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COMMUNITY ONCOLOGY PROGRAM

UPCON
Uniting Primary Care and Oncology

Blood Disorders Day 2016

FOR
Health Professionals

Could this patient have myelodysplastic syndrome?

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Disclosures

FINANCIAL DISCLOSURE

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Speaker bureau/Honoraria: Novartis

Advisory boards: Celgene, Roche

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Objectives

1. Know when to suspect myelodysplastic syndrome (MDS) in patients presenting with cytopenias.
2. Be familiar with the diagnostic approach and criteria to establish a diagnosis of MDS
3. Be aware of the treatment options and prognosis for patients with MDS

Myelodysplastic Syndromes (MDS)

- **MDS:** group of clonal myeloid neoplasms characterized by one or more peripheral blood **cytopenias** + morphologic **dysplasia** in hematopoietic cells (in bone marrow)

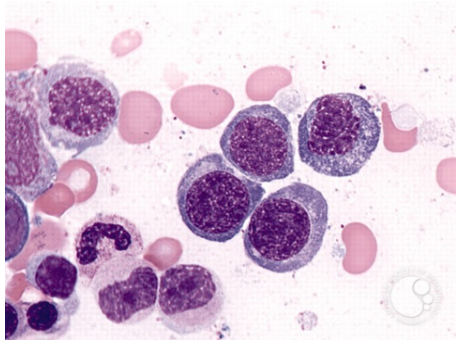
- **Causes of cytopenias:**
  - Many etiologies: as shown in algorithms for various cytopenias.

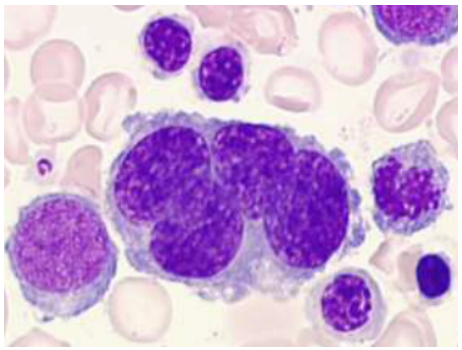
- **Reactive causes of dysplasia:**
  - Many: nutritional deficiencies, cytotoxic therapy, infections, inflammation

- Even normal individuals may have dysplasia

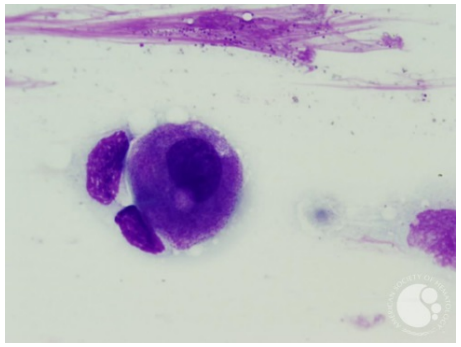
Dysplasia in bone marrow cells

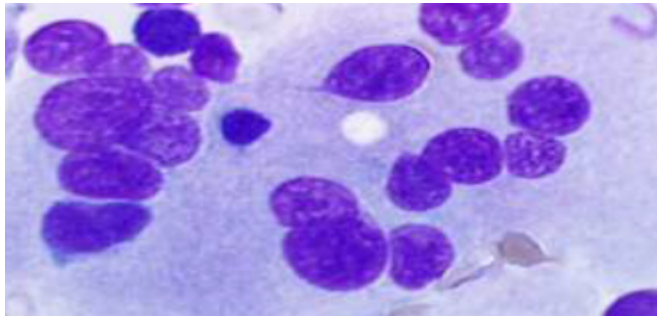
Erythroid



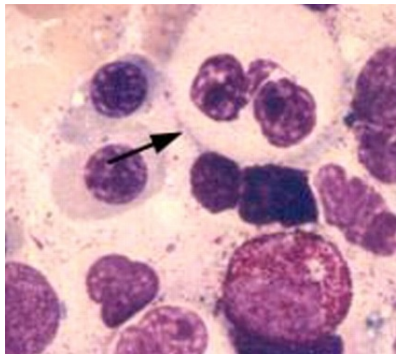


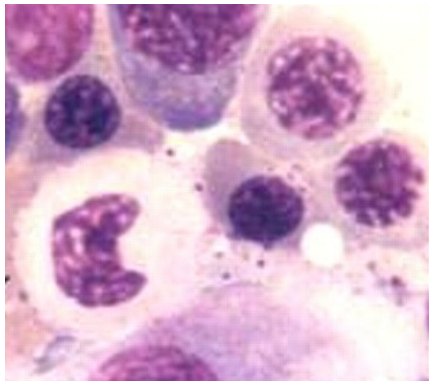
Megakaryoctyes





Myeloid





- **Reactive causes of dysplasia:**
  - Vit def: B12, folate, pyridoxine
  - Drugs: chemo, methotrexate, azathioprine
  - Infections: sepsis, viral, TB
  - Alcohol, Inflammation
- Identification of dysplasia not always reproducible: **inter-observer variation**

