

Myelodysplastic Syndromes

Karen WL Yee, MD, FRCPC

Division of Medical Oncology & Hematology
Princess Margaret Hospital



Overview

- Myelodysplastic Syndromes (MDS)
- Risk-Based Treatment Strategies in MDS:
 - Lower (Low & Int-1) Risk
 - Lenalidomide
 - Iron Chelation
 - Higher (Int-2 & High) Risk
 - Hypomethylating Agents

Myelodysplastic Syndrome (MDS)

- Heterogeneous group of disorders where the bone marrow fails to produce healthy blood cells => ↓ red blood cells, ↓ white blood cells &/or ↓ platelets
- Hypercellular bone marrow - abnormal increase in the number of (abnormal appearing) cells present in the bone marrow

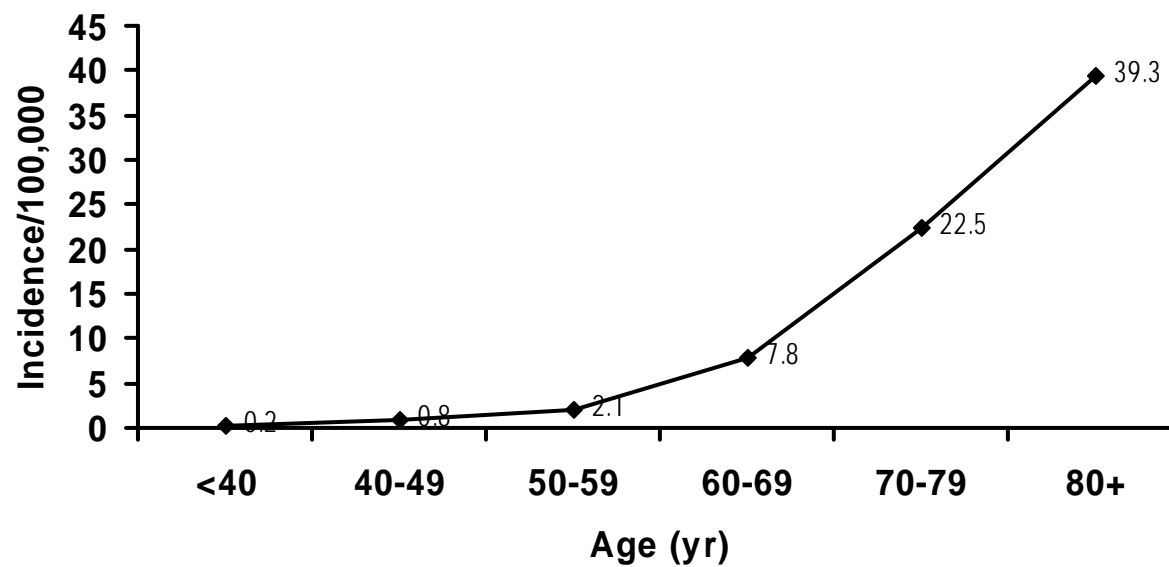
Myelodysplastic Syndrome (cont'd)

- Can lead to accumulation of blast cells (immature or so called leukemic cells) in the bone marrow
 - MDS: <20% blast cells
 - Acute myeloid leukemia (AML): >20% blast cells

MDS: Epidemiology

- Exact number of people with MDS is unknown as it can go undiagnosed
- USA SEER Estimates (2001-2003):
Incidence: 14,648 cases/yr (2003)
- Canadian estimates:
Incidence: 1,628 cases/yr ??

MDS Age-Specific Incidence Rates (2001-2004)



Statistics Canada 2006
NCI-SEER 2006
National Vital Stats 2006

Prognostic Indicators in MDS:

International Prognostic Scoring System (1997)

International Prognostic Scoring System (IPSS) Risk Classification

Prognostic Variable	Score Value				
	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	—	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, ≥ 2.5 .

* Good, normal, $-Y$, $\text{del}(5q)$, $\text{del}(20q)$; Poor, complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

Survival & Risk of AML Evolution by IPSS Score

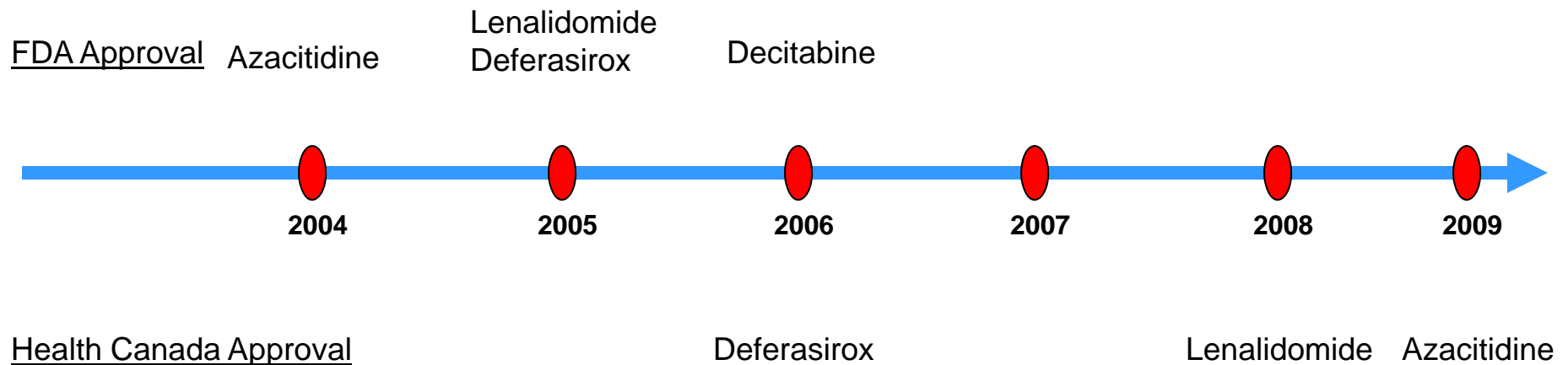
	IPSS Risk Group			
	Low	Int-1	Int-2	High
Score	0	0.5–1.0	1.5–2.0	≥ 2.5
Lifetime AML Evolution	19%	30%	33%	45%
Median Years to AML [†]	9.4	3.3	1.1	0.2
Median Survival (years)	5.7	3.5	1.2	0.4

