

Case #2
IRON CHELATION
Treatment Indications
and Approaches

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Case #2 – Introduction

- **68 year-old accountant with low-risk MDS of RA FAB subtype**
 - **BMA:** 3% blasts; hyperplastic erythropoiesis, dysplastic megakaryocytes and granulocytes; and slightly increased iron stores
 - **FBC:** WBC 2400/ μ L (N 42%, L 45%, M 7%, B 2%, E 4%); Hb 8.4 g/dL; MCV 96 fL; Plat 123,000/ μ L
 - **Cytogenetics:** Trisomy 21 with no further abnormalities
 - **EPO:** 512 U/L

International Prognostic Scoring System (IPSS)

Prognostic variable	Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	< 5	5–10		11–20	21–30
Karyotype*	Good	Intermediate	Poor		
Cytopenias⁺	0/1	2/3			

*Karyotype: good: normal, -Y, del(5q), del(20q); poor: complex (≥ 3 abnormalities) or chr 7 anomalies; and intermediate: other abnormalities.

Score	IPSS subgroup	Median survival (years)
0	Low	5.7
0.5–1.0	Int-1	3.5
1.5–2.0	Int-2	1.2
> 2.5	High	0.4

⁺Hb < 10.0 g/dL; ANC < $1.8 \times 10^9/L$; platelet count < $100 \times 10^9/L$

1st Line of Therapy

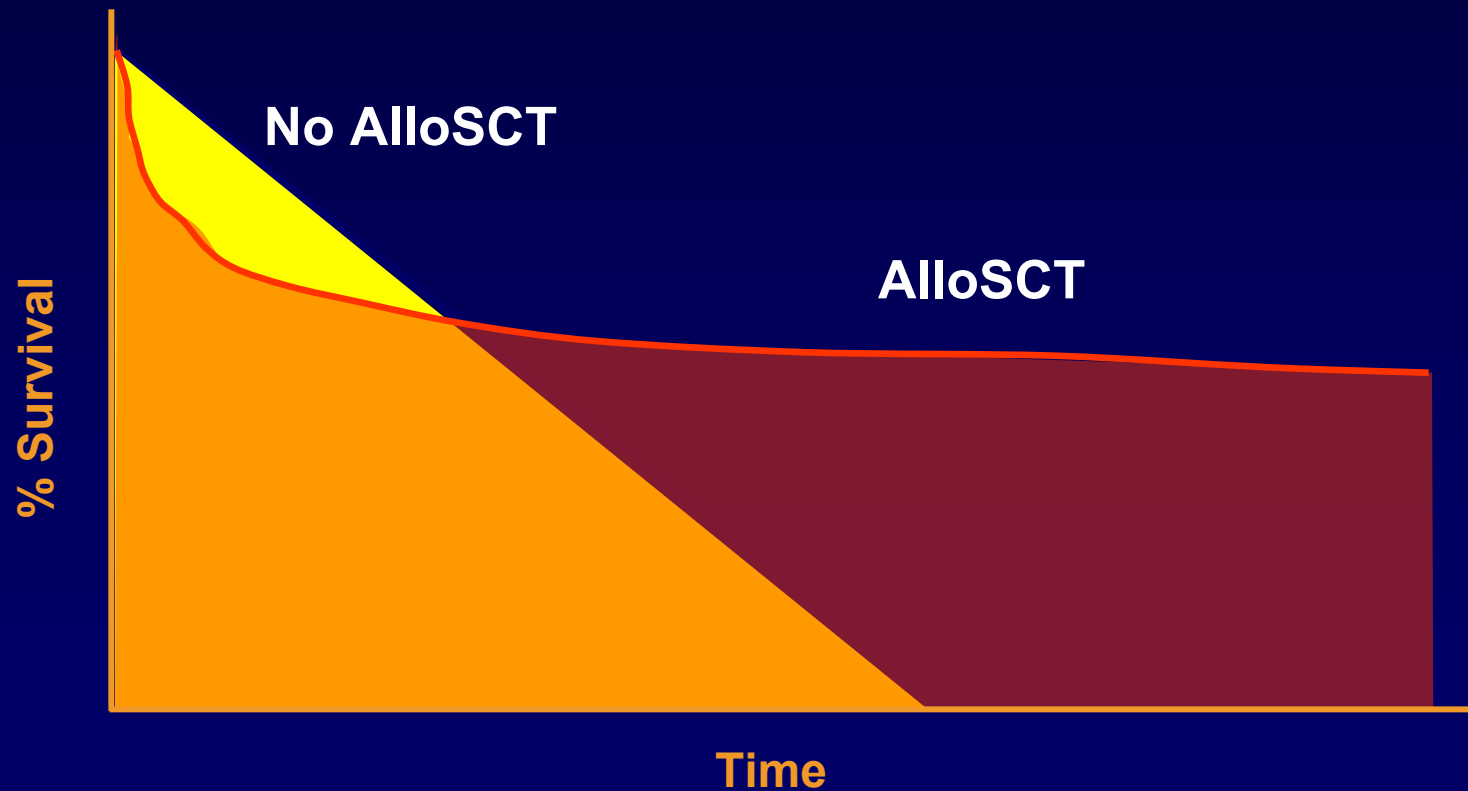
- Treated with regular pRBC transfusions for one year. At this point:
 - Serum ferritin 1600 ng/mL
 - 20 pRBC units
 - Platelets dropped to 89,000/ μ L
 - Feeling relatively well

