

Novel Treatment Strategies in Myelodysplastic Syndromes

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BCOP
Recertification

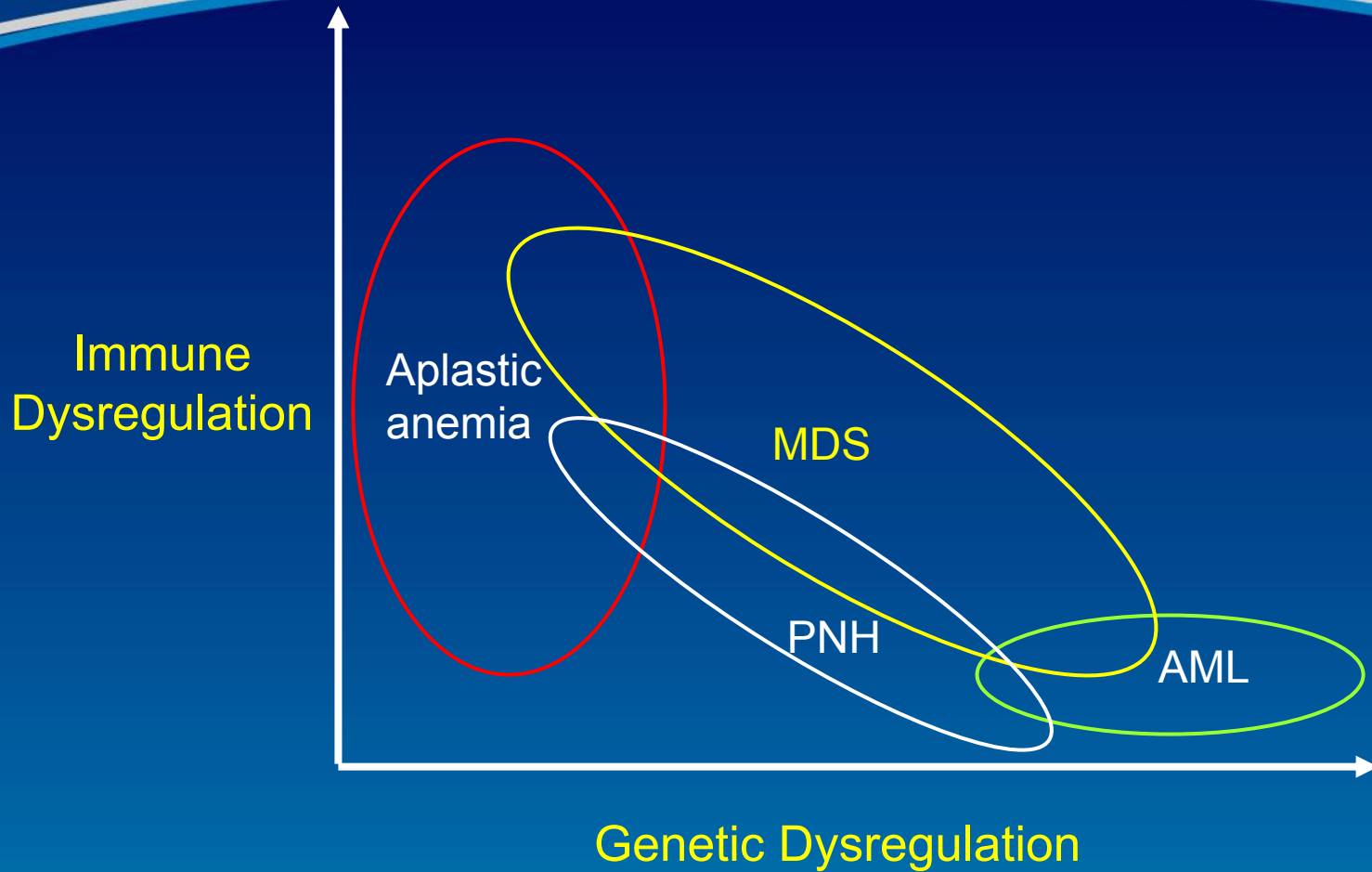
Disclosure

- **R. Donald Harvey, PharmD, has no real or apparent conflicts of interest to report**

Learning Objectives

- Describe the role of the International Prognostic Scoring System (IPSS) in therapeutic decision making in myelodysplastic syndromes (MDS)
- Analyze the clinical trial results of hypomethylating agents in the treatment of low, intermediate, and high risk MDS
- Differentiate individualized therapy for patients who are positive for 5q- and HLA-DR15 typing
- Evaluate the outcomes and role of nonmyeloablative allogeneic hematopoietic cell transplantation (HCT) in patients with MDS
- Discuss utilization of supportive care therapies in patients with MDS, with a focus on red cell support options, iron chelation, and colony-stimulating factors

MDS Is Not Simply *Preleukemia*



Management of MDS: Critical Questions

Who is the patient?

What is the major *problem* for the patient?

What are the *goals* of therapy?

Ineffective hematopoiesis

Progression toward
acute leukemia

Life-threatening complications of MDS

WHO vs FAB Classification of MDS

FAB

- RA
- RARS
- RAEB
- **RAEB-T**

WHO

- RA
- 5q- syndrome
- RCMD
- MDS-U
- RARS
- RCMD-RS
- RAEB-1
- RAEB-2
- **AML**

WHO = World Health Organization; FAB = French-American-British; RA = refractory anemia; RCMD = refractory cytopenia with multilineage dysplasia; MDS-U = myelodysplastic syndrome, unclassifiable; RARS = refractory anemia with ringed sideroblasts; RCMD-RS = cytopenia with multilineage dysplasia and ringed sideroblasts RAEB = refractory anemia with excess blasts; RAEB-T = refractory anemia with excess blasts in transformation; AML = acute myelogenous leukemia.