[†] Time to 25% of patients evolving to AML

Goals of Therapy in MDS

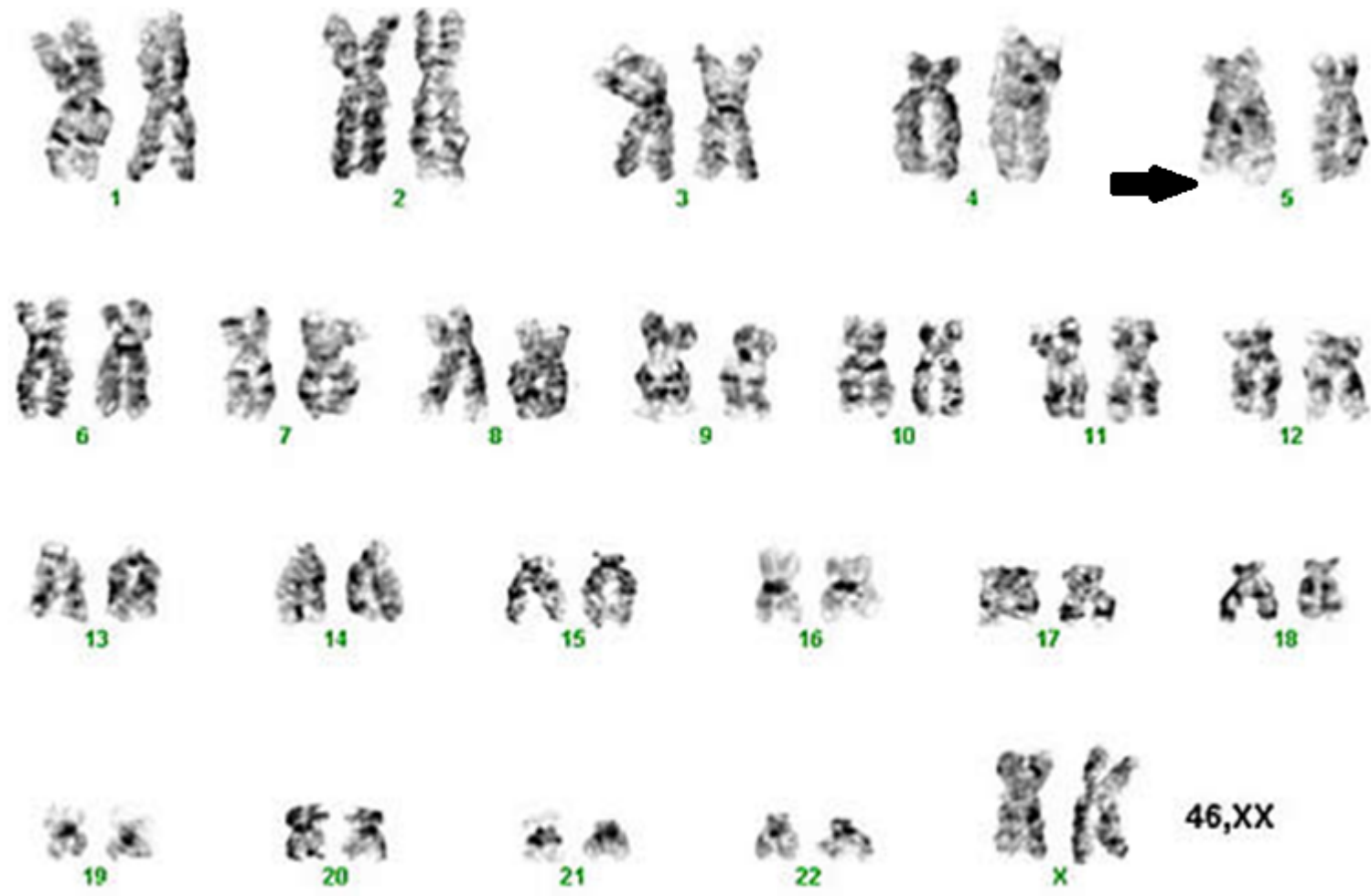
- Based on age, functional status, other medical conditions, and IPSS risk group
- Decrease disease-related complications (improve blood counts)
- Improve quality of life
- Change the natural history of disease (increase survival; delay leukemic transformation; potential for cure)

New Drug Approval Timelines



Lenalidomide in patients with
lower-risk MDS &
del(5q) abnormalities

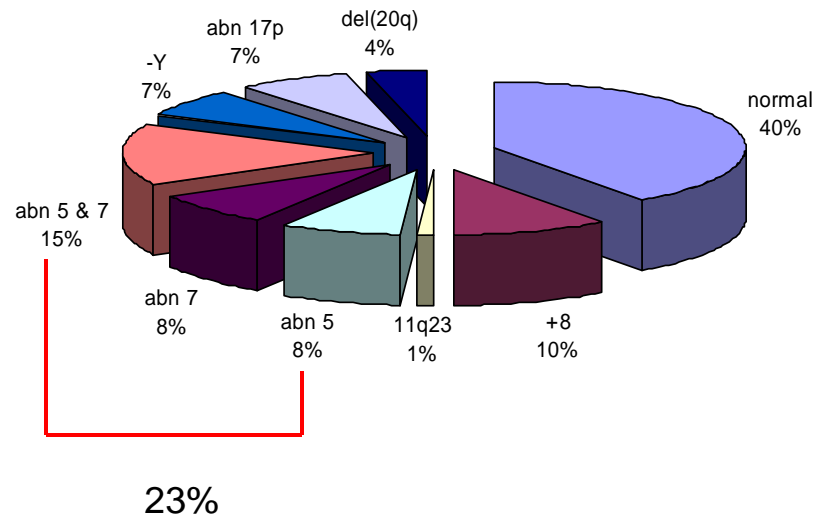
Cytogenetics --



Cytogenetic analysis reveals loss of a portion of the long arm of chromosome 5.