What would be your approach to this patient's management?

1. Best supportive care
2. I would try erythropoietin
3. I would go for ATG/CsA
4. He is slowly worsening. Because he is in excellent health, I would prepare him for allogeneic stem cell transplantation

4. AlloSCT at this point?

TIME OF ALLO-SCT

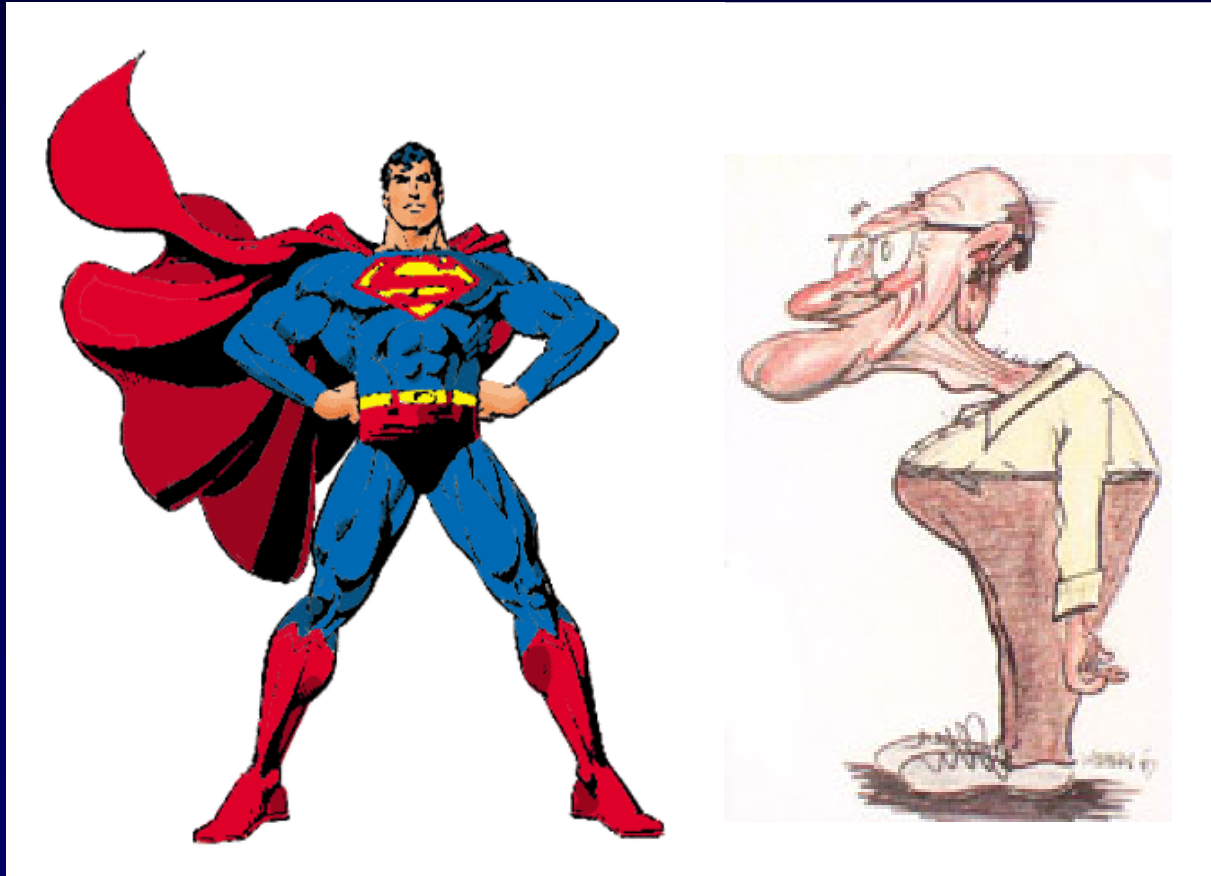


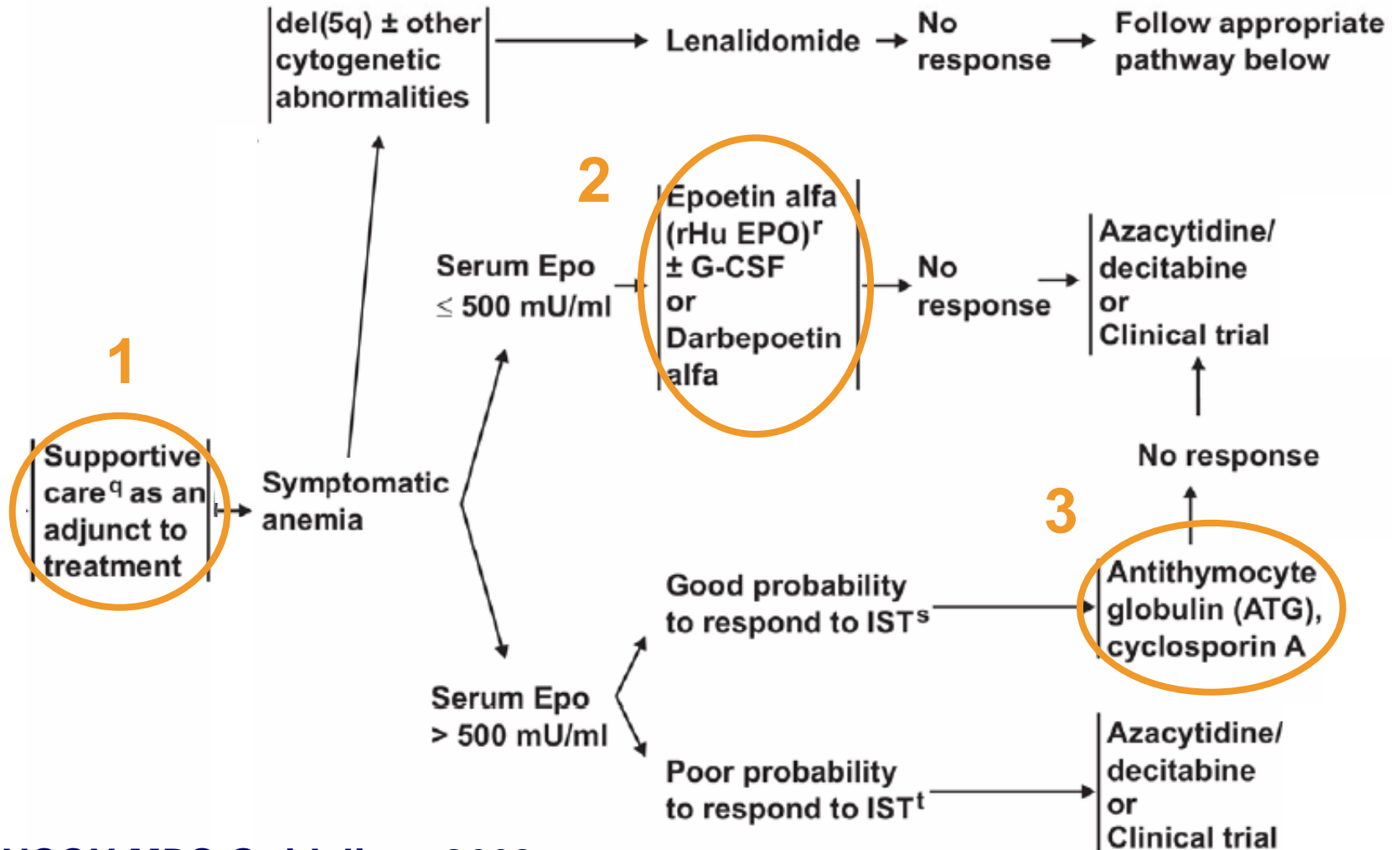
4. AlloSCT at this point?

