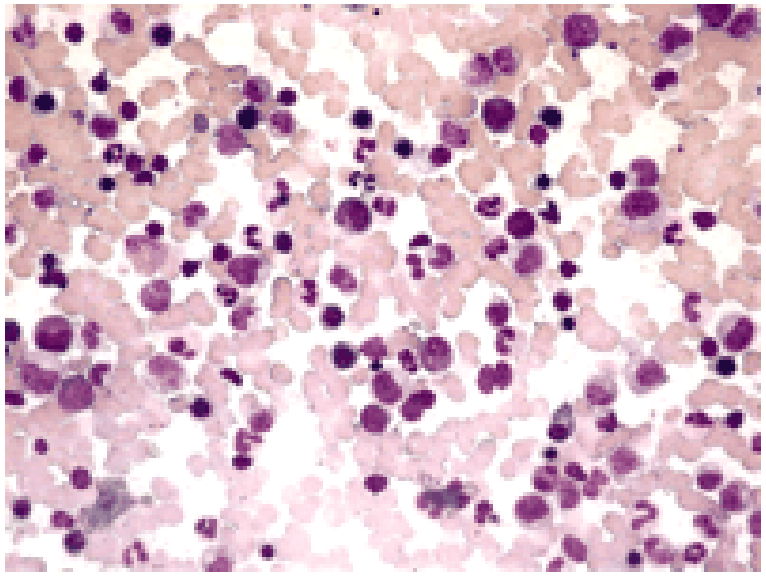
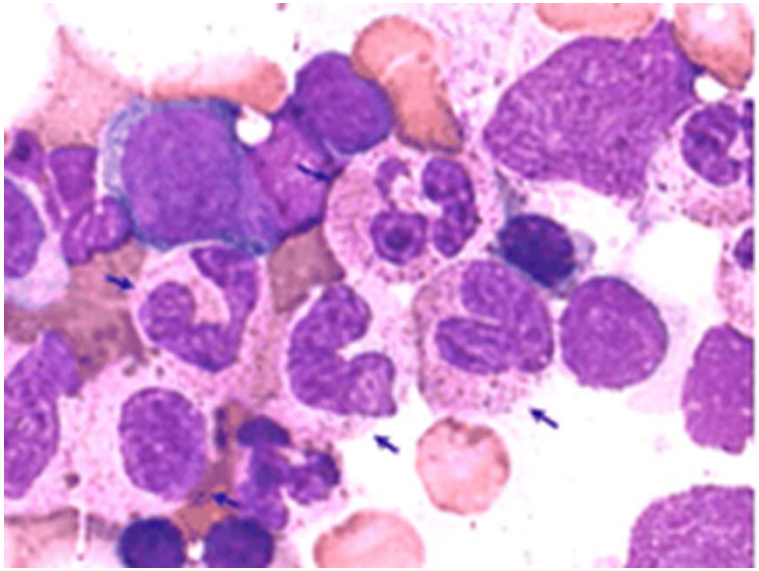
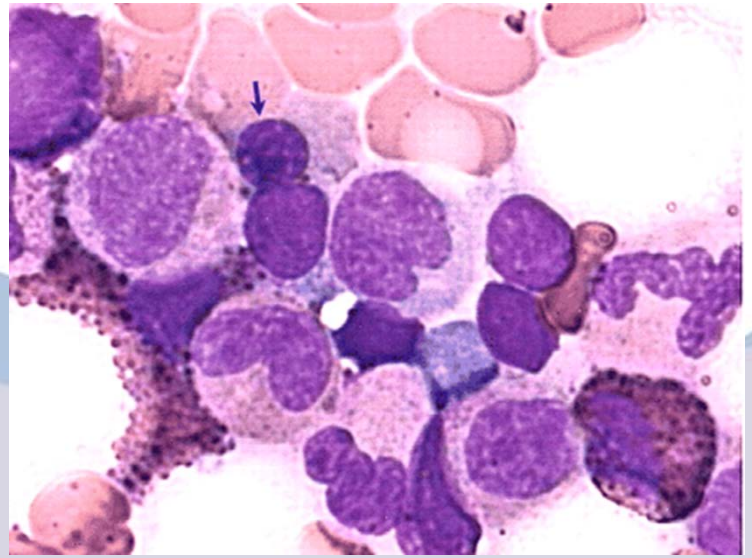
Normal bone marrow
Aspirate

Low power view (x10)



High power view (x10)