The International Prognostic Scoring System (IPSS)

- Uses marrow blast percentage, cytogenetics, and cytopenias to develop a total score

Variable/Score	0	0.5	1	1.5	2.0
% BM Blasts	<5	5–10	---	11–20	21–30
Karyotype	Good (nl, 5q-, 20q-, -Y)	Intermediate (other)	Poor (Complex ≥ 3 , abn. chr. 7)	---	---
# Cytopenias	0–1	2–3	---	---	---

- Cytopenias: ANC <1800/ μ L, Hgb <10 g/dL, platelets <100,000/ μ L

BM = bone marrow; ANC = absolute neutrophil count; Hgb = hemoglobin.

Greenberg P, et al. *Blood*. 1997;89:2079-88.

The International Prognostic Scoring System

Total Score	Risk Group	Time for 25% to Progress to AML Without Therapy (yrs)	Median Survival (yrs)
0	Low	9.4	5.7
0.5–1	Intermediate-1	3.3	3.5
1.5–2	Intermediate-2	1.1	1.2
>2	High	0.2	0.4

Individualizing Patient Management

- Are they a candidate for allogeneic stem cell transplant?
 - Only curative option
- What risk category are they?
 - Most low-risk patients do not need intensive therapy
- Do they have features that predict response to specific therapies?
 - 5q-, HLA-DR +
- What supportive care is needed?

Allogeneic Transplant Challenges

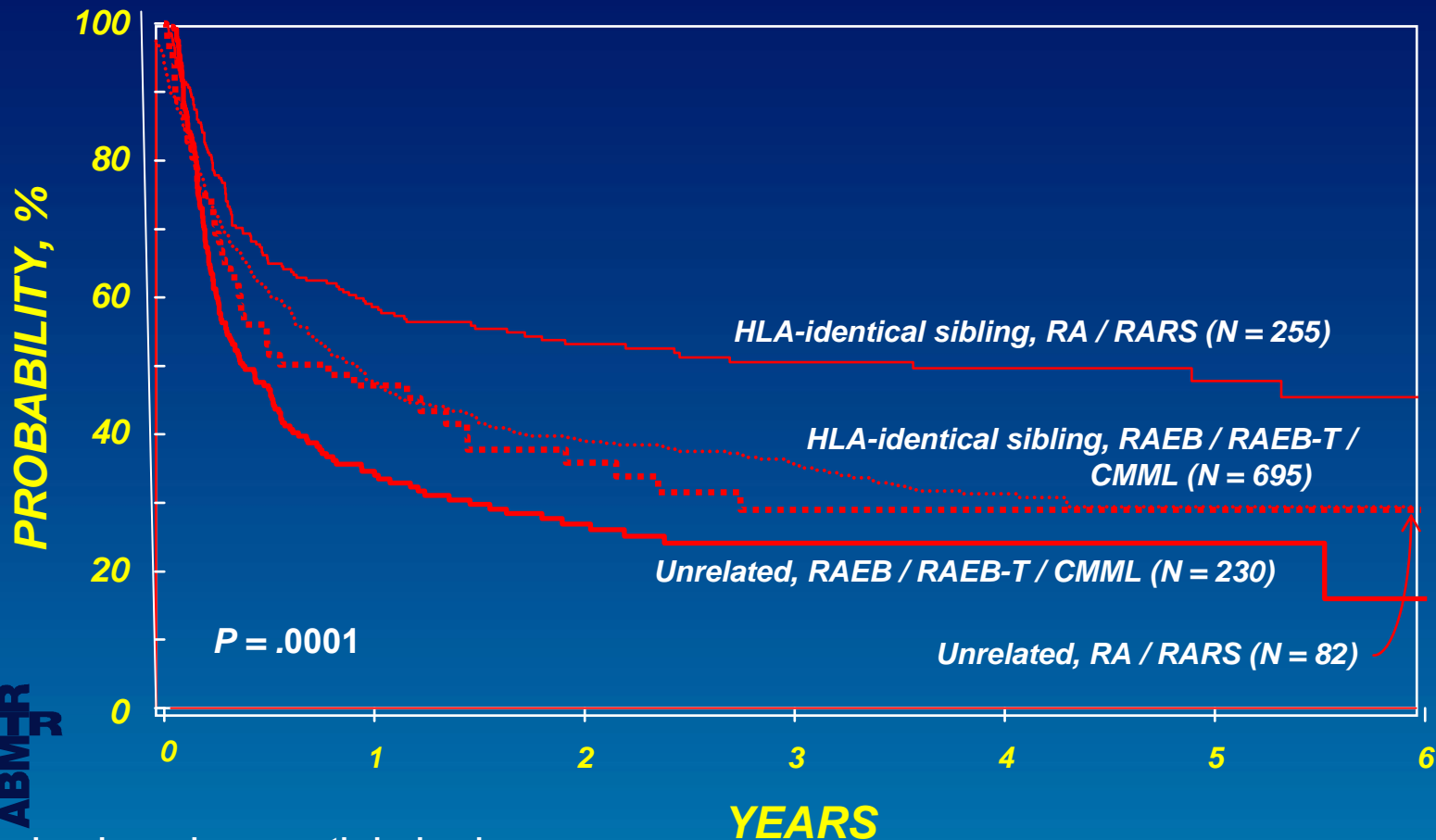
■ IPSS data

- Median patient age = 69 years
 - 75% >60 years
- But – those >60 with high risk IPSS (≥ 2) live a median of 6 months
- Patients <60 with low/intermediate-1 risk live 5 to 10 years
 - But – best outcomes with transplant
 - 5 year: OS = 42 to 57%, relapse = 48 to 64%
- Subsequent introduction/adoption of novel agents

OS = overall survival.

Greenberg P, et al. *Blood*. 1997;89:2079-88; Runde V, et al. *Bone Marrow Transplant*. 1998;21:255-61.

Survival With Conventional Allogeneic Transplant



CMML = chronic myelomonocytic leukemia.

<http://www.cibmtr.org/PUBLICATIONS/Newsletter/DOCS/2002Feb.pdf>. Accessed 6/9/08.