TIME OF ALLO-SCT

	Immediate	At progression
Low	6.51	7.21
Int-1	4.61	5.16
Int-2	4.93	2.84
High	3.20	2.75

4. AlloSCT at this point?





NCCN MDS Guidelines 2008

What would be your approach to this patient's management?

1. Best supportive care

- Patient remained on pRBC transfusions
- HLA-typing was performed and an unrelated HLA-identical donor was found
- He remains on chronic blood transfusions

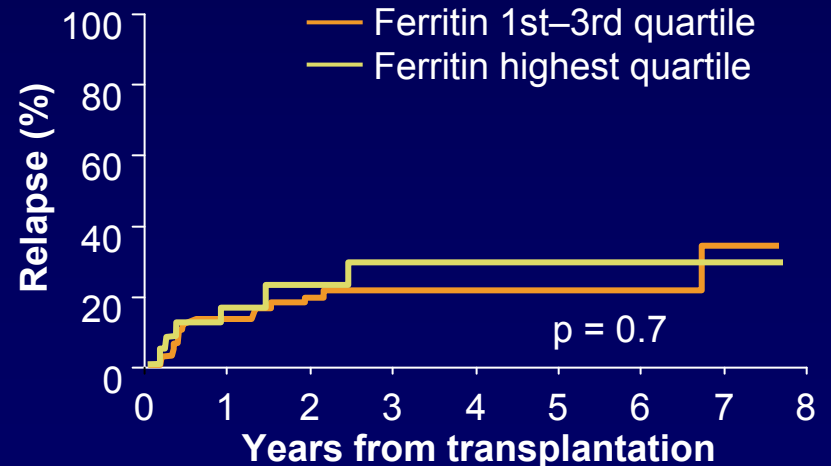
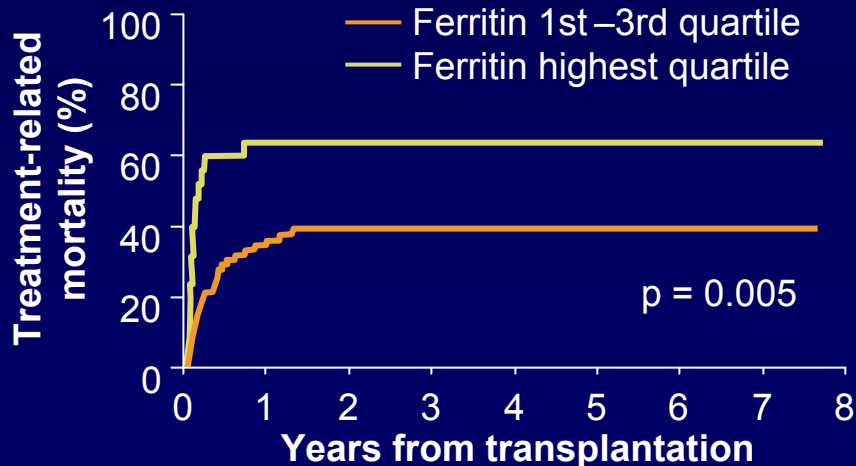
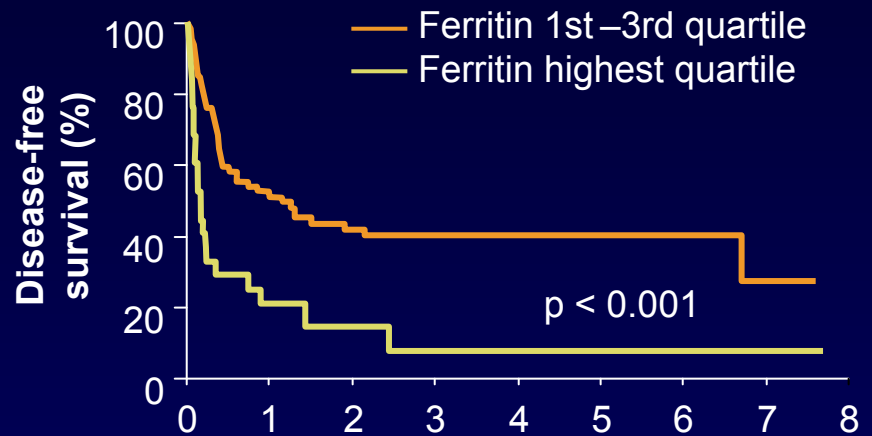
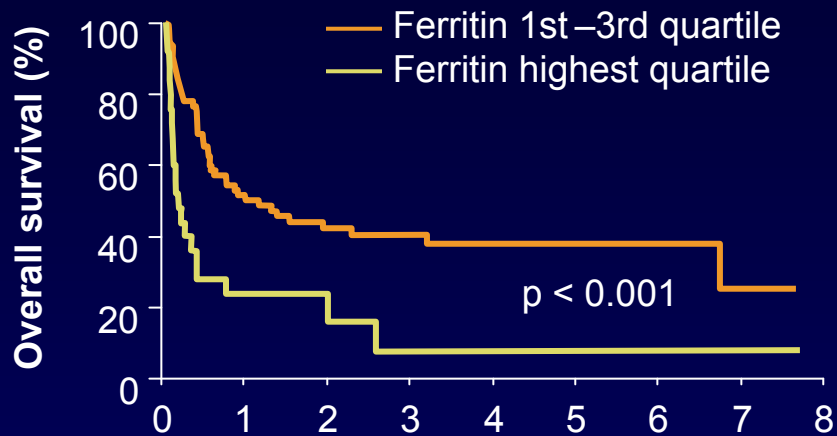
What would be your approach to iron overload in this patient?