Diagnosis MDS (WHO criteria)
Peripheral blood
Cytopenias (one or more): Hb <100 g/L; Plat <100 x10^9/L; ANC <1.8 x10^9/L
+ Bone Marrow
Dysplasia: 10% or more in erythroid, myeloid or megakaryoctes OR
Myeloblasts: ≥ 5% (or ≥ 1% in blood) OR
Cytogenetics: MDS defining, by conventional karyotyping
Exclude Reactive Causes of Dysplasia

Who should be referred for investigation of MDS?

Criteria for Observation vs Urgent or Emergent referral given in Algorithms for

Anemia, Leucopenia, Thrombocytopenia and Pancytopenia

MDS is one of the causes of cytopenias

Diagnosis of MDS should be made in a Hematology Centre

MDS more likely in:

- Elderly (median age 70)
- Unexplained macrocytic anemia
- Previous myelotoxic drugs, radiation

Classification and Management of MDS is Evolving

The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes

James W. Vardiman,[1] Jüergen Thiele,[2] Daniel A. Arber,[3] Richard D. Brunning,[4] Michael J. Borowitz,[5] Anna Porwit,[6] Nancy Lee Harris,[7] Michelle M. Le Beau,[8] Eva Hellström-Lindberg,[9] Ayalew Tefferi,[10] and Clara D. Bloomfield[11]

Review Series

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

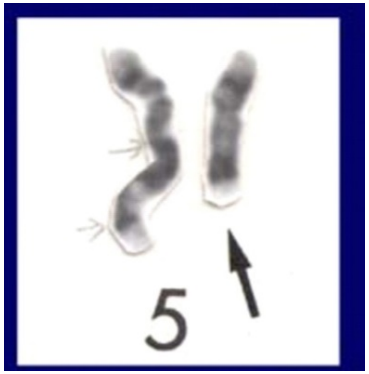
The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Daniel A. Arber,[1] Attilio Orazi,[2] Robert Hasserjian,[3] Jürgen Thiele,[4] Michael J. Borowitz,[5] Michelle M. Le Beau,[6] Clara D. Bloomfield,[7] Mario Cazzola,[8] and James W. Vardiman[9]

Myelodysplastic syndrome (MDS)	**Myelodysplastic syndromes (MDS)**
Refractory cytopenia with unilineage dysplasia	MDS with single lineage dysplasia
Refractory anemia	MDS with ring sideroblasts (MDS-RS)
Refractory neutropenia	MDS-RS and single lineage dysplasia
Refractory thrombocytopenia	MDS-RS and multilineage dysplasia
Refractory anemia with ring sideroblasts	MDS with multilineage dysplasia
Refractory cytopenia with multilineage dysplasia	MDS with excess blasts
Refractory anemia with excess blasts	MDS with isolated del(5q)
Myelodysplastic syndrome with isolated del(5q)	MDS, unclassifiable
Myelodysplastic syndrome, unclassifiable	*Provisional entity: Refractory cytopenia of childhood*
Childhood myelodysplastic syndrome	
Provisional entity: refractory cytopenia of childhood	

Referral to Hematology

- 52M, had travelled North, developed shortness of breath → Hb 45g/L. Transfused blood and referred for Inv Anemia.
- No history of blood loss or jaundice. Clinical: pallor, no other finding
- Hb 66g/L WBC 6.3 $x10^9$/L, Neutr 6.2 $x10^9$/L Plate 255 $x10^9$/L, retic 0.50%, retics:12.6 $x10^9$/L, MCV 95.2fl, MCH 30.7pg.
- Ferritin 1128, LDH 186
- Bone marrow: **Refractory cytopenia with multilineage dysplasia (RCMD)**
- BM cytogenetics: 46 XY, del (5q)
- Diagnosis: **MDS – del (5q)**
- ? Prognosis ? Treatment



Risk Stratification by Prognostic Scoring

1997 International Prognostic Scoring System (IPSS)

	Score				
Prognostic Variable	**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	--	--	--

*Karyotype risk groups: Good = normal, -Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes

** Qualifying Cytopenias: Hb < 10 g/dL, ANC <1800/µL, platelets <100,000/µL

*** 20% or more blasts now (WHO) considered AML, but was still MDS (FAB) at the time this system was developed

Score sum	IPSS Risk Category	Median survival for over age 60 group (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