Reduced Intensity or Non-Myeloablative Conditioning

Pre-transplant
Chemotherapy ± Radiation
(immune suppression)

Donor Immune (T-cell)
Response



Goals

- Reduce early toxicities
- Shorten the period of pancytopenia
- ?Reduce risk of GVHD

- Reduce transplant-related risks
- Allow safer transplantation of older patients and those with prior autologous BMT

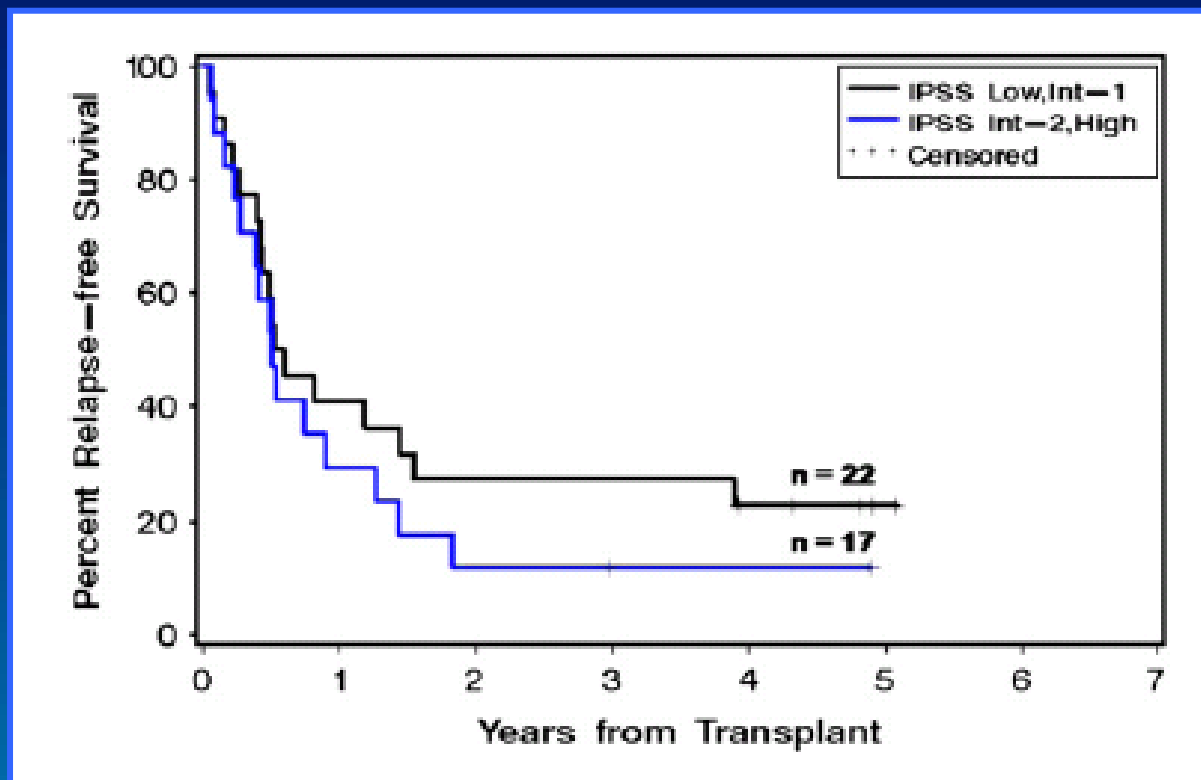
Outcomes With Non-Myeloablative Transplants

- N = 114 conditioned with fludarabine 30 mg/m² days -4 to -2 with 2 Gy TBI day 0
 - De novo MDS (n = 40)
 - Median age = 60
 - Risk: 22 low/int-1 risk, 17 int-2/high risk IPSS
 - Donor source: MRD in 23/40
- De novo MDS results
 - 3-year OS = 23%
 - Relapse at 3 years = 40%

TBI = total body irradiation; MRD = minimal residual disease.

Laport GG, et al. *Biol Blood Marrow Transplant.* 2008;14:246-55.

Outcomes With Non-Myeloablative Transplants



Reprinted from Laport GG, et al. *Biol Blood Marrow Transplant.* 2008;14:246-55. Copyright 2008, with permission from Elsevier.