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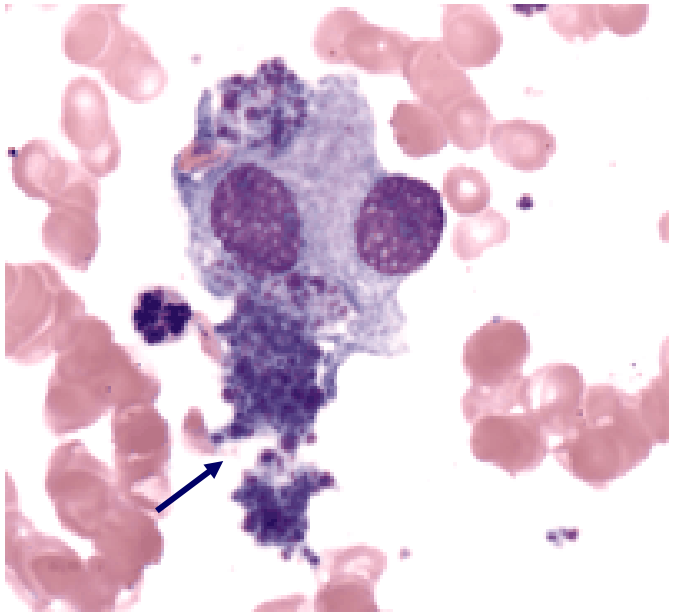
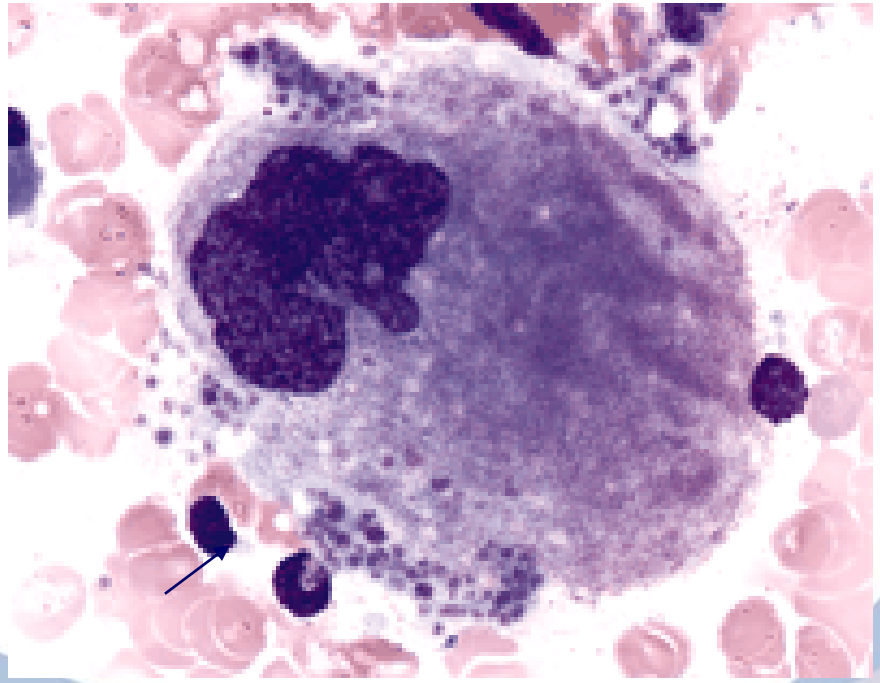
Normal bone marrow
Aspirate



Clusters or chains of platelets

Platelets seen as individual structures forming on the periphery of this megakaryocyte



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Myelodysplastic Syndrome (MDS)
(Pre-leukemic syndrome)

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MYELODYSPLASTIC SYNDROMES (MDS)

- A clonal disorder of the pluripotent stem cell
- Heterogenous (1-10 year life expectancy)
- Dysplastic differentiation of hematopoietic progenitors
- Ineffective cell proliferation and increased apoptosis

- **Characterized by hypercellular bone marrow, pancytopenia and likelihood of transformation to AML**

- Death likely 2º infection, bleeding, leukemia
- Older patients (70's), rare < 50

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Epidemiology of MDS

- The most common class of acquired bone marrow failure syndromes in adults.
  - Between 30 000 and 40 000 new cases of MDS in US

- De novo
- Therapy-related
  - –Chemotherapy
  - –Radiation therapy
  - - Autologous stem cell transplantation

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MDS is a clonal disorder

- Caused by acquired somatic mutation
- Clonal karyotypic abnormalities
  - Translocations
  - **5q**-, 7q-, 20q-
- Numerical abnormalities
  - trisomy 8
  - monosomy 7

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Chromosomal translocations in MDS or t-MDS/AML

Translocation	Fusion Gene
t(3; 21)(q26; q22)	*AML1/EVI1*
t(11; 16)(q23; p13.3)	*MLL/CBP*
t(11; 19)(q23; p13.1)	*MLL/ELL*

Animal Models of MDS/AML

Retroviral Transduction

AML1/EVI1

MLL/CBP

MLL/ELL

AML

long latency
(100-300 days)

- subtle proliferative advantage conferred by fusion
- second mutations are probably necessary for progre