Chromosomal Abnormalities

De novo MDS



MDS-003:

Phase II Lenalidomide in **del(5q)** MDS

Lenalidomide
(n=148)

Transfusion-Independence

99 (67%)

Complete Remission

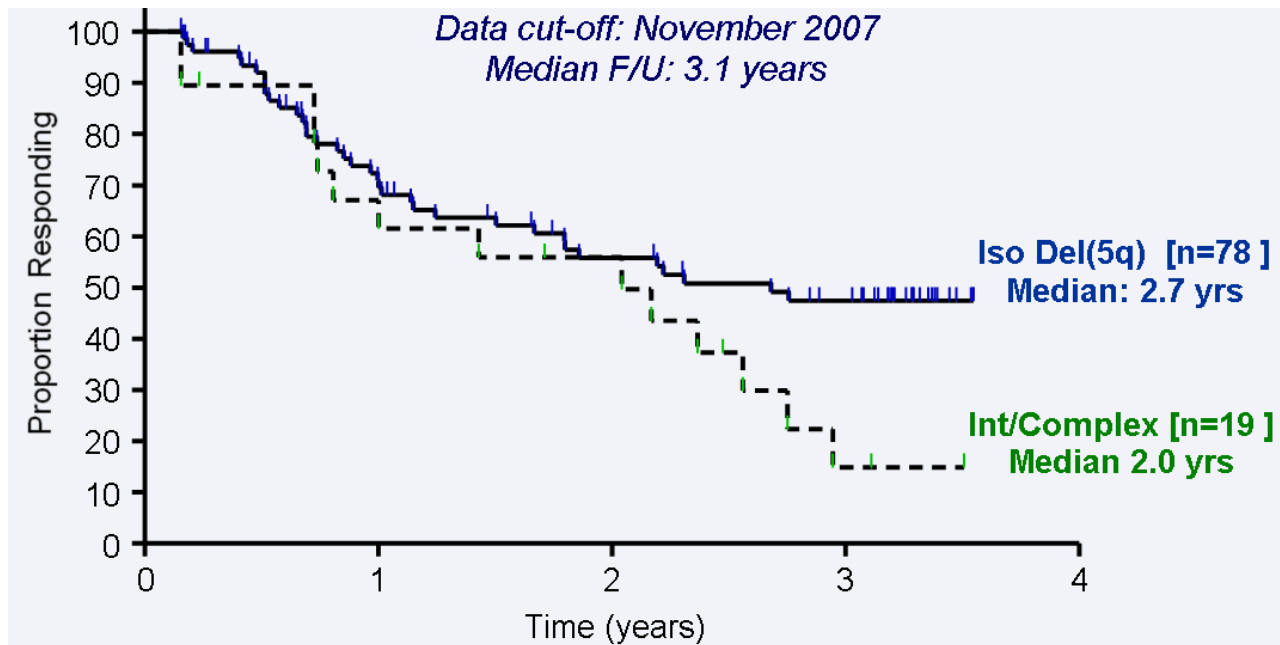
38 (36%)

Median time to response 4.6 wks; Median max. Hgb 134 g/L

Median F/U >26 mos; Median response duration is not reached (> 104 wks)

Response adversely affected by baseline ↓plt & > 4U PRBCs/8 wks; Cytogenetic response correlated with transfusion-independence

Duration of Major Erythroid Response Isolated del(5q) v Int/Complex [N=97]



§Symbols are censored patients who remain TI at time of data cut-off or at time of study discontinuation.

MDS-004: Phase III Lenalidomide in del(5q) MDS

N=205

- Low or Int-1 MDS
- Transfusion-dependent
- Del 5q
- Lenalidomide naïve

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Lenalidomide 5 mg/d x 28d (N=69)

Lenalidomide 10 mg/d x 21/28d
(n=69)


Placebo (N=67)

Stratify:

- IPSS
- Cytogenetic complexity

Responders (after 16 wks of treatment) continued treatment until erythroid relapse or disease progression; Crossover permitted for nonresponders (after 16 wks of treatment) on placebo and lenalidomide 5 mg/d arms

MDS-004: Response & Tolerance

	Placebo (N=51)	LEN 5 mg (N=46)	LEN 10 mg (N=41)
RBC Transfusion Independence (TI \geq 26 wks)	3 (6%)	19 (41%)*	23 (56%)* 
Hematologic AEs \geq grade 3			
Neutropenia	15%	74%	75%
Thrombocytopenia	2%	33%	41%
Dose Reduction	0	52%	58%
Discontinuation due to AEs	5%	16%	9%

* $P < 0.001$ v placebo; *** $P = 0.01$ v placebo

Long-Term Outcomes

- Median F/U 36 mos
- 22% patients progressed to AML (median time to progression not reached)
- 48% patients have died
 - Median OS 3.68 y
 - OS_{3y} 56%
- Achievement of RBC-TI for ≥ 26 weeks with lenalidomide was associated with \downarrow risk of AML progression & death ($P=0.021$)

Predictors of Response to Lenalidomide in del(5q) MDS Patients

MDS-003 Study		
Variable	Odds Ratio	<i>P</i>
Decline in platelets ($\geq 50\%$ v $< 50\%$)	4.68	0.008
Decline in ANC ($\geq 75\%$ v $< 75\%$) [†]	4.56	0.056

[†] In patients with normal baseline ANC; ANC – absolute neutrophil count

MDS-002:

Phase II Lenalidomide in **nondel(5q)** MDS

Lenalidomide
(n=214)

Transfusion-Independence

56 (26%)

Complete Remission (n=105)

1 (1%)

*as defined by IWG criteria 2000

Median time to beginning of transfusion-independence 4.8 wks (range, 1-39 wks); Median max Hgb 116 g/L

Median F/U 19 mos (n=56 transfusion-independent responders);

Median response duration 10.2 mos [20 (36%) pts had response duration > 1 y]

Of the 56 patients who achieved TI: 45 (80%) good karyotype; 10 (18%) intermediate; 0 poor

Comparison of Responses to Lenalidomide: del(5q) vs nondel(5q) MDS

	MDS-003: Del(5q) MDS (n=148)	MDS-002: Nondel(5q) MDS (n=214)	
Transfusion Response	112 (76%)	93 (43%)	←
Transfusion-Independence (TI)	99 (67%)	56 (26%)	←
> 50% reduction in transfusion	13 (9%)	37 (17%)	
Median time to response	4.6 wks	4.8 wks	←
Median response duration (TI)	26 mos	10.2 mos	
Grade 3/4 neutropenia	81 (55%)	54 (25%)	
Grade 3/4 thrombocytopenia	65 (44%)	43 (20%)	

MDS-005: Phase III Lenalidomide in non-del(5q) MDS

N=375 (2:1 randomization in favor of lenalidomide)

- Low/Int-1 risk
- Non-del(5q)
- Not responsive to ESAs *or* EPO > 500 U/L
- RBC transfusion dependent

Primary Outcomes:

- Proportion of subjects that become transfusion independent
- Proportion of subjects with an erythroid differentiation gene expression signature that become transfusion independent