Outcomes With Non-Myeloablative Transplants

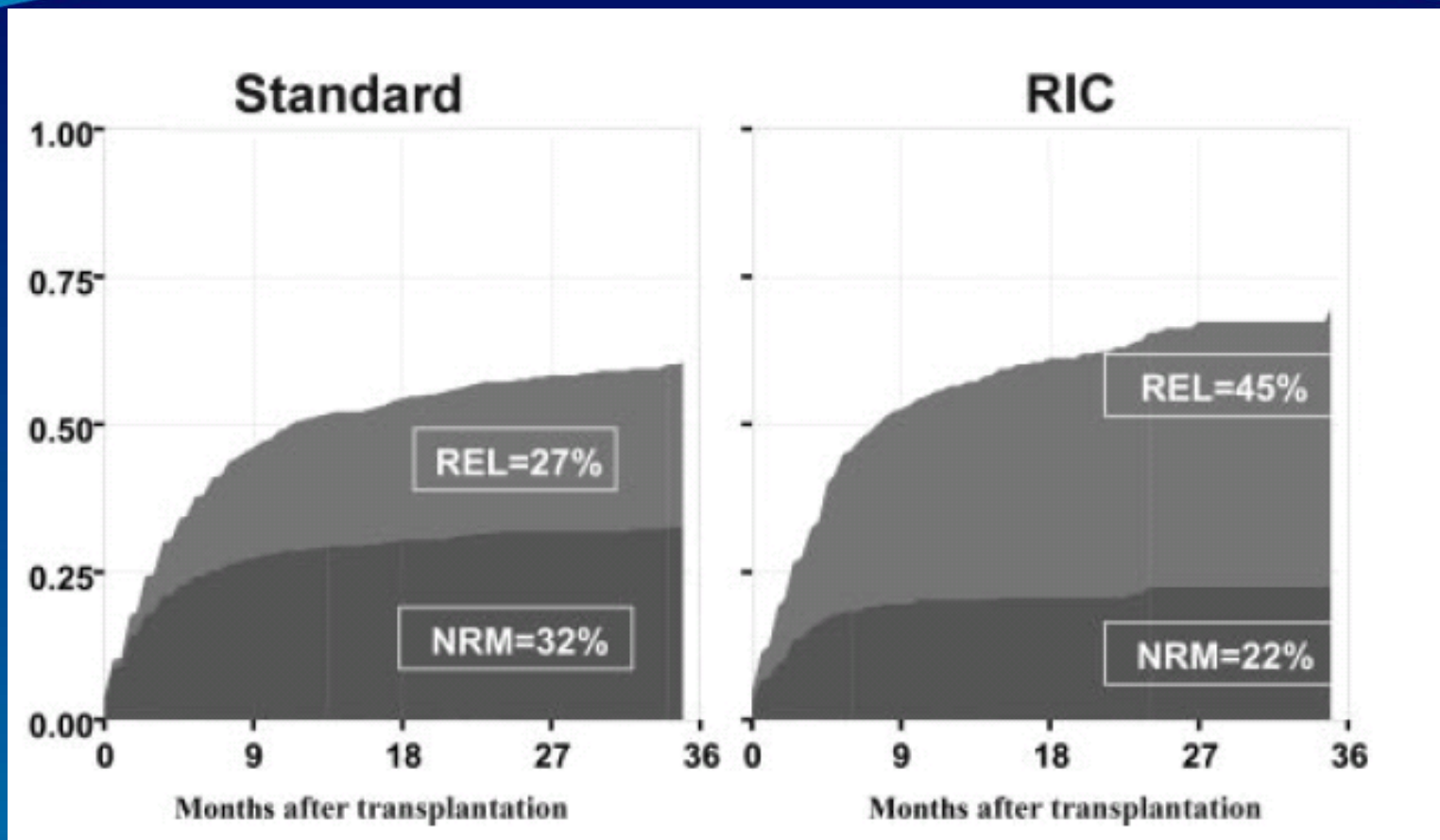
- EBMTR retrospective comparison of 836 transplants 1997-2001

Result	Conventional (N = 621)	Non-Myelo (N = 215)
Median age (yrs)*	45	56
Int-2, high risk	66%	69%
PBSC source*	51%	87%
3-year NRM*	32%	22%
3-year OS	45%	41%
3-year relapse rate*	27%	45%

EBMTR = European Bone Marrow Transplant Registry;
 PBSC = peripheral blood stem cell; NRM = nonrelapse mortality.
 Martino R, et al. *Blood*. 2006;108:836-46.

* $P < .05$

Outcomes With Non-Myeloablative Transplants



RIC = reduced-intensity conditioning.

Martino R, et al. *Blood*. 2006;108:836-46. This research was originally published in *Blood*. ©the American Society of Hematology.

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- What supportive care is needed?

Intermediate-2, High-Risk Patients

- Assess ability to tolerate therapy
 - Age, PS, comorbidities
- Goals of therapy = prolong survival and delay evolution to AML
- High-intensity options
 - Intensive chemotherapy
 - AML induction regimens
 - Hypomethylating agents
 - Azacitidine
 - Decitabine

PS = performance status.

From the NCCN (V2.2008) Myelodysplastic Syndrome Guideline, Clinical Practice Guidelines in Oncology. ©National Comprehensive Cancer Network, 2008. Available at:[http:// www.nccn.org](http://www.nccn.org). Accessed 5/13/08. To view the most recent and complete version of the guideline, go online to www.nccn.org.

Intermediate-2, High-Risk Patients

Intensive Chemotherapy

- Review of outcomes with topotecan, cytarabine, idarubicin, cyclophosphamide-containing regimens
 - N = 510
 - Cytarabine/idarubicin-containing (270)
 - Median age = 63
 - Secondary MDS = 32%
 - All received antifungal, antibacterial prophylaxis
- Results
 - CR = 55%
 - Induction mortality = 17%
 - 5-year survival = 8%
 - Positive prognostic variables: age <55, PS ≤2, platelet >100,000/mm³, diploid/-Y cytogenetics, treatment in laminar air flow room