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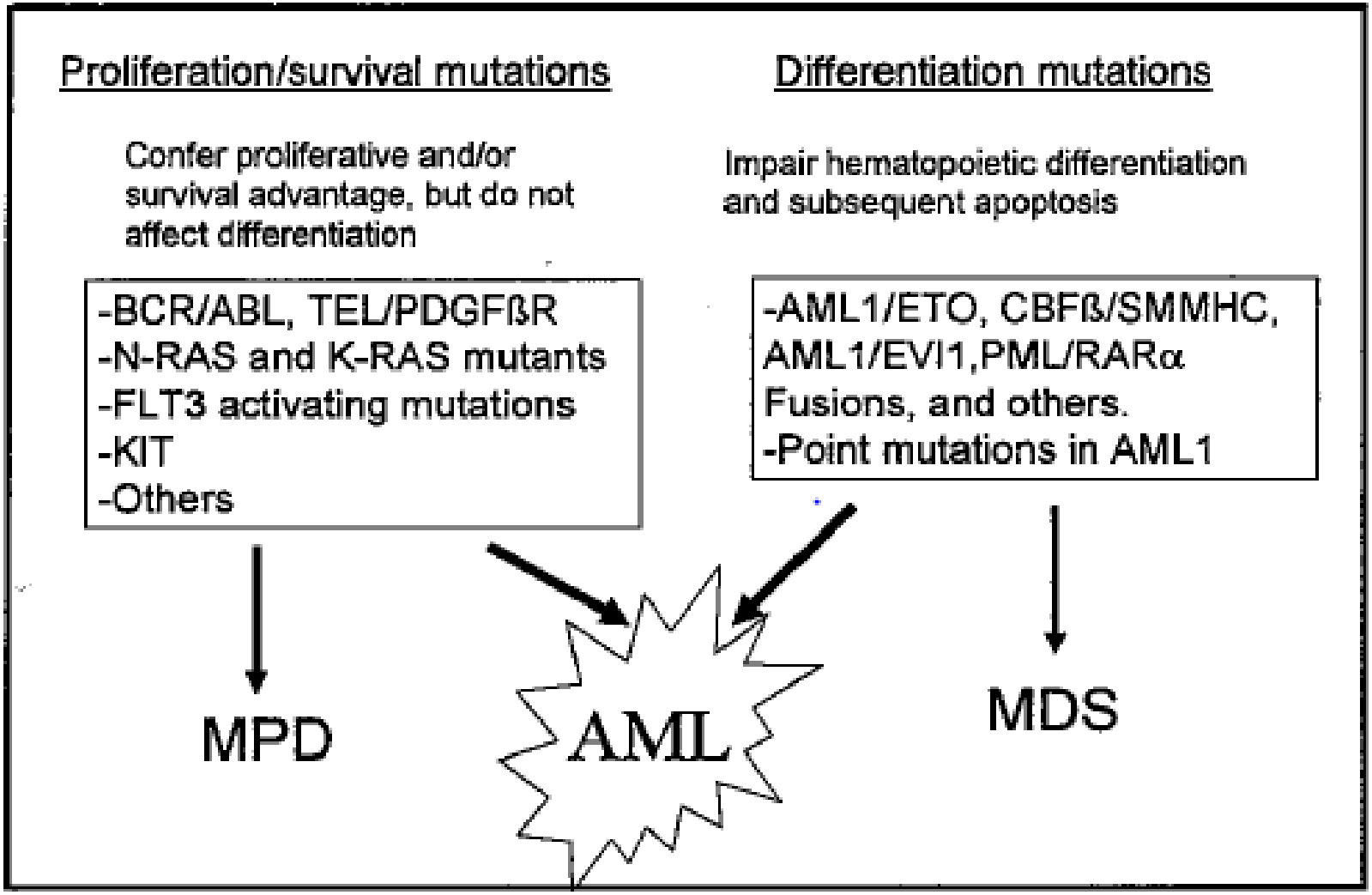

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MDS Clinic

- Cytopenia (single or multilineage)
- Hypercellular Bone Marrow
- Dysplastic appearance of erythroid ± myeloid ± megakaryocytic lineage
- Various proportion of blasts (<20%)

Prognosis depends on

1) Presence of anemia, thrombocytopenia and leukopenia
2) Blast count in the BM (<5% vs. >5%)
3) Associated Chromosomal abnormalities in BM cells

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3. Morphological features suggesting myelodysplasia

Lineage	Bone Marrow	Blood
megakaryocytic	hypolobation	giant platelets
myeloid	- Pseudo-pelger-Huet (bilobed polys)	bilobed polys
	- hypogranulation	
	- N:C dysynergy	
erythroid	-megaloblastoid	dimorphic
	- nuclear karyorrhexis	