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Lenalidomide 10 mg daily

Placebo

Recommendations for Lenalidomide

- Low/Int-1 risk red cell transfusion-dependent *de novo* MDS with interstitial deletion involving 5q31
- Recent data suggest administering lenalidomide 10 mg as a starting dose, with dose reductions or discontinuations if needed
- Role in Low/Int-1 risk red cell transfusion-dependent *de novo* MDS without interstitial deletion involving 5q31 is currently being evaluated

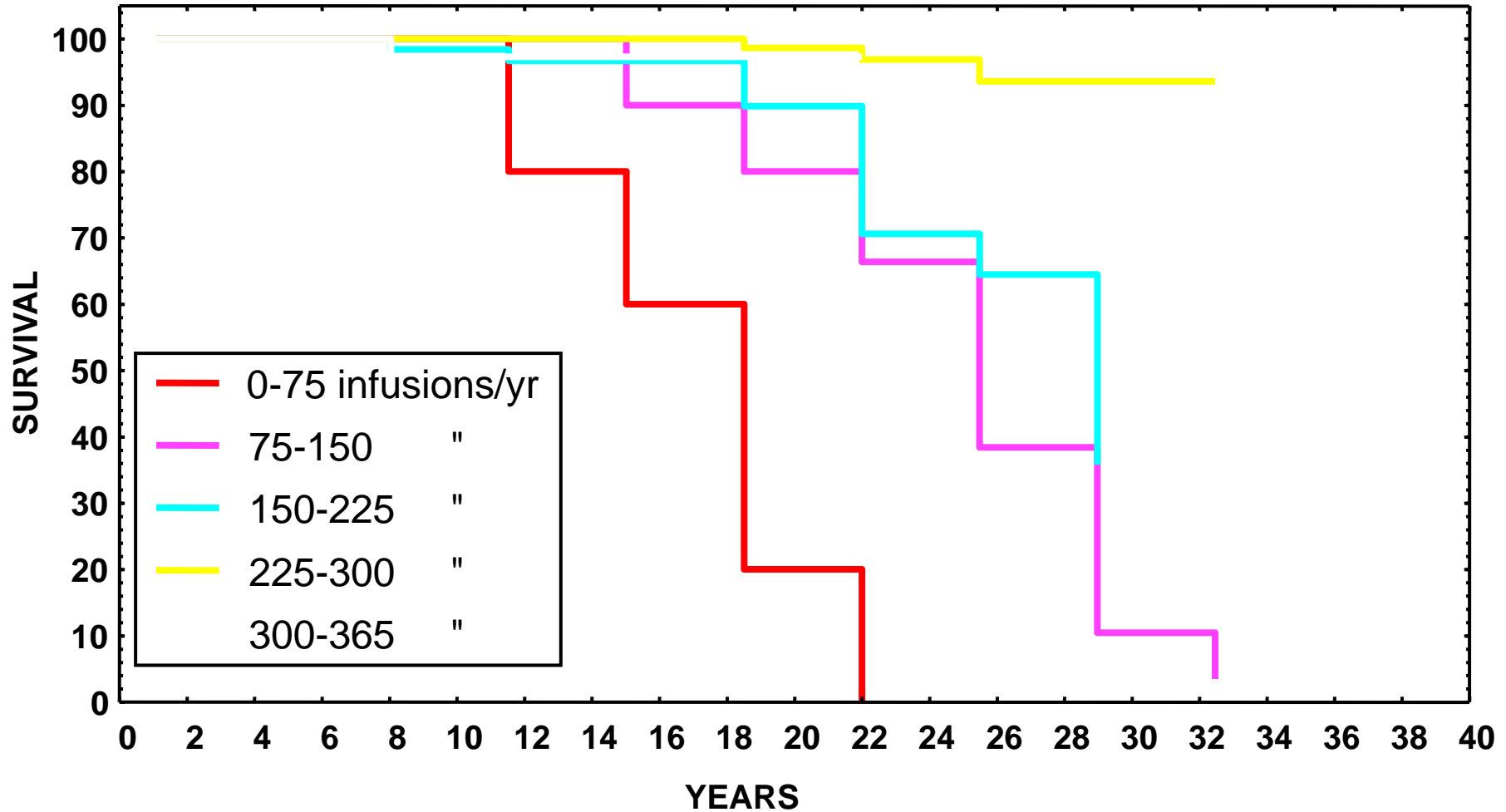
What is the role for iron
chelation therapy in patients
with MDS?

Evidence for Iron Chelation in MDS

- Paucity of prospective data in MDS – most extrapolated from hemoglobinopathies
- Retrospective studies indicating complications from secondary hematochromatosis in patients with MDS (n \approx 120) *Schafer et al. 1982; Jaeger et al. 1992; Cazzola et al. 1988; Jensen et al. 2003; Ferte et al. 2006*
- Shorter OS for transfusion-dependent patients than those not requiring transfusions ($p < 0.001$) *Malcovati et al. 2005*
- Retrospective study indicating IPSS score (Low/Int-1; $p < 0.008$) & iron chelation ($p < 0.02$) predictive of OS on multivariate analysis (160 mos vs 40 mos) *Leitch et al. 2006*