- 1. He is a high-risk patient. Iron chelation is not indicated.**
- 2. Iron chelation will be indicated after alloSCT.**
- 3. Iron chelation should be started right away to reduce the alloSCT-related risk.**

Impact of iron overload in early toxicity, infections and mortality after SCT

- **IOL (high Ferritin & Transferrin Saturation) associate with TRM and OS**
- **IOL associates with mucositis, bacteraemia and days with fever**
- **Liver IOL (biopsy at autopsy) associates with invasive aspergillosis (*RR=9; p=0.035*)**
- **Effect apparently restricted to AutoSCT**

Outcome According to Serum Ferritin Level



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Which drug(s) would you use to chelate this patient?

1. Deferoxamine (Desferal®)
2. Deferiprone (Ferriprox®)
3. Deferasirox (Exjade®)
4. Deferoxamine in combination with deferiprone
5. Deferoxamine in combination with deferasirox

Overview of Deferoxamine

Property	Deferoxamine (DFO)
Usual dose	25–60 mg/kg/day
Route	SC, IV 8–12 h, 5 days/week
Half-life	20–30 min
Excretion	Urinary, faecal
Adverse effects	Local reactions, ophthalmologic, auditory, growth retardation, allergic
Status	Licensed
Approved indications	Treatment of chronic iron overload due to transfusion-dependent anaemias

Overview of Deferiprone

Property	Deferiprone
Usual dose	75 mg/kg/day
Route	Oral 3 times daily
Half-life	3–4 h
Excretion	Urinary
Adverse effects	GI disturbances, agranulocytosis/ neutropenia, arthralgia, elevated liver enzymes
Status	Not licensed in USA or Canada
Approved indications	Thalassaemia

Overview of Deferasirox

Property	Deferasirox
Usual dose	20–30 mg/kg/day
Route	Oral once daily
Half-life	8–16 h
Excretion	Faecal
Adverse effects	GI disturbances, rash, mild non- progressive creatinine increase, ophthalmologic, auditory, elevated liver enzymes
Status	Licensed
Approved indications	Treatment of chronic iron overload due to frequent blood transfusions

Which drug(s) would you use to chelate this patient?