Intermediate-2, High-Risk Patients

Hypomethylating Agents

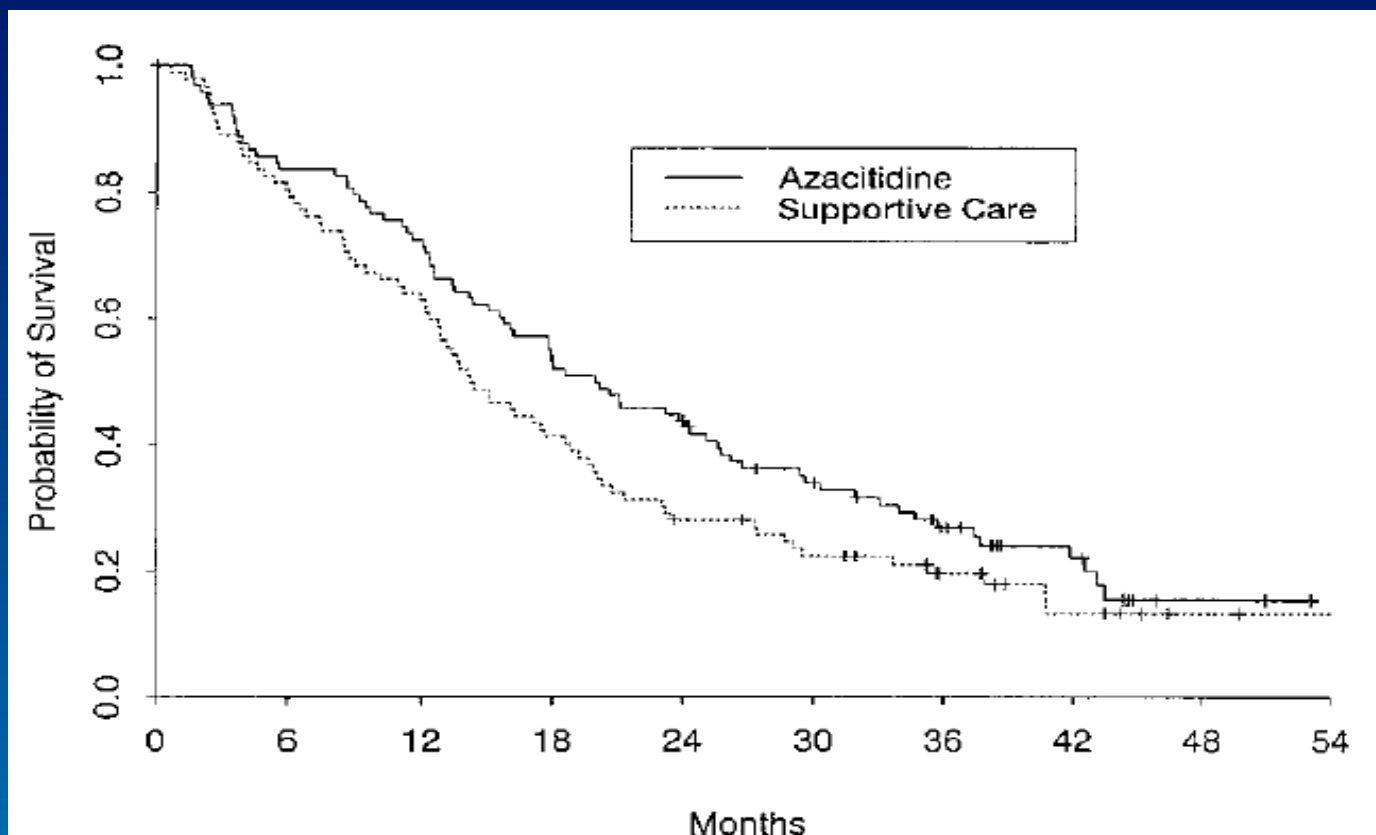
- In vitro evidence of hypermethylation in a variety of cancer types:
 - Genome-wide (global) increases in CpG methylation
 - Increased methylation of specific genes, eg, cyclin-dependent kinase inhibitors (p15, p16, p21, p57), MLH1 (DNA mismatch repair)
- MDS and AML
 - p15^{INK4B} hypermethylation is found in >50% of cases, and is associated with progression of MDS to AML

Intermediate-2, High-Risk Patients

Azacitidine

- Licensing trial – CALGB 9221 (n = 191)
- Azacitidine 75 mg/m² SQ daily x 7/28 days vs supportive care
 - Crossover allowed at 2 to 4 months if progression
- IPSS – (n = 99)
 - Low – 2%
 - Int-1 – 26%
 - Int-2 – 11%
 - High – 9%
- Trilineage response 23% vs 0%

Intermediate-2, High-Risk Patients *Azacitidine*



Silverman LR, et al. *J Clin Oncol*. 2002;20:2429-40. (Reprinted with permission from the American Society of Clinical Oncology.)

Intermediate-2, High-Risk Patients

Azacitidine

- CALGB 9221 additional findings
 - QOL significantly improved on azacitidine arm
 - Transient myelosuppression most common severe toxicity
 - No increase in rates of infection or bleeding
 - Responses may not be seen until 3 to 4 cycles of therapy
 - Mechanism of action/target genes remain to be identified

QOL = quality of life.

Silverman LR, et al. *J Clin Oncol*. 2002;20:2429-40.