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

IPSS-R

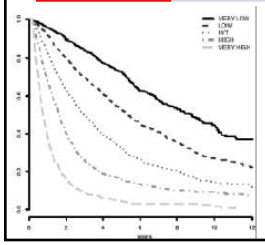
Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤2%	>2 - <5%	5 - 10%	>10%	
	0	1	2	3	
Hemoglobin	≥10 g/dL	8 - <10 g/dL	<8 g/dL		
	0	1	1.5		
Absolute neutrophil count	≥0.8 x 10^9/L	<0.8 x 10^9/L			
	0	0.5			
Platelet count	≥100 x 10^9/L	50 - 100 x 10^9/L	<50 x 10^9/L		
	0	0.5	1		

Possible range of summed scores: 0-10

Greenberg P et al *Blood* ePub 27 Jun 2012

IPSS-R

Risk group	Points	% patients (n=7,012; AML data on 6,485)	Median survival, years	Median survival for pts under 60 years	Time until 25% of patients develop AML, years
Very low	0-1.5	19%	8.8	Not reached	Not reached
Low	2.0-3.0	38%	5.3	8.8	10.8
Intermediate	3.5-4.5	20%	3.0	5.2	3.2
High	5.0-6.0	13%	1.5	2.1	1.4
Very high	>6.0	10%	0.8	0.9	0.7

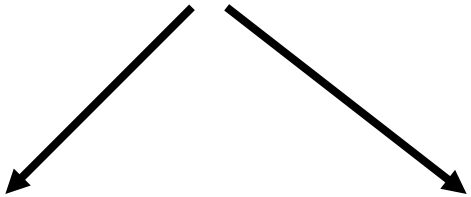


Using IPSS-R:
27% of IPSS lower risk "upstaged"
18% of IPSS higher risk "downstaged"

Greenberg P et al *Blood* ePub 27 Jun 2012

Risk Stratification in MDS

According to Scoring Systems
IPSS/IPSS-R/WPSS/MPSS



Lower risk

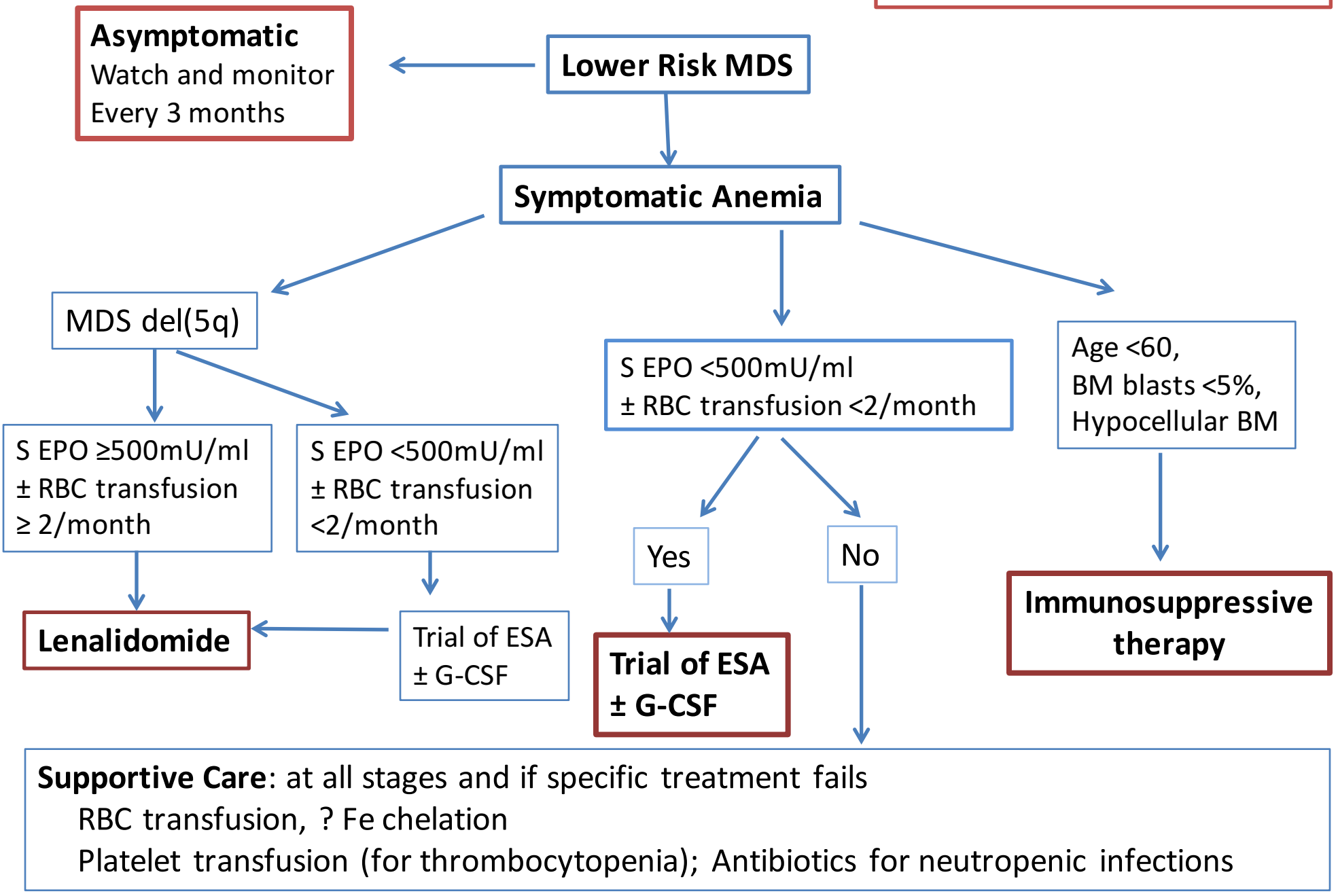
Mild cytopenias
Low blast counts
"good" cytogenetics