1. Deferoxamine (Desferal®)
2. Deferiprone (Ferriprox®)
3. **Deferasirox (Exjade®)**
4. Deferoxamine in combination with deferiprone
5. Deferoxamine in combination with deferasirox

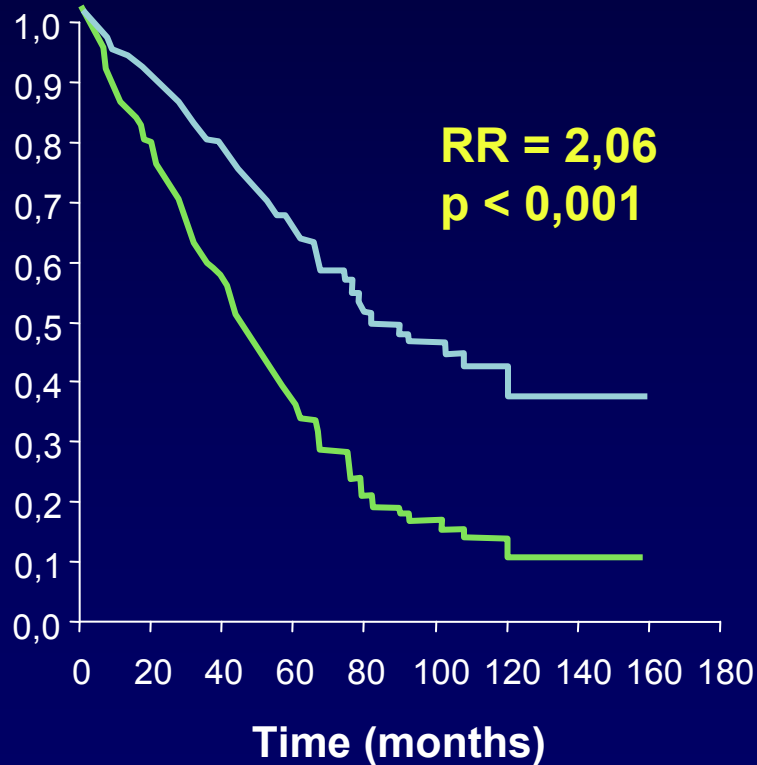
Generally speaking, which MDS patients do you feel should get iron chelation therapy?

1. Only patients under the age of 65
2. Only patients with hereditary transfusion dependency (e.g. sickle cell anemia or thalassemia)
3. All patients with iron overload (i.e. high ferritin) regardless of age and disease status
4. In MDS, I would base my decision according to risk group and overall survival prognosis

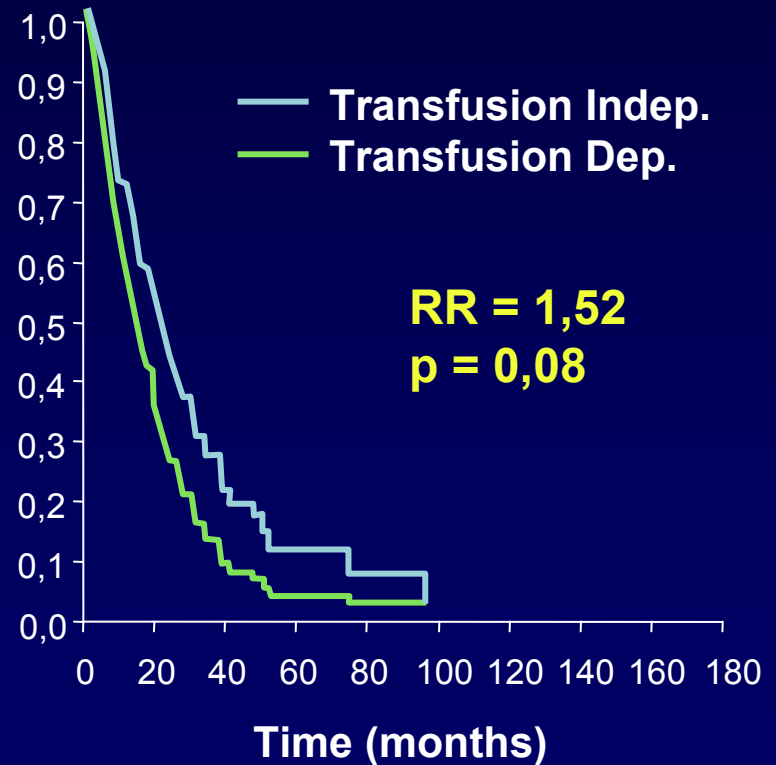
Transfusion Dependency - Iron Overload & Survival in MDS: Percentage of Blasts

N= 457

No Excess Blasts MDS



Excess Blasts MDS



Iron Chelation & Survival in MDS

- Retrospective analysis in 178 MDS patients
- Overall survival prognostic factors:
 - IPSS ($P < 0.008$)
 - Iron chelation ($P < 0.02$)