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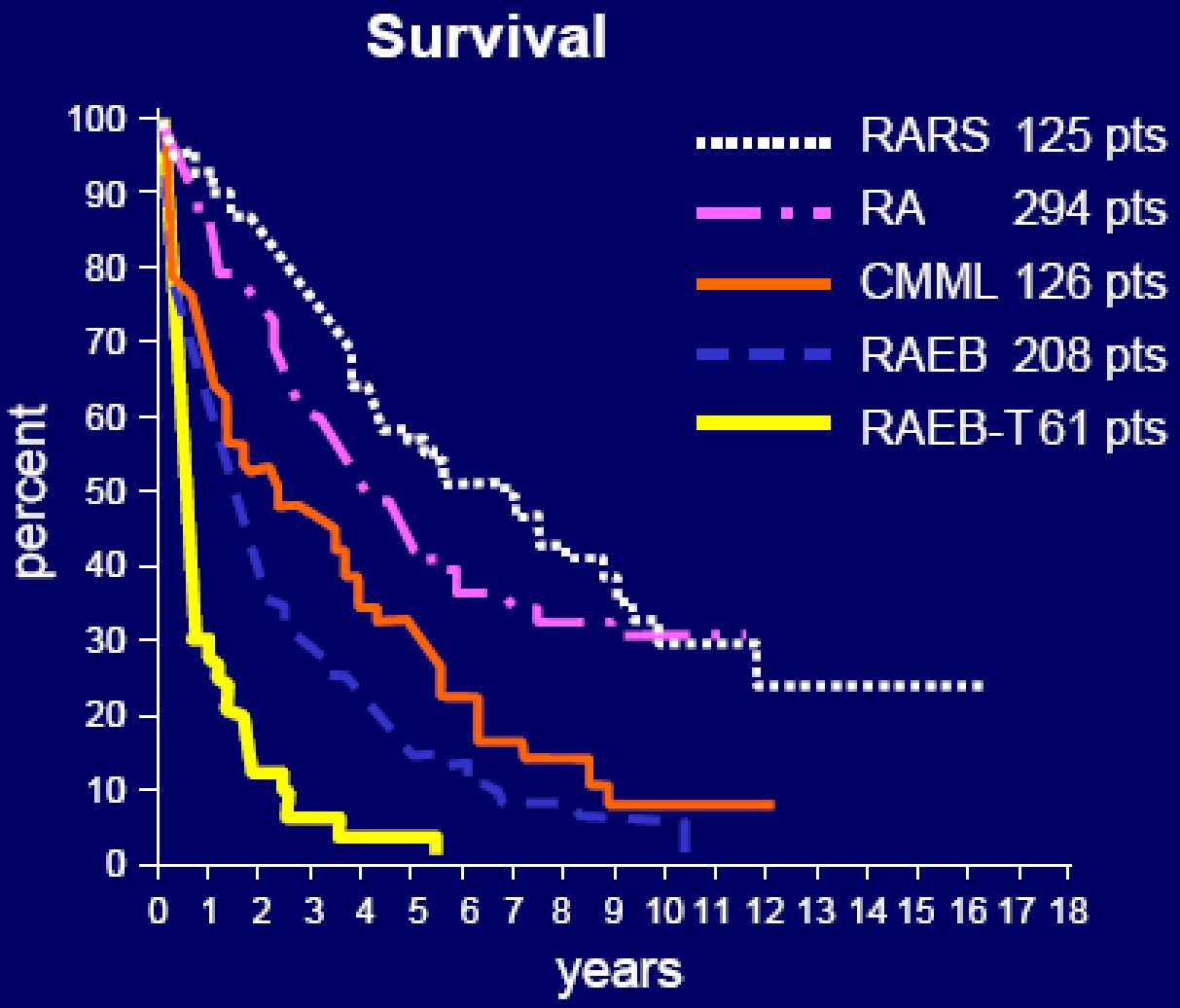
MDS
FAB classification

- Refractory anemia (<5% blasts in B.M. 0% blast in blood)
- Refractory anemia with ringed sideroblasts (>15% of nucleated RBCs have iron granules in halopattern)
- Refractory Anemia-Excess Blasts (RAEB), 5-20% blasts in B.M.
- RAEB-t up to 20% blasts in bone marrow
- Chronic Myelomonocytic Leukemia (CMML)
  - 0-20% blast in BM or blood. >1000 monocyte/microL

MDS: FAB Classification



From Greenberg P, et al. International Scoring System for Evaluating Prognosis in Myelodysplastic Syndrom *Blood* 1997:89:2079-88.

WHO Classification of MDS

- Myelodysplastic/myeloproliferative diseases
  - Chronic myelomonocytic leukemia
  - Atypical chronic myelogenous leukemia
  - Juvenile myelomonocytic leukemia
- Myelodysplastic syndromes
  - Refractory anemia
    - With ringed sideroblasts
    - Without ringed sideroblasts
  - Refractory cytopenia (myelodysplastic syndrome) with multilineage dysplasia
  - Refractory anemia (myelodysplastic syndrome) with excess blasts
  - 5q- syndrome
  - Myelodysplastic syndrome, unclassifiable

B. Myelodysplasia: a) The most commonly used system is the International Prognostic Scoring System (IPSS)[35]

	Survival and AML Evolution Score Value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
Marrow Blasts (%)	< 5	5 – 10	--	11 – 20	21 – 30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Risk Category	Combined Score
LOW	0
INT-1	0.5 – 1.0
INT-3	1.5 – 2.0
HIGH	≥ 2.5

	Median Survival (Years)				
	N	low	int1	int2	high
Age ≤ 60	205	11.8	5.2	1.8	0.3
Age > 60	611	4.8	2.7	1.1	0.5

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SOMATIC MUTATIONS IN ANY OF THE 5 GENES
TP53, EZH2, RUNX1, ASLX1 or ETV6 have prognostic significance in Low risk MDS.