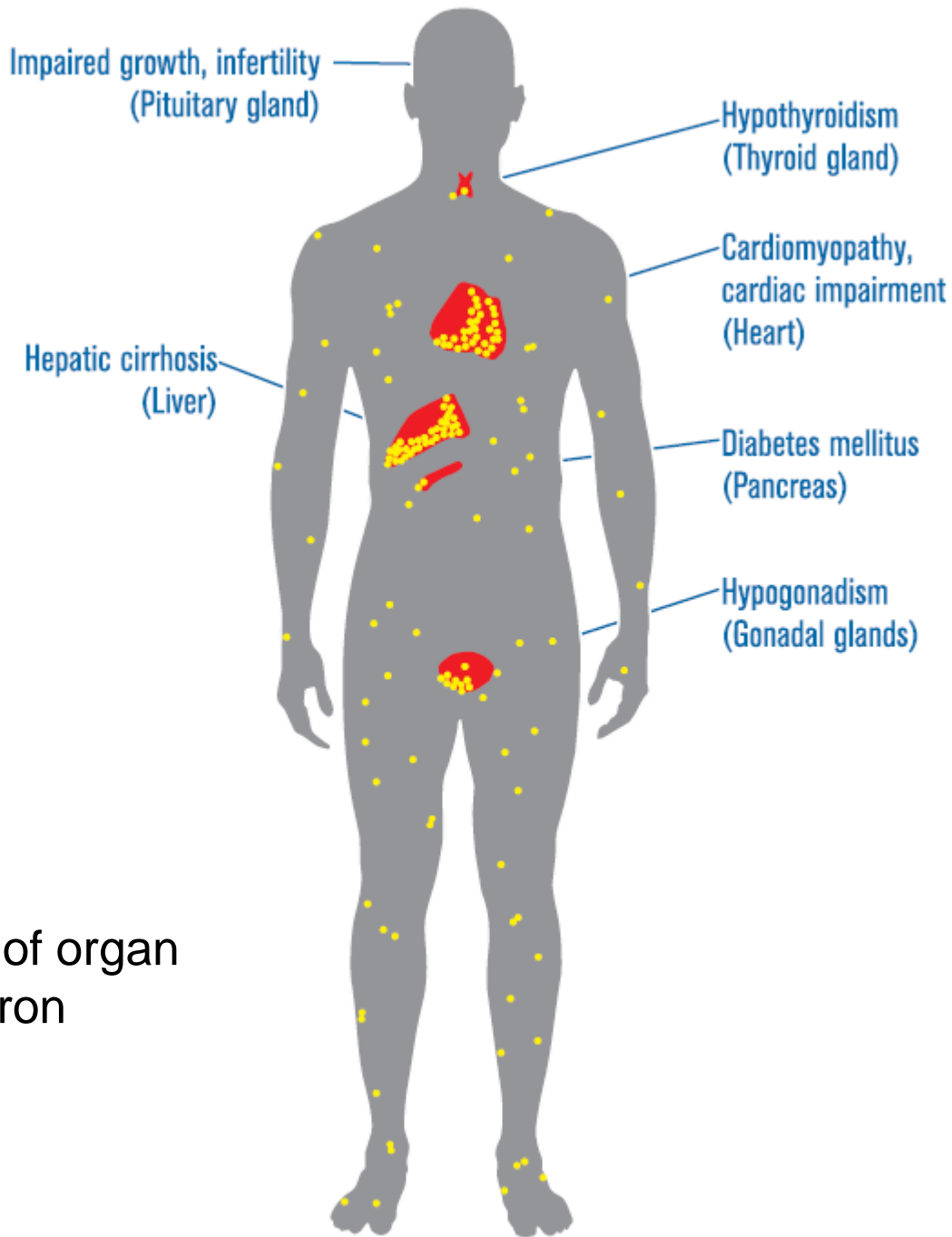
Impact of Compliance on Effectiveness of Therapy with Deferoxamine

Kaplan-Meier Analysis of Survival in 257 Consecutive Thalassemic Patients
According to the Mean Compliance with s.c. DFO Therapy



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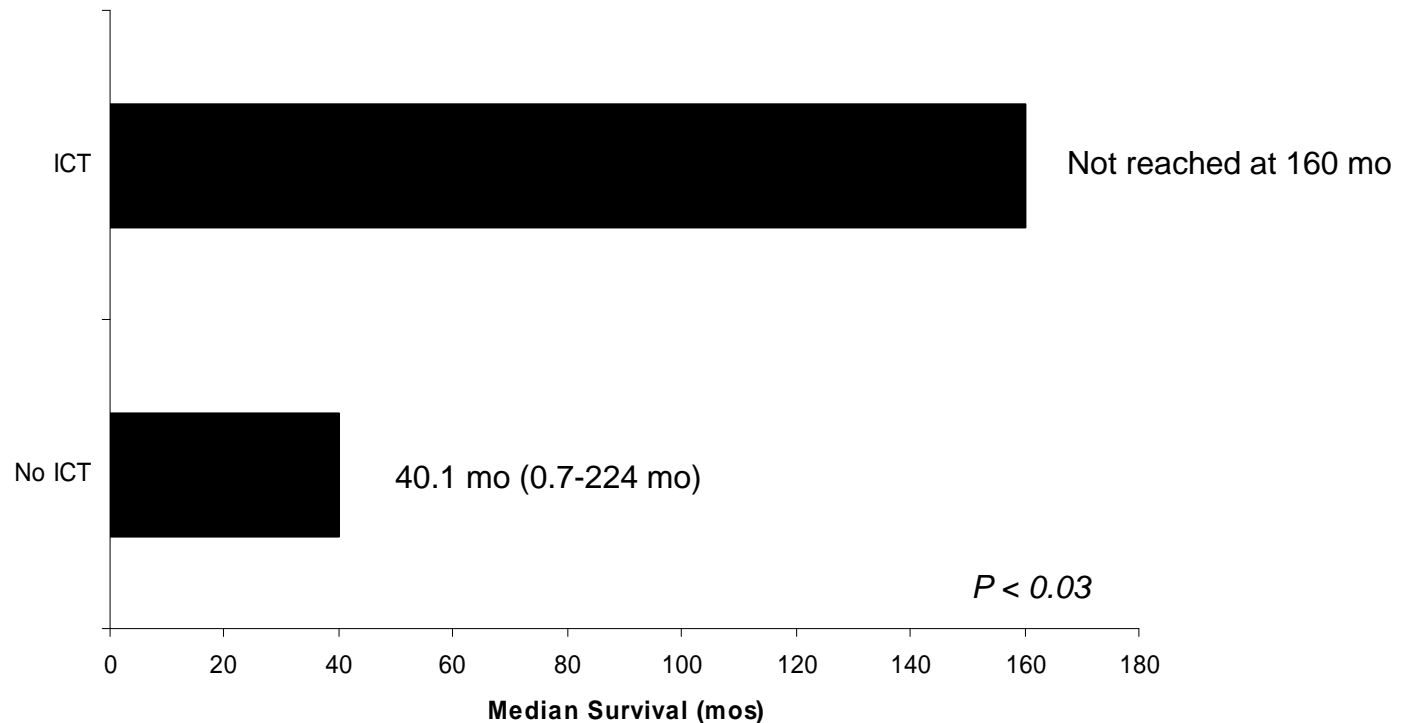
Potential sites of organ
damage from iron
overload

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Improved Survival in Low/Int-1 MDS Patients Receiving Iron Chelation Therapy (ICT)

In Cox-regression analysis, the only factors significant for OS were IPSS score ($p < 0.008$) and ICT ($p < 0.02$)



For patients with Low and Int-1 MDS, ICT was associated with a significant improvement in overall survival

Evidence for Iron Chelation in MDS (cont'd)

- Retrospective analysis of MDS alloSCT recipients (n=103) indicated that high pre-transplant ferritin levels associated with increased risk of death (p=0.003) and TRM (p=0.002) *Armand et al. 2007*

Goals of Iron Chelation Therapy

- Prevention of end-organ damage due to excessive tissue iron deposition (hepatic, cardiac, endocrine)
- Reversal of end-organ damage due to excessive tissue iron deposition (hepatic, cardiac, endocrine)
- Improve overall survival
- Improve quality of life
- Improve hematopoiesis?