Higher risk

Severe cytopenias
High blast counts
"poor" cytogenetics

Our Patient had IPSS score: 0, Low Risk

Therapeutic Algorithm

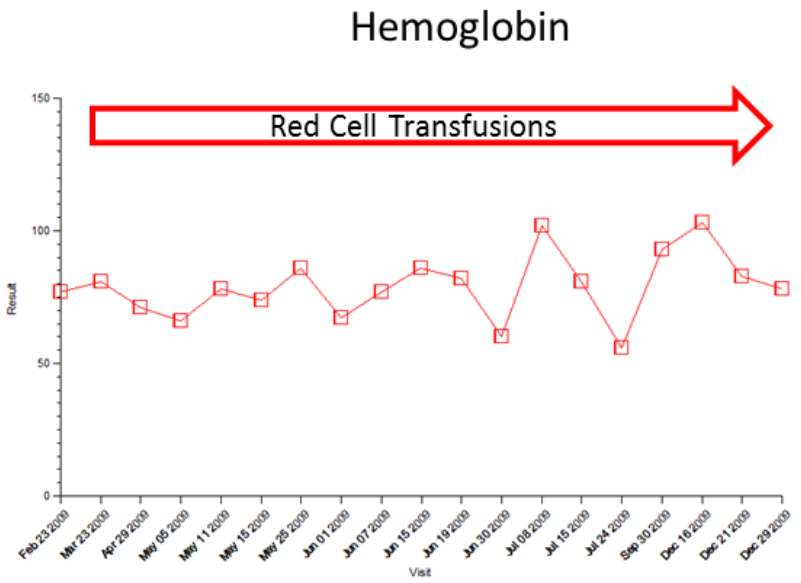


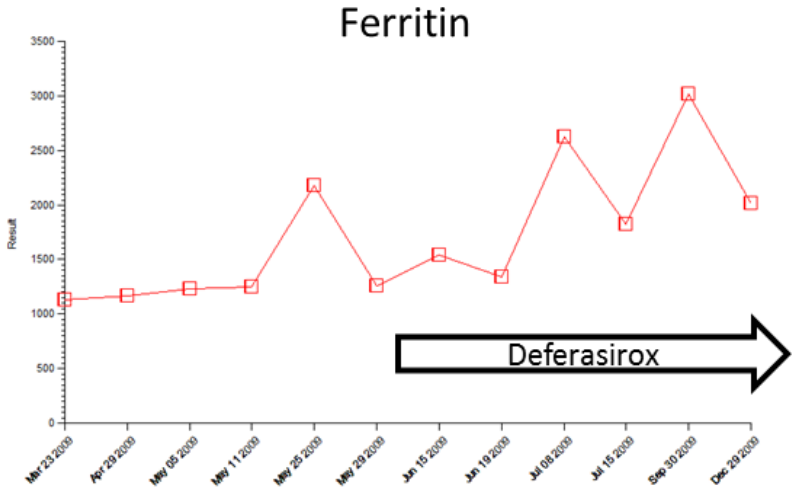
Our Patient: MDS del (5q)

- Sr erythropoietin 600 IU/ml.
- Lenalidomide not available in early 2009.