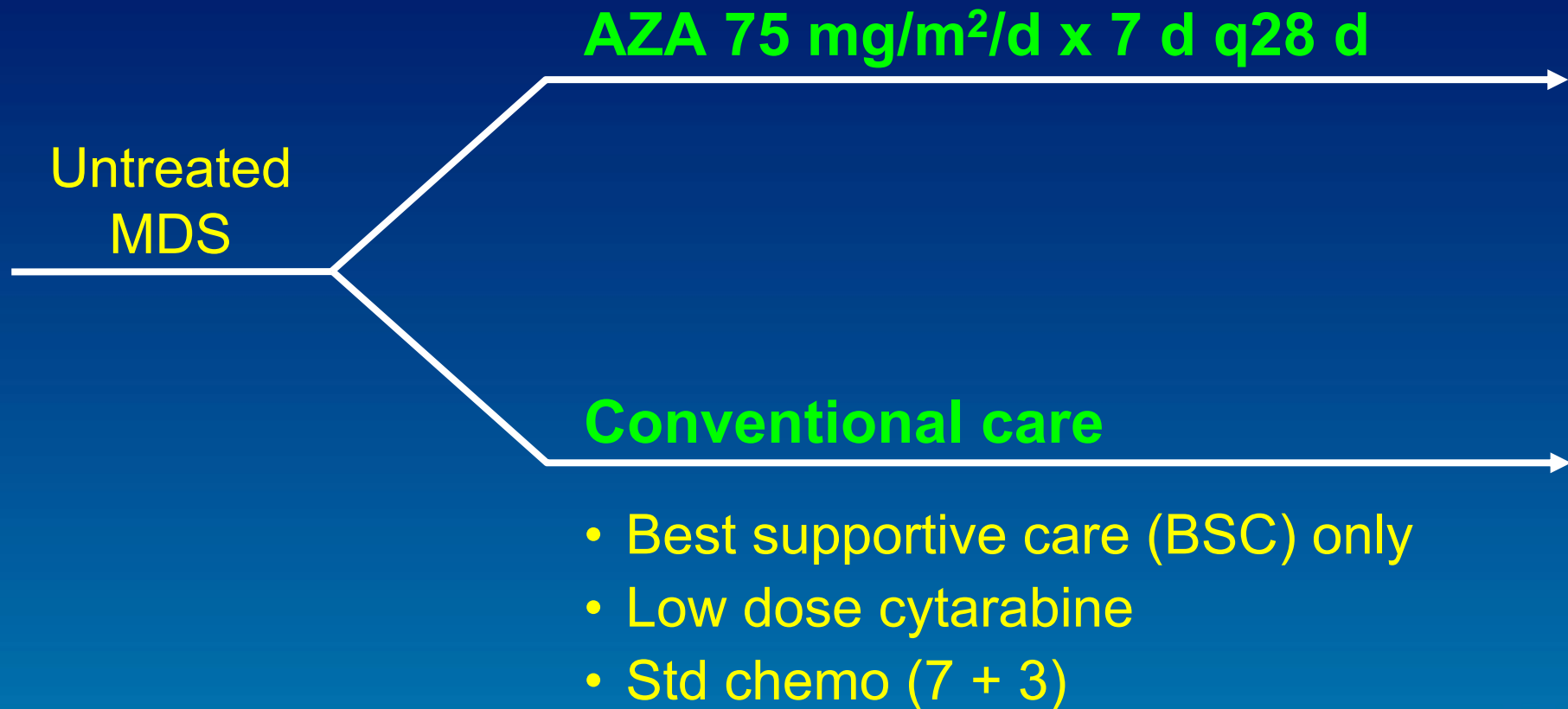
Intermediate-2, High-Risk Patients

Azacitidine

- AZA-001: Phase 3, international, multicenter, prospective, randomized, controlled, parallel-group study
- Inclusion criteria
 - High-risk MDS patients:
 - RAEB, RAEB-T or CMML according to FAB
 - IPSS score of int-2 or high

Intermediate-2, High-Risk Patients

Azacitidine



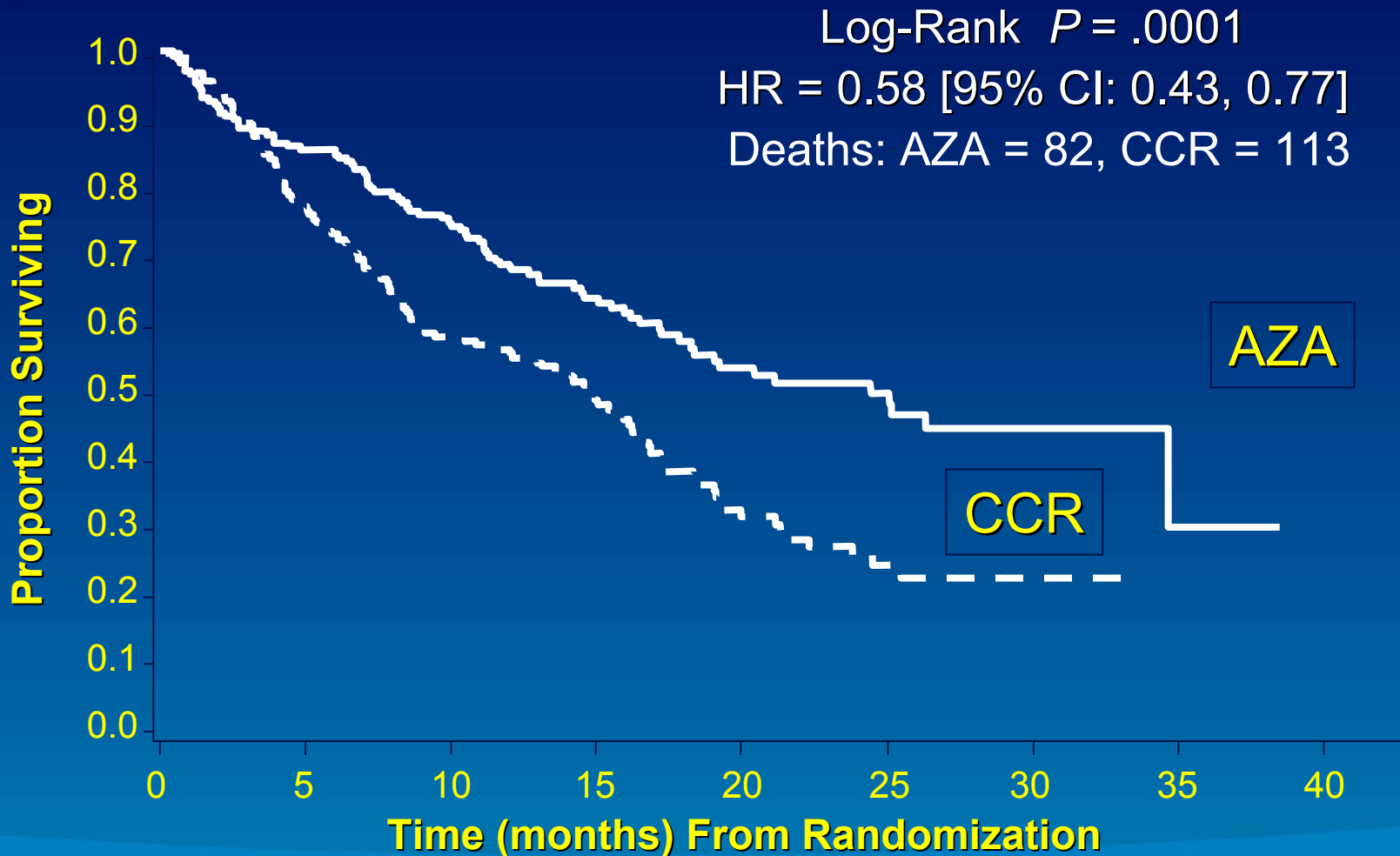
Intermediate-2, High-Risk Patients

Azacitidine

Parameter	CCR Regimens				
	AZA N = 179	CCR N = 179	BSC Only N = 105	LDAC N = 49	Std Chemo N = 25
Age (yrs) Median	69	70	70	71	65
Pts ≥65 (%)	68	76	77	86	52
FAB (%)					
RAEB	58	58	65	51	40
RAEB-T	34	35	29	39	52
CMML	3	3	4	2	0
IPSS (%)					
INT-1	3	7	9	4	8
INT-2	43	39	44	43	12
High	46	48	44	43	72