Who should receive iron
chelation therapy?

When should iron chelation
therapy be initiated?

Recommendations for Iron Chelation

- Consider iron chelation in transfusion-dependent patients with MDS:
 - (a) IPSS score Low/Int-1 or WHO classification RA, RARS, 5q-syndrome & are candidates for alloSCT or have life expectancy > 1 year
 - (b) IPSS score Int-2/High & are candidates for alloSCT or have life expectancy > 1 year
- Initiate iron chelation when:
 - (a) have received at least 20 units of PRBCs &
 - (b) ferritin > 1000 $\mu\text{g/L}$ and transferrin saturation > 0.5, or
 - (c) evidence iron-related organ damage

Recommendations for ICT (cont'd)

- Deferoxamine 20-50 mg/kg/d sc or IV infusion over 12-15 hours or by sc bolus injections bid 5 days/week

OR

- Deferasirox 20-30 mg/kg/d orally daily

Iron status monitoring while on iron chelation therapy – ferritin q3months

TELESTO: Phase III Deferasirox in MDS

N=630 (2:1 randomization in favor of deferasirox)

- Low/Int-1 risk
- Ferritin > 1000 $\mu\text{g/L}$ & < 3500 $\mu\text{g/L}$ at screening
- 20 - 75 PRBC transfusions
- Chelation naïve

Primary Outcome:

EFS (i.e. composite primary endpoint incl. death & non-fatal events related to cardiac & liver function) in patients receiving deferasirox vs placebo

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Deferasirox (N=315)

Placebo (N=315)

The role of hypomethylating agents in patients with MDS

Hypomethylating Agents:

(a) Azacitidine

(b) Decitabine

AZA-001: Phase III Azacitidine in Higher-risk MDS

Physician Choice of 1 of 3
Conventional Care Regimens

1. BSC only *or*
2. LDAC (20 mg/m²/d sc x 14/28-42d) *or*
3. 3+7 induction + 1-2 consolidations

Stratify:

- FAB – RAEB, RAEB-T, CMML
- IPSS – Int-2, High

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Azacitidine 75 mg/m²/d x 7/28-35d
(N=179)

Conventional Care Regimens
(N=179)

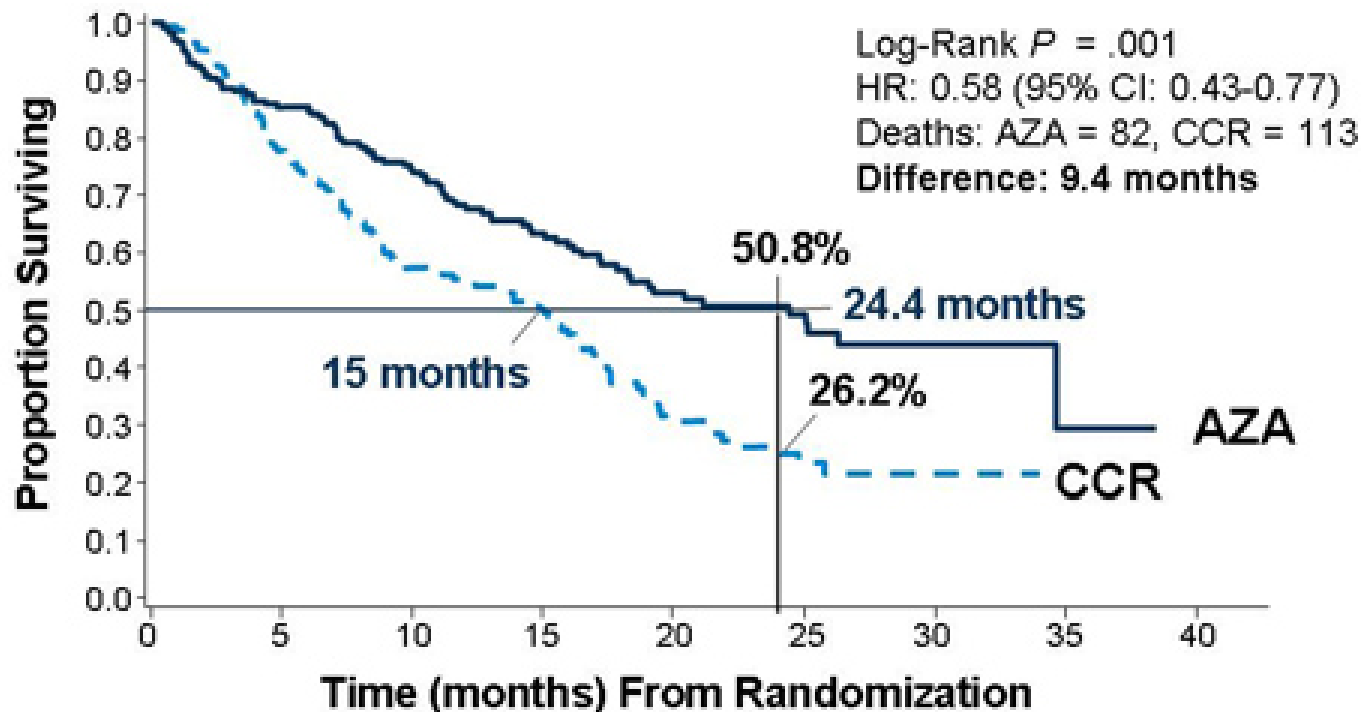
Treatment continued until unacceptable toxicity or AML transformation or disease progression

AZA-001: Response Rates

	Azacitidine (n=179)	CCR (n=179)
Overall Response (CR+PR, %)	29	12
CR	17	8
PR	12	4

Azacitidine was administered for a median of 9 cycles; 81% achieved a first response by 6 cycles & 90% achieved a first response by 9 cycles