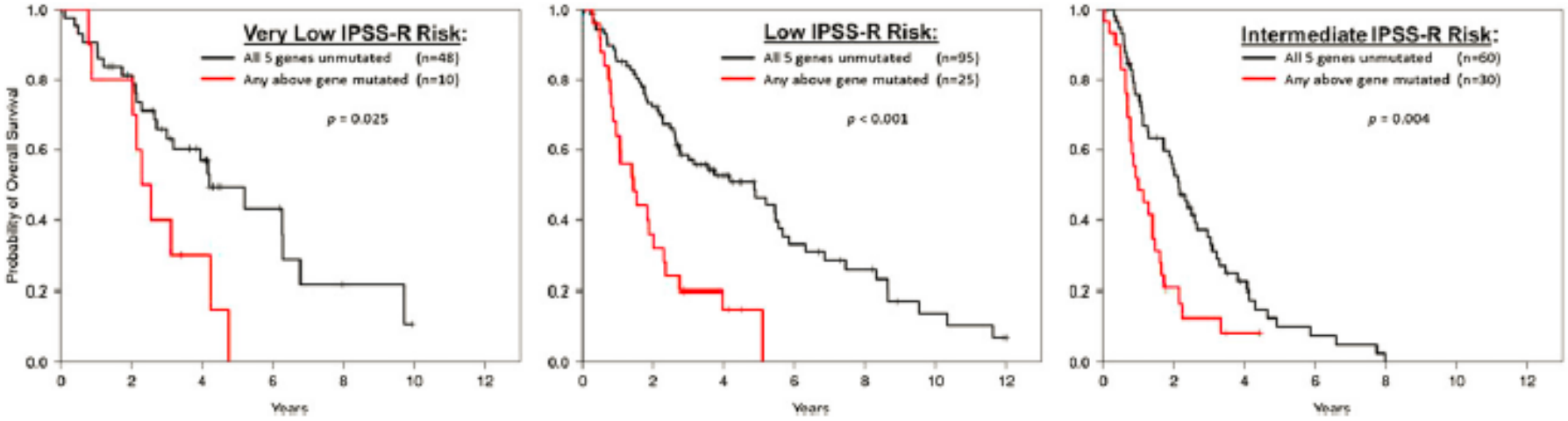

Figure 3. Somatic mutation in any of the 5 genes (*TP53*, *EZH2*, *RUNX1*, *ASLX1*, or *ETV6*) shown in Bejar et al[48] to have prognostic significance independent of the International Prognostic Scoring System (IPSS) identifies patients from that same cohort with shorter overall survival than predicted by Revised IPSS (IPSS-R) for the 3 lowest IPSS-R risk groups. One-third of patients in the IPSS-R Intermediate risk group have shorter than predicted overall survival and may better categorized using mutation analysis as having higher risk disease. Modified from Bejar[127] and used with permission.

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Treatment of MDS

In myelodysplasia, since chemotherapy is generally not used, and the disease is heterogenous, treatment must be individualized. Except for patients who are young enough and have aggressive enough disease to warrant an allogeneic bone marrow transplant, the goal is usually palliative and the decision re supportive care 'vs' treatment trial 'vs' clinical trial is difficult.

MDS - Treatment

- Hypomethylating/differentiating agents (Azacitidine, Decitabine)
  - 50-60% response (10-30% CR) rate
  - Not curative
- Supportive therapy, granulocyte colony stimulating factor, erythropoietin
- Allogeneic stem cell transplantation
  - Cure 40%

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Allogeneic stem cell transplant in MDS

Myelodysplasia

There is no standard approach. A practical approach[114] follows:

1. Consider a patient for an allogeneic transplant (potentially curative) if aged less than 55-60 (related donors) or 45-50 for unrelated donors) and the prognosis is not highly favorable.[115] IBMTR data[116] (n = 452; median age = 38) 3 yr transplant-related mortality: 37%, relapse: 23%, and overall survival: 42%.

Hematopoietic Growth Factors in MDS

Consider a trial of erythropoietin (recommended dose = 10,000 units sc qd, practical dose is 20-40,000 units/week). G-CSF may be added because of potential synergy re: erythropoiesis, but quality of life and survival benefits may be noted if any. Response to EPO +/- G-CSF (overall 20-35%) may be higher in those with lower endogenous EPO levels and in those with less aggressive histologies. [117]

Other treatments in MDS

Low dose ara-C - 10-20% response rate,[128] rarely used now and is probably less effective than 5-aza.