Intermediate-2, High-Risk Patients

Azacitidine



Intermediate-2, High-Risk Patients

Azacitidine

- Median number of cycles = 9
- Median survival
 - 24.4 mos with AZA vs 15 mos with CCR, $P = .0001$
- Time to AML or death
 - 13 mos with AZA vs 7.6 mos with CCR, $P = .003$
- RBC transfusion independence
 - 45% with AZA vs 11% with CCR, $P < .0001$

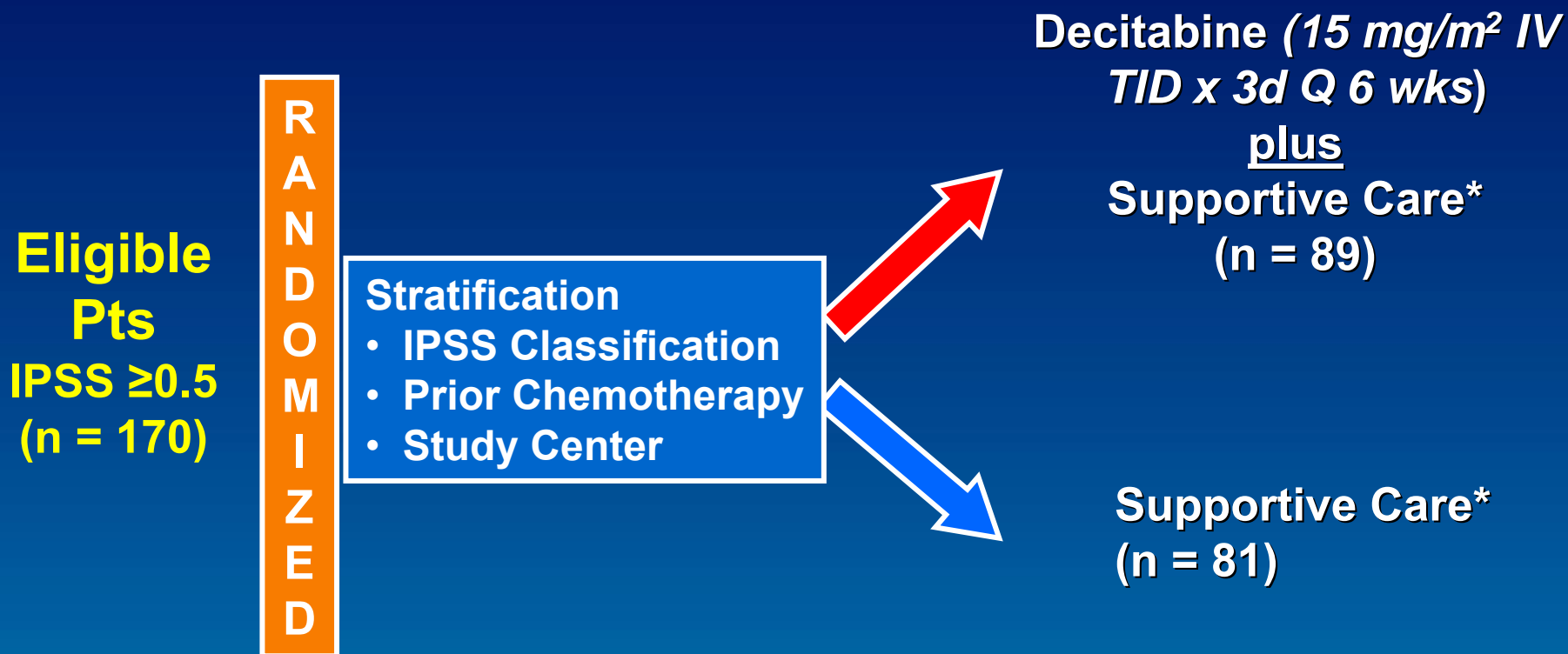
RBC = red blood cell.

Fenaux P, et al. ASH. 2007;101:Abstract 817.

Intermediate-2, High-Risk Patients

Decitabine

- ◆ Open label, 1:1 randomized study



*Antibiotics, growth factors, and/or transfusions.

IV = intravenous.

Kantarjian H, et al. *Cancer*. 2006;106:1794-803.