Overall Survival: Azacitidine vs CCR ITT Population



Number at

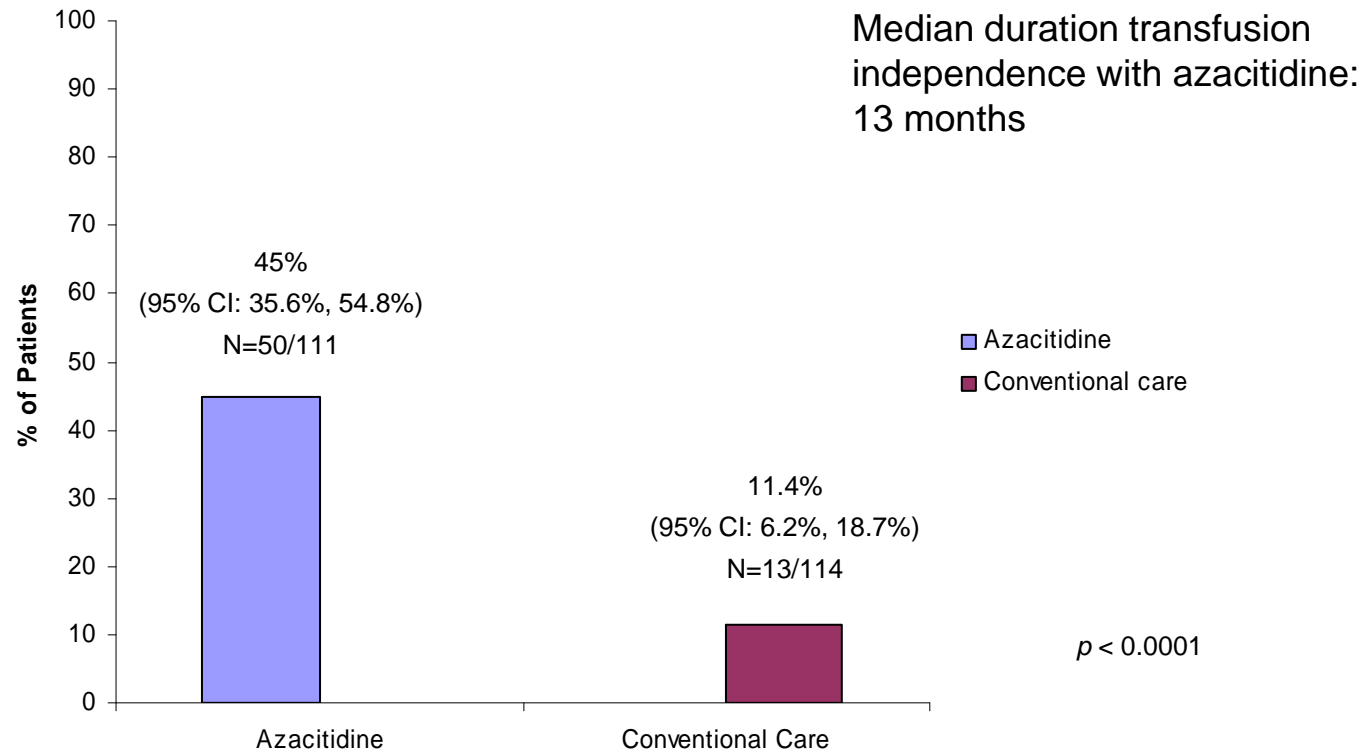
Risk

AZA	179	152	130	85	52	30	10	1
CCR	179	132	95	69	32	14	5	0

Azacitidine Prolongs Time to Development of AML or Death

	Azacitidine (n=179)	CCR (n=179)	<i>P</i> value
Time to AML or Death (mos)	13	7.6	0.003
Time to AML (mos)	26.1	12.4	0.004

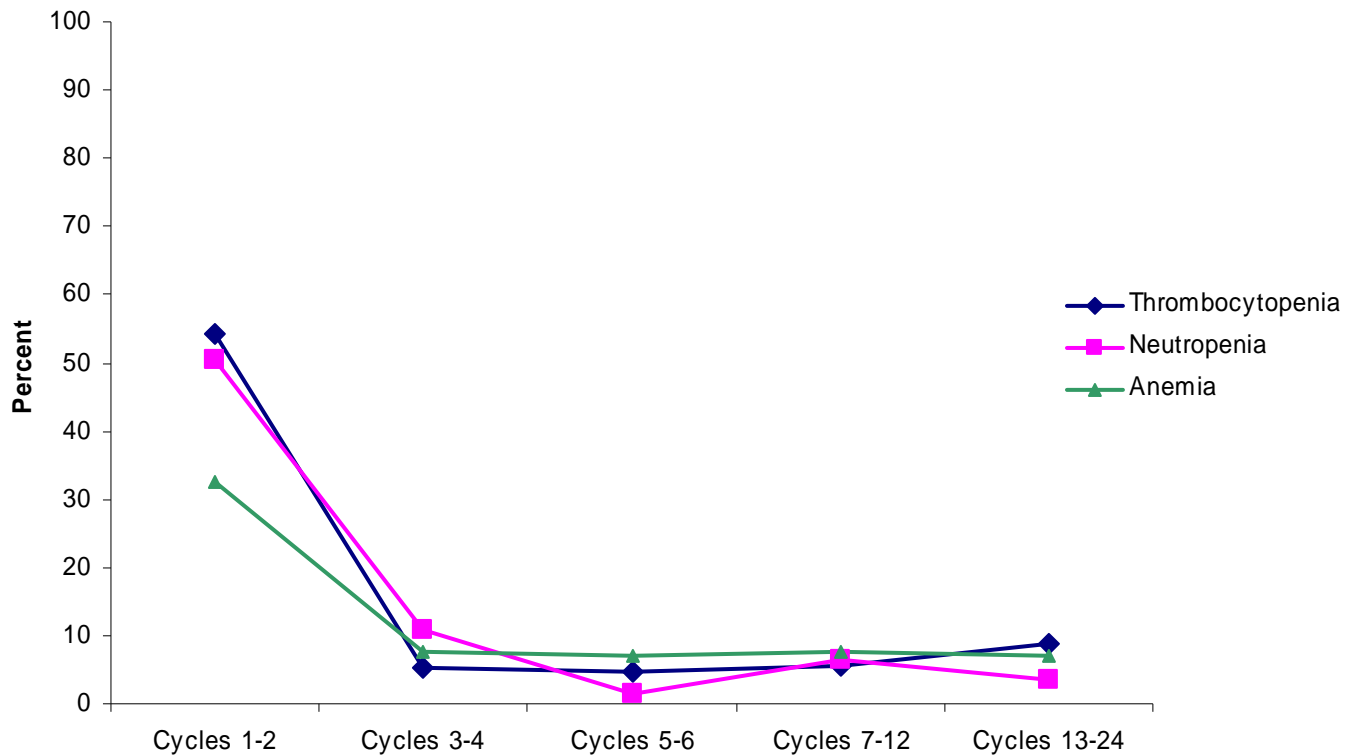
Azacitidine & Red Blood Cell Transfusion Independence