Immunosuppression: Antithymocyte globulin can produce CRs in indolent MDS. ATG at 40mg/kg/d x 4 d yields a 34% RBC transfusion-independent rate and a 50% chance of platelet or ANC improvement. Responses more likely in those with HLA-DR 15, younger, and shorter duration of RBC tx.[129]

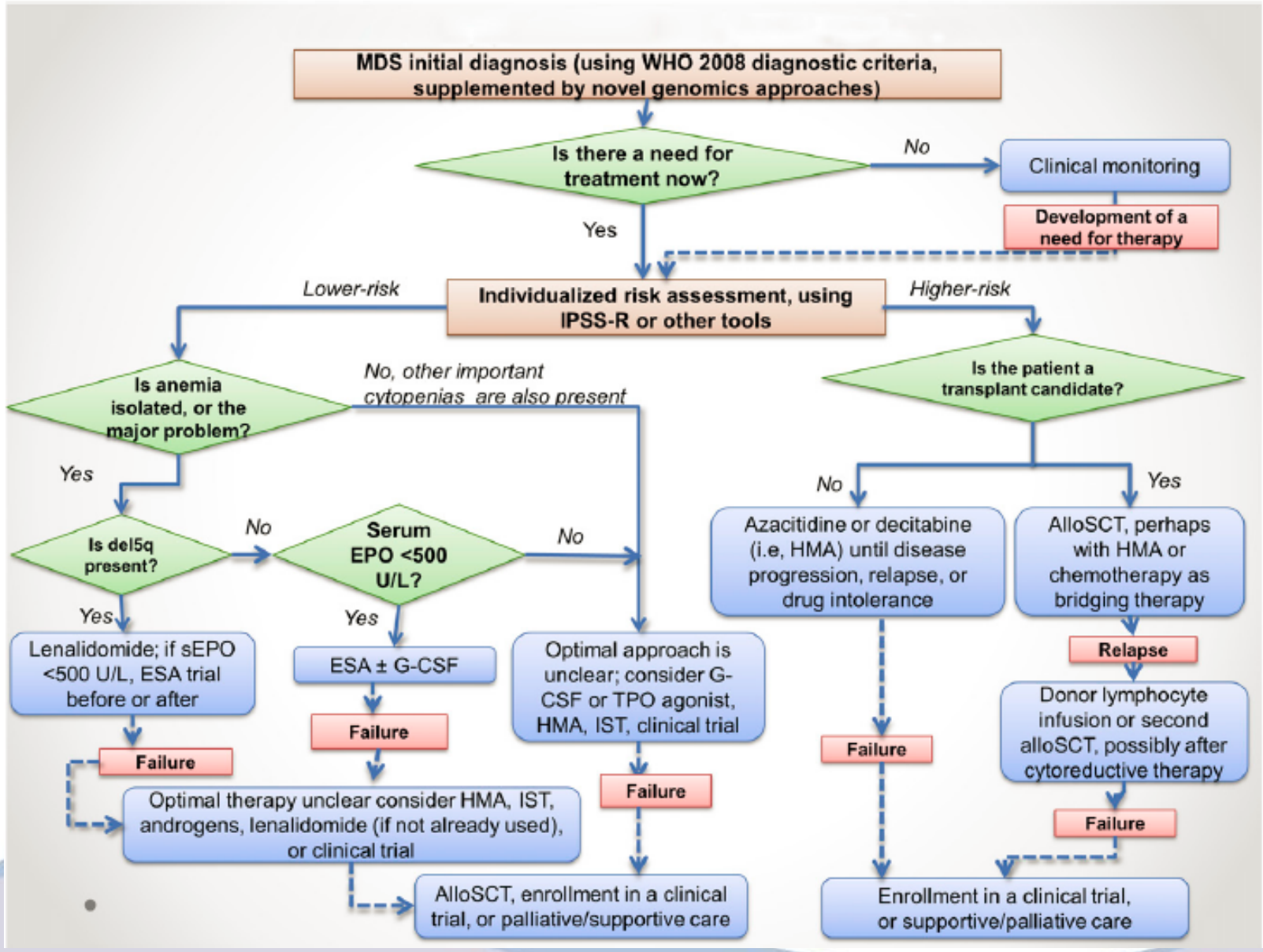
Other Treatments in MDS

Arsenic trioxide therapy is associated with responses but should not be used outside the context of a clinical trial. [130]

Signal transduction inhibitors: imatinib mesylate has induced impressive responses in those rare CMML patients with t(5;12) and other PDGFRß mutations.[131]

Chemotherapy. If a patient has > 20% blasts in marrow or blood and is younger than age 60, otherwise fit, AML-type treatment is appropriate.[8] Although one would be concerned about an intrinsically damaged stem cell, there may be a benefit for autologous BMT in selected patients.[132]

Iron chelation. Treatment with SC as po iron chelators can reduce storage iron which could be toxic, but he clinical benefits are unclear.[133]



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Bejar and Steensma Blood. 2014;124(18):2793-2803

Demethylation in MDS

- Aberrant methylation of selected promoters has been observed in MDS and other cancers
- Demethylating agents, such as 5-azacytidine have shown clinical efficacy in MDS
- 5-azacytidine is an FDA approved for treatment of all subtypes of MDS
  - Potentially decrease transfusion requirement
  - Delay leukemic transformation

Demethylation in MDS

5-azacytidine (a DNA hypomethylating agent) shown to be effective in MDS in a prospective randomized trial, lengthens time to transformation to AML improves QOL and trend toward longer survival in all risk groups (see chart below).[123] This drug, given at a dose of 75mg/m^2 sc x 7d q 28d, is well tolerated and produces a 60% response rate (only 7% CR, 16% PR). FDA approval for use in all MDS subtypes took place in 2004. Recent data suggest that in advanced MDS patients (IPSS int-2 and high) 5-aza leads to a nine month prolongation of median survival compared with 'doctor's choice' (supportive care or induction chemo or low dose ara-C).[124] Other schedules including a 5 day regimen may be equivalent in efficiency to the 7d schedule,[125] (A similar drug, decitabine (given IV q 8h x 3d per cycle) was approved in 2006.[126] A non-approved but commonly used decitabine regimen (20 mg/m2/d IV d1-5) yielded a 39% CR rate in high risk MDS patients.[127]