Rx

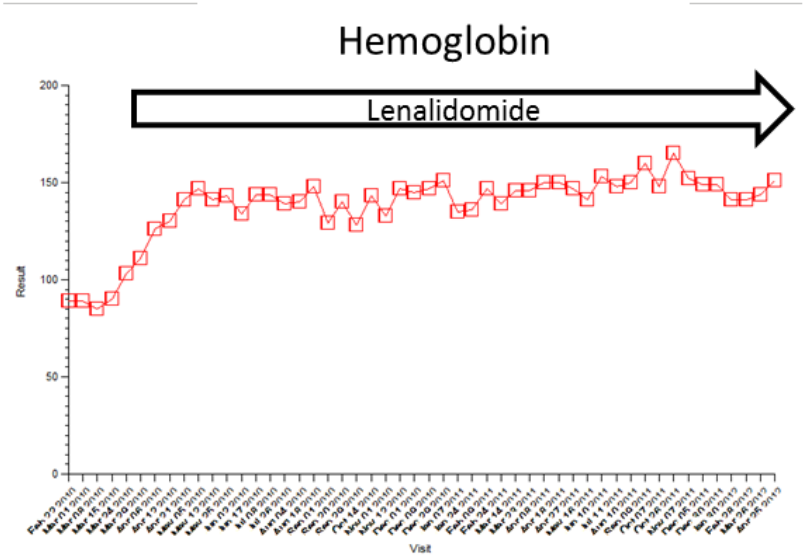
- Regular packed cell transfusions: 4-6 per month.
- Increase in iron and ferritin
- Added iron chelator: Deferasirox

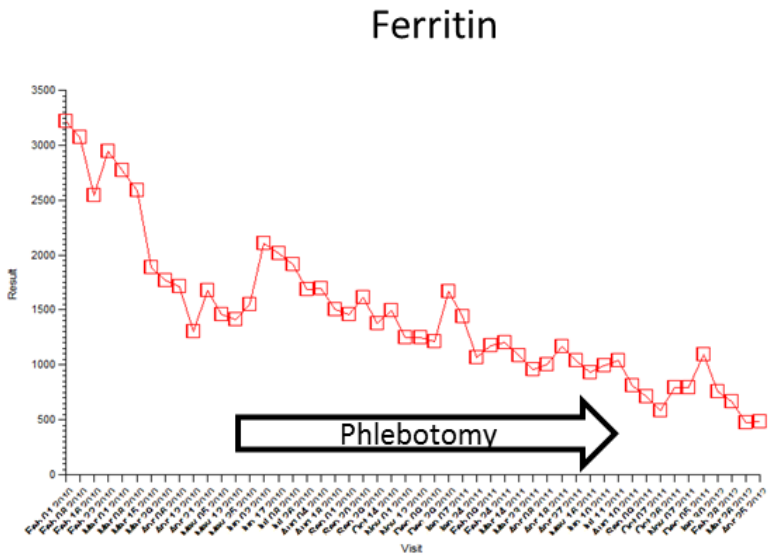




Course of Illness

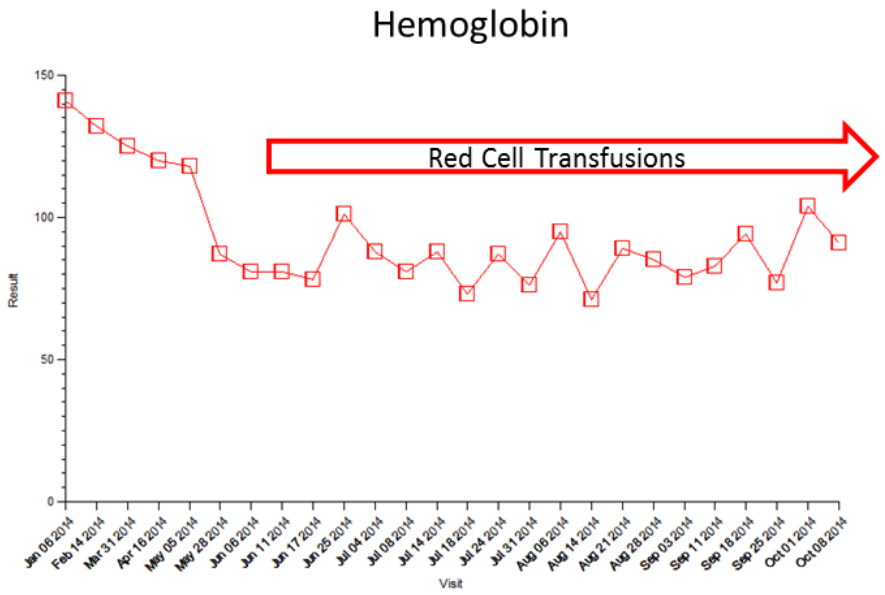
- 2010: Lenalidomide available.
- Sustained rise in Hemoglobin
- Hb range: 140-160g/L
- After 6 months, repeat bone marrow: Complete Remission (CR). Normal cytogenetics
- Deferasirox stopped
- Phlebotomy 500ml once a month → ferritin normal