SURVIVAL	Chelation (n= 18)	No chelation (n=160)	<i>p</i>
Median (months)	NR at 160	40	<0.03
% at 4 years	80	44	0.02

Iron Chelation & Survival in MDS

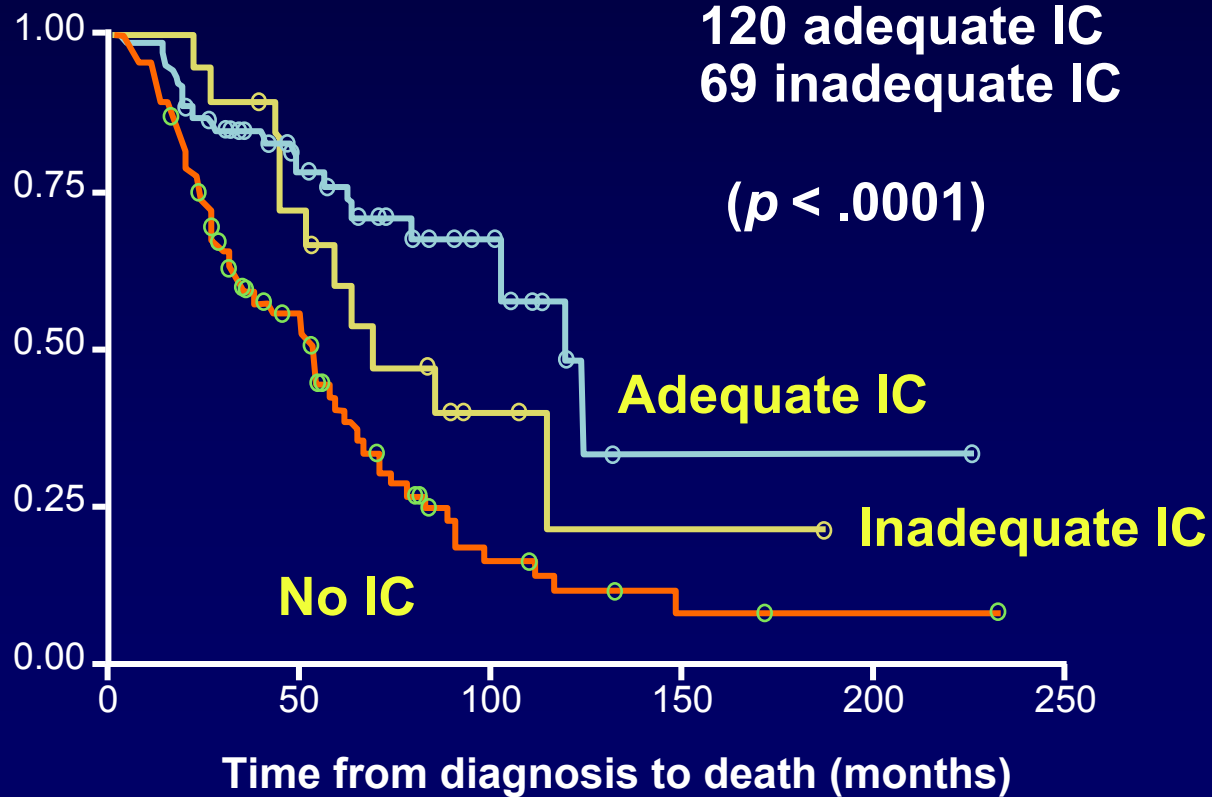
- **Prospective analysis in 165 MDS patients from 18 French centers**
- **Patients referred for transfusion during a 1 month period in 2005**
- **Follow-up and analysis of survival May 07**
- **Chelation:**
 - Adequate n=57
 - Inadequate n=19
 - No chelation n=89

Patients characteristics

	All (n=165)	No IC (n=89)	IC (n=76)	<i>p</i>
Age	73	76	70	0.006
Transfusions	49	43	76	<0.001
IPSS				
- Low	39%	27%	49%	0.044
- Int-1	44%	54%	36%	
- Int-2 / High	17%	19%	15%	

Survival by IC

Median OS: 63 months All cases
51 months No IC
115 months any IC
120 adequate IC
69 inadequate IC



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