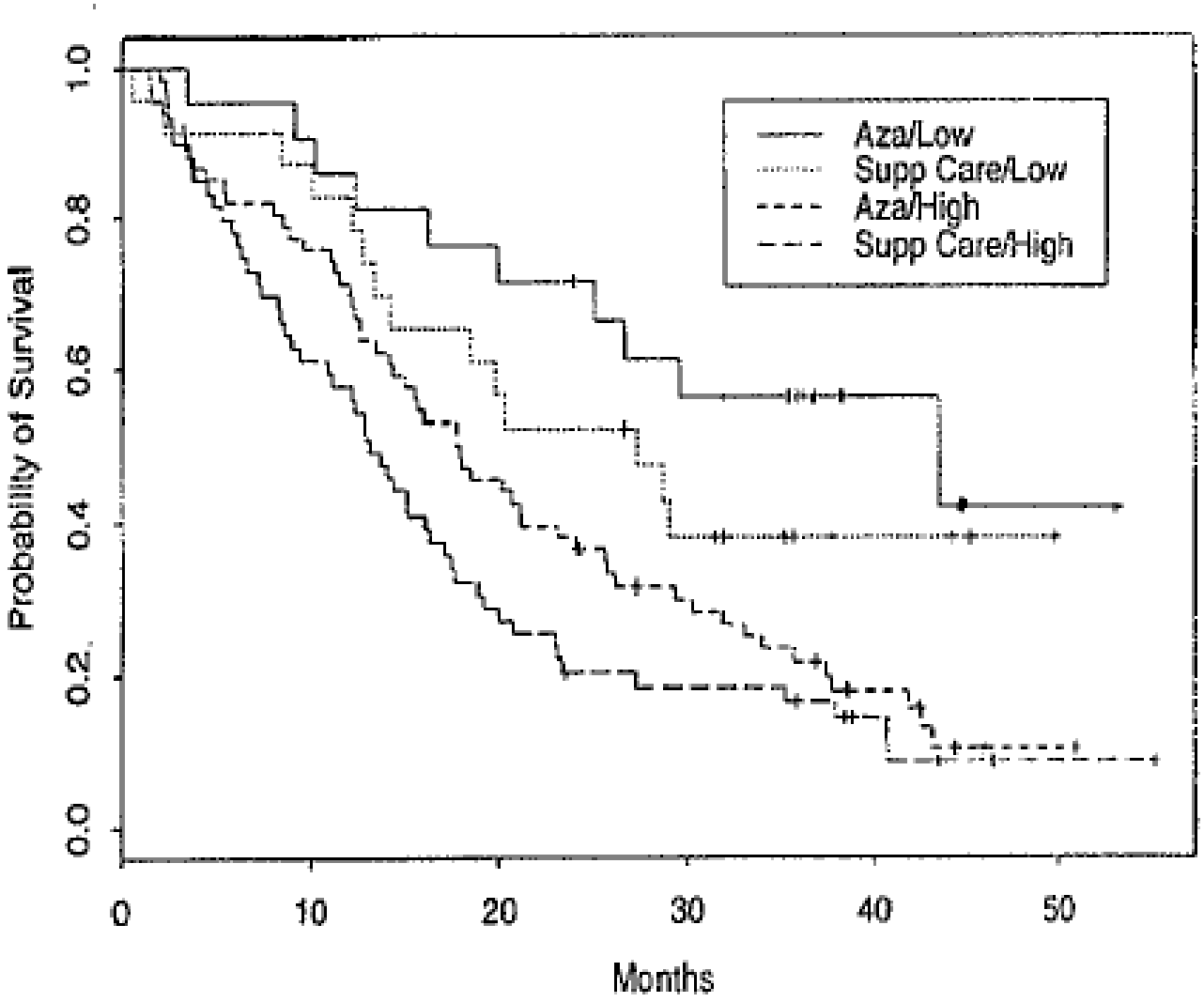

Fig 7. Survival by randomized arm and FAB subtype. FAB subgroups were divided into low-risk (RA/RARS) and high-risk (RAEB, RAEB-T, or CMMoL) groups. Median survival: Aza/Low, 44 months; supportive care (SC)/Low, 27 months; Aza/High, 18 months; SC/High, 13 months.