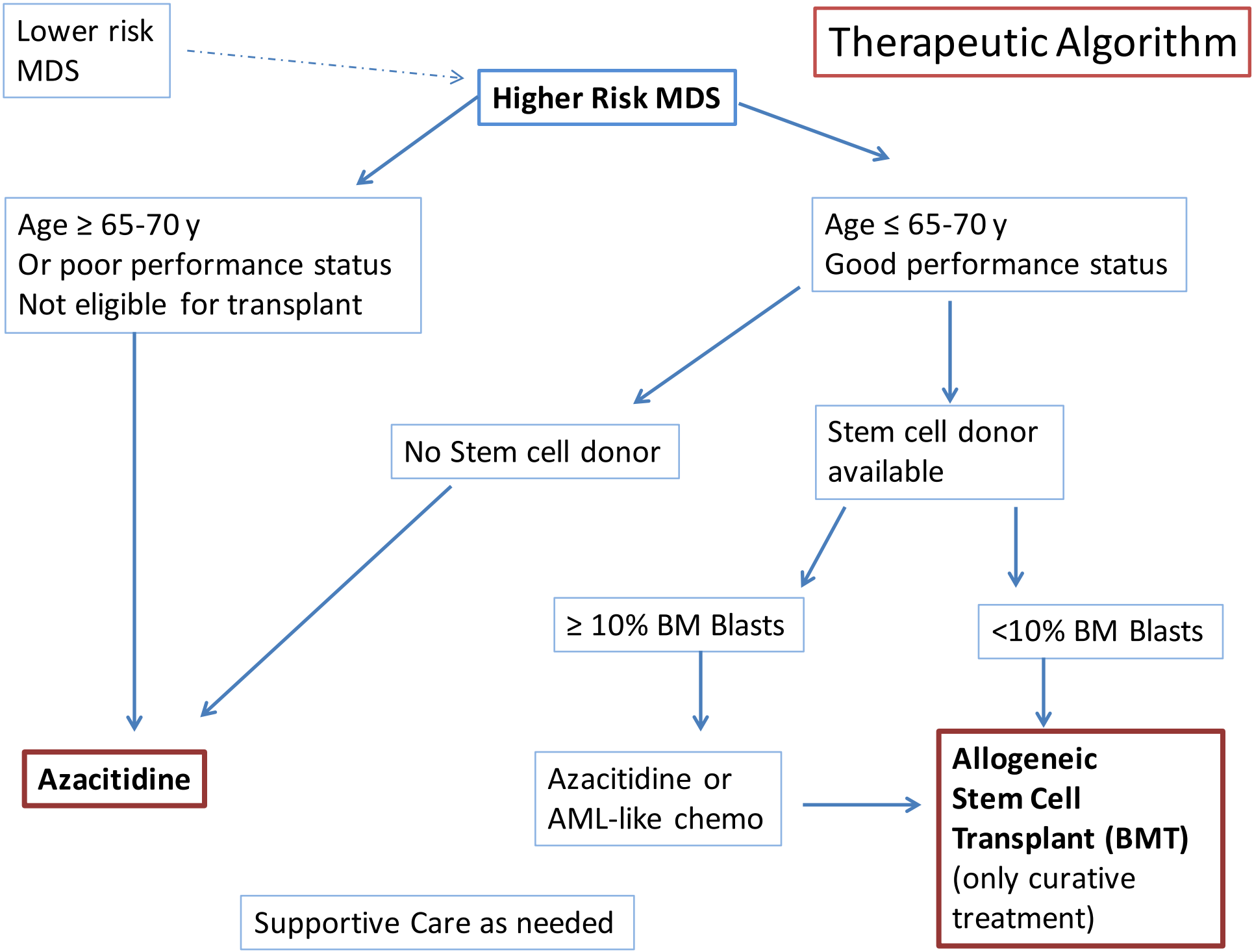




Four years later….