Azacitidine: Side Effects

- Cytopenias – low neutrophil counts, low platelets, & anemia
- Nausea & vomiting
- Injection site reactions
- Constipation (?due to anti-nausea medication)

Azacitidine: Incidence of Cytopenias



	Cycles 1-2	Cycles 3-4	Cycles 5-6	Cycles 7-12	Cycles 13-24
Thrombocytopenia	54.3%	5.4%	4.6%	5.6%	8.9%
Neutropenia	50.3%	10.9%	1.5%	6.5%	3.6%
Anemia	32.6%	7.5%	6.9%	7.5%	7.1%

32% lower annual risk of infections requiring IV antimicrobials compared to CCR
($p = 0.0032$)

Scoring System Predicting Survival (with Azacitidine)

	Score Value		
	0	1	2
ECOG status	0/1	≥ 2	-
Presence of circulating blasts	N	Y	-
RBC transfusion dependency (Units/8 wks)	0-3	≥ 4	-
IPSS cytogenetic risk*	Good	Intermediate	Poor

Scores for risk groups are as follows: Low (0), Intermediate (1-3), and High (4-5)

* Good (normal, -Y, del(5q), or del(20q)); Poor (complex (≥ 3 abnormalities) or chr(7) anomalies); Intermediate (other abnormalities)

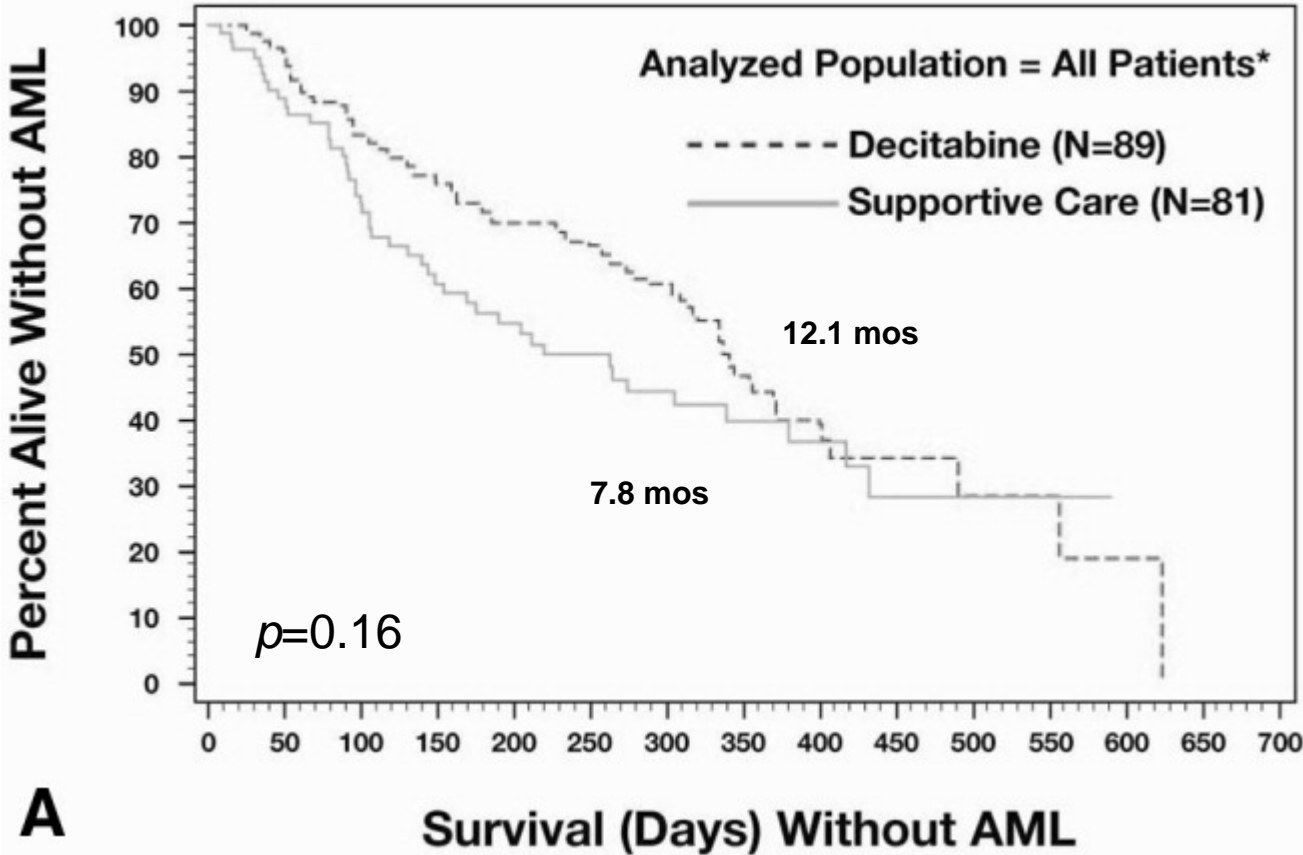
Itzykson et al. Blood 2010

Survival (with Azacitidine) by Risk Group

	Risk Group		
	Low	Intermediate	High
Score	0	1-3	4-5
Median Survival (months)*	Not reached	15	6.1

* $P < 0.0001$

Phase III Decitabine in MDS



Phase III Azacitidine v Decitabine Higher-risk MDS

N=280

- IPSS Int-1 (transfusion-dependent), Int-2, or High-risk

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Azacitidine 75 mg/m²/d x 7/28

Decitabine 20 mg/m²/d x 5/28

Primary Outcome:

Overall response rate

Recommendations for Hypomethylating Agents

- Azacitidine in patients with Int-2/High-risk MDS who are not transplant candidates
- Benefit of hypomethylating agents in patients with Low/Int-1 risk MDS is unclear
- Phase III trial is currently underway to evaluate response rates in patients receiving azacitidine vs decitabine. However, not designed to assess differences, if any, in OS
- Role of hypomethylating agents as a bridge to allogeneic stem cell transplant is being evaluated

Closing Comments

- Iron chelation may benefit patients with Low/Int-1-risk MDS & Higher-risk patients who are eligible for alloSCT – await results of TELESTO trial
- Lenalidomide yields durable erythroid responses (i.e. RBC transfusion independency in patients with del(5q) MDS
- Currently, azacitidine is the only hypomethylating agent that has shown an improved OS in patients with Int-2/High-risk MDS