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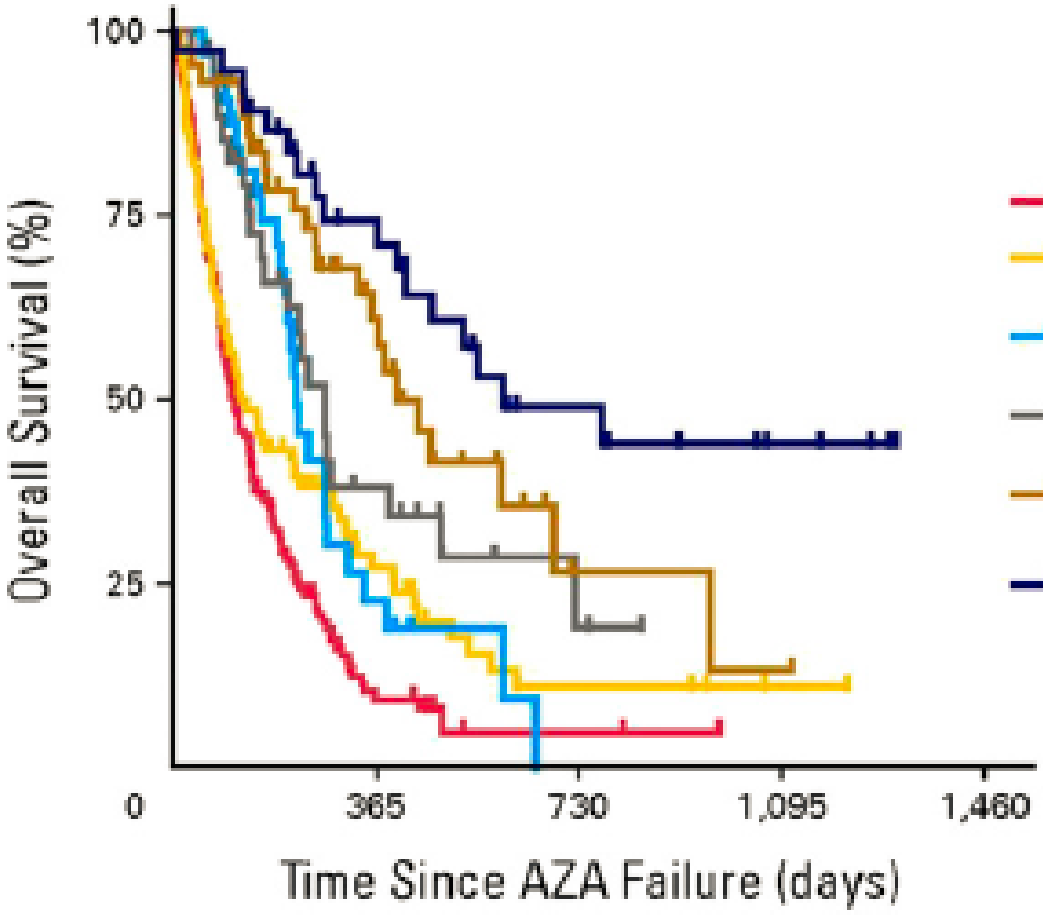
Treatment of MDS

Anti-angiogenic agents in MDS

- MDS, like other cancers, is associated with increased angiogenesis
- Lenalidomide, an inhibitor of angiogenesis, has shown efficacy in treatment of MDS
- **Lenalidomide is now FDA approved for treatment of MDS, and appears to be most effective in treating 5q- patients**

Anti-angiogenic agents in MDS

Anti-angiogenesis. For patients with a 5q- chromosomal abnormality (alone or with other lesions) lenalidomide (thalidomide[118] analog) should be the treatment of choice. Lenalidomide is associated with a 66% transfusion independence rate (75% cytogenetic response rate) in 5q- patients[119] (approved indication) and 26% in non 5q-patients.[120] All patients treated with lenalidomide in these clinical trials were low or int-1 IPSS and had preserved ANC trial platelet count, but selected (5q- sole abnormality) higher risk patients may benefit.[121] Cytopenias predict response in 5q- subset and may represent a 'treatment effect' rather than myelosuppression MDS. [122]



Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

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Review Series

BONE MARROW FAILURE

Recent developments in myelodysplastic syndromes

Rafael Bejar[1] and David P. Steensma[2]

[1]Division of Hematology and Oncology, University of California at San Diego Moores Cancer Center, La Jolla, CA; and [2]Division of Hematological Malignancies, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Once thought to be rare disorders, the myelodysplastic syndromes (MDS) are now recognized as among the most common hematological neoplasms, probably affecting >30 000 patients per year in the United States. US regulatory approval of azacitidine, decitabine, and lenalidomide between 2004 and 2006 seemed to herald a new era in the development of disease-modifying therapies for MDS, but there have been no further drug approvals for MDS indications in the United States in the last 8 years. The available drugs are not curative, and few of the compounds that are currently in development are likely to be approved in the near future. As a result, MDS diagnoses continue to place a heavy burden on both patients and health care systems. Incomplete understanding of disease pathology, the inherent biological complexity of MDS, and the presence of comorbid conditions and poor performance status in the typical older patient with MDS have been major impediments to development of effective novel therapies. Here we discuss new insights from genomic discoveries that are illuminating MDS pathogenesis, increasing diagnostic accuracy, and refining prognostic assessment, and which will one day contribute to more effective treatments and improved patient outcomes. (*Blood*. 2014;124(18):2793-2803)

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