- Gradual decrease in Hb, WBC, ANC and platelets.
- Transfusion dependent
- Lenalidomide stopped
- Bone marrow: MDS, blasts 12%, cytogenetics del (5q)
- Diagnosis: **Refractory Anemia with Excess Blasts-2 (RAEB-2)**
- ?Prognosis
- ?Treatment




Therapeutic Algorithm
Lower risk MDS
Higher Risk MDS
Age ≥ 65-70 y
Or poor performance status
Not eligible for transplant
Age ≤ 65-70 y
Good performance status
No Stem cell donor
Stem cell donor available
≥ 10% BM Blasts
<10% BM Blasts
Azacitidine
Azacitidine or AML-like chemo
Allogeneic Stem Cell Transplant (BMT) (only curative treatment)
Supportive Care as needed

Our Patient: managing progression to high-grade MDS

Rx

- Azacitidine (hypomethylating agent)- Outpatient Rx
  - Inj 75mg/m^2 S/C once a day x 7 days (every 28 days)
- After 3 cycles: repeat BM → no response

Azacitidine increases overall survival.
Response is slow;
Improvement in 50% cases.

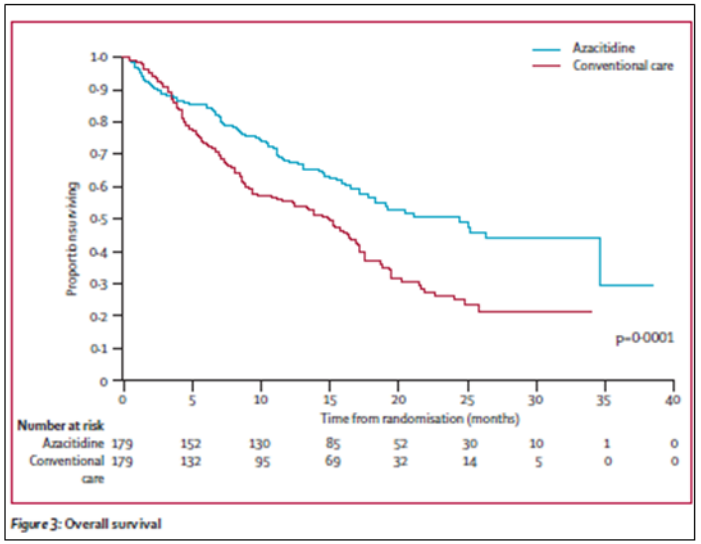


Figure 3: Overall survival

Lancet Oncol 2009

- Admit to HSC – GD6 ward: Intensive chemotherapy (as for AML)
  - ➢ Daunorubicin + Cytarabine
- After 4 weeks: No response, BM Blasts 9.8%.

Further therapy: Allogeneic stem cell transplant

- Matched unrelated donor (MUD) identified
- Risks of transplant explained:
  - Toxicity of procedure
  - Graft versus host disease (GVHD)
  - Relapse of MDS
- Admitted to GD6 for transplant
  - Myeloablative conditioning (to eliminate disease and clones)
  - Infused donor peripheral blood stem cells
  - Hematopoietic recovery in 14 days
- Discharged home: developed GVHD
- Repeat Bone marrow: Normal (100% Donor)
- Outcome:
  - Cured of MDS
  - Suffering from GVHD

Most of the monitoring and support by the CCP Physician and Family doctor

Take Home Messages

- MDS presents with gradual onset of anemia, or other cytopenias, usually in elderly
- Diagnosis should be made in a hematology center, BM exam is critical.
- Therapy is evolving, but majority will be managed primarily with supportive therapy
- The Family physician has a crucial role in managing along with the hematologist

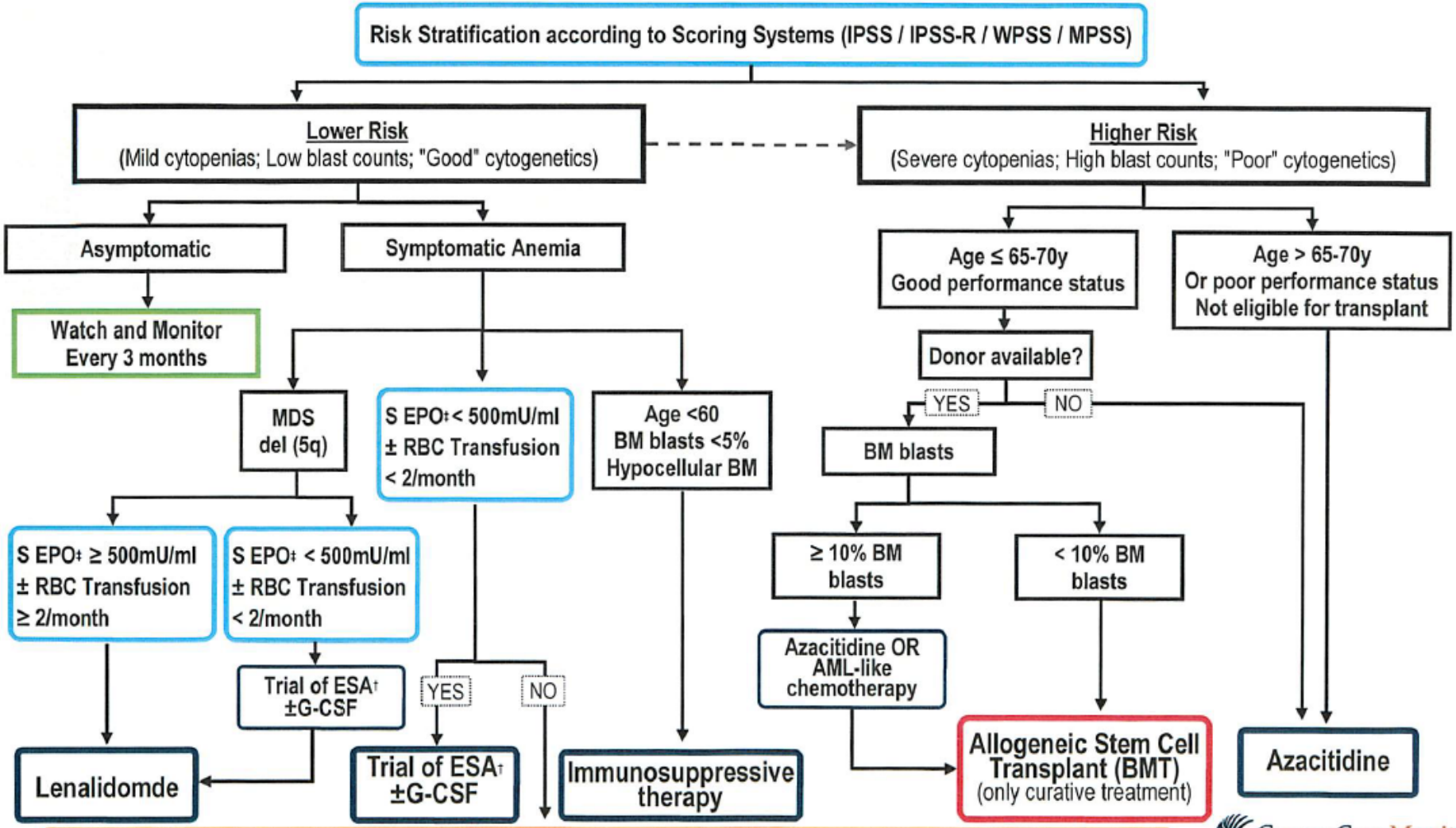
Algorithm for Myelodysplastic Syndrome (MDS)

MDS is one of the causes of cytopenias

Criteria for Observation vs Urgent or Emergent referral given in Algorithms for Anemia, Leucopenia, Thrombocytopenia and Pancytopenia

DIAGNOSIS: Peripheral Blood: (1) Cytopenia(s): Hb<100g/L; Platelets <100x10 /L; ANC <1.8 x10/L AND (2) Bone Marrow (BM): Dysplasia: 10% or more in erythroid, myeloid or megakaryocytes OR Myeloblasts ≥5% (or ≥1% in blood) OR Cytogenetics MDS defining (by conventional karyotyping) (3) Exclude Reactive Causes of dysplasia

MDS more likely in: Elderly (median age 70 years); Unexplained macrocytic anemia; Previous myelotoxic drugs, radiation.
Even normal individuals may have dysplasia. Identification of dysplasia not always reproducible (i.e. inter-observer variation). Diagnosis of MDS should be made in a Hematology Centre.



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†Erythropoietic Stimulating Agents ‡ Erythropoietin

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.

References

- European Leukemia Net. Blood 2013; 122: 2943-2964.
- 2016 WHO Classification. Blood 2016; 127:2391-2405.

MDS Clear Path:
A Canadian physician Consensus
http://www.mdsclearpath.org/

MDS CLEAR PATH

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myelodysplastic Syndromes

Version 1.2016

NCCN.org

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Questions?

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QUESTION

A 64 year man was detected to have hemoglobin 60g/L (requiring 4 units packed cells per month), retics 0.5%, normal leucocytes, platelets, B12, folate and chemistry. Bone marrow shows significant dysplasia, no increase in blasts, chromosome analysis showed deletion 5(q).

What is the best treatment?

a) Hematopoietic stem cell transplant (Bone marrow transplant)
b) Erythropoietin 40,000Units subcutaneous / week.
c) Lenalidomide
d) Azacitidine

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