Intermediate-2, High-Risk Patients

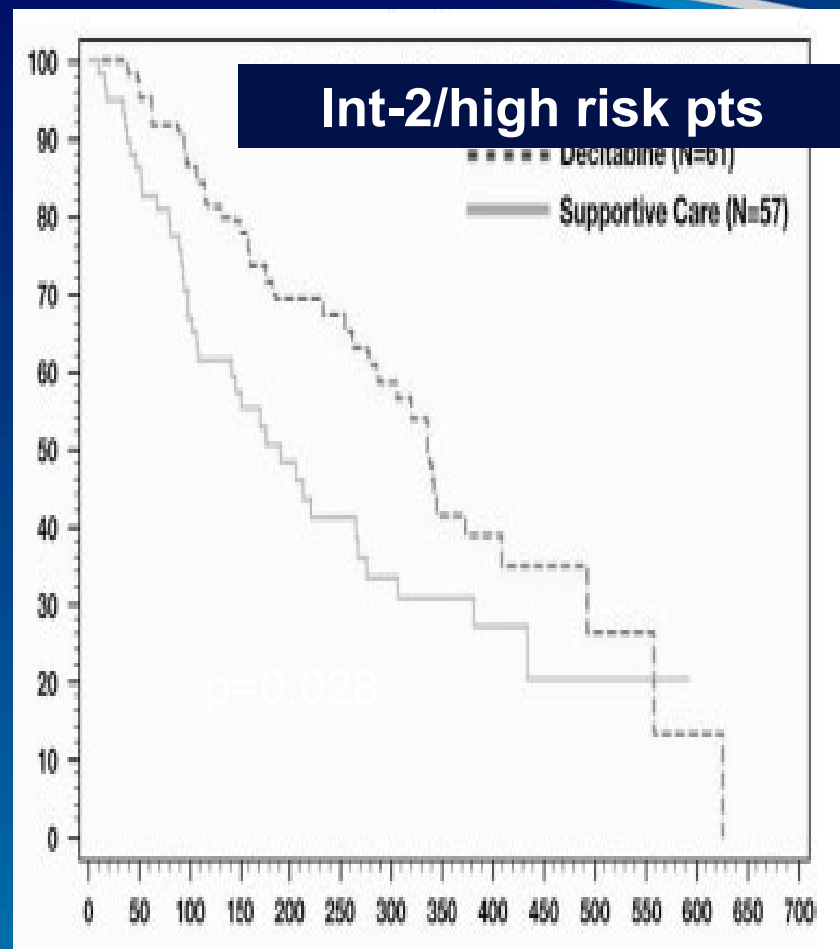
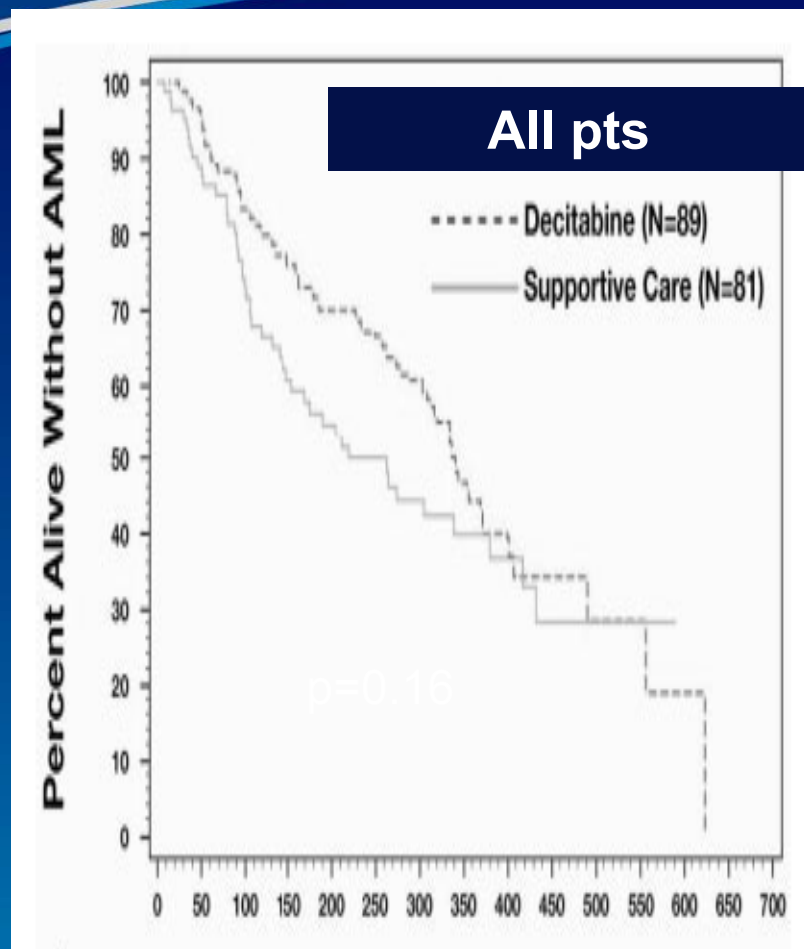
Decitabine

IWG Response Rate	Decitabine (n = 89)	Supportive Care (n = 81)
Response Rate (CR+PR+HI)	27 (30%)	6 (7%)
Median Time to Response (mo)	3.3 (2.0 – 9.7)	N/A
Median Duration of Response (mo)	10.3 (4.1 – 13.9)	

IWG = International Working Group; PR = partial response; HI = hematologic improvement.
Kantarjian H, et al. *Cancer*. 2006;106:1794-803.

Intermediate-2, High-Risk Patients

Decitabine



Kantarjian H, et al. *Cancer*. 2006;106:1794-803. (Copyright© 2006, American Cancer Society. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

What Are the Optimal Schedules for the Hypomethylating Agents?

Randomized Phase 2 Trial of 3 Dosing Schedules of Decitabine in MDS/CMML

- Schedules (Q month)
 - 20 mg/m² IV daily x 5 days
 - 20 mg/m² SQ daily x 5 days
 - 10 mg/m² IV daily x 10 days
- Patient population: Int-1,2 or high risk (IPSS), MDS or CMML
- Adaptive randomization based on CR rate after 45 patients

Randomized Phase 2 Trial of 3 Dosing Schedules of Decitabine in MDS/CMML

- Overall RR 70%
 - CR 35%
 - BM CR + HI 12%
 - BM CR (blasts) 10%
 - PR 2%
 - HI 10%
- Median # cycles: ≥ 7
- Hospitalization for complications: 14%
- Median survival: 22 mos
- Median time to next cycle: 35 days

Schedule	CR %
20 mg/m ² IV x 5	39% (33 of 84)
20 mg/m ² SQ x 5	21% (3 of 14)
10 mg/m ² IV x 10	24% (4 of 17)

Alternative Dosing Schedules for Azacitidine

Can the Need for Weekend Dosing Be Eliminated?

	AZA 5-2-2 (75 mg/m ²)	AZA 5-2-5 (50 mg/m ²)	AZA 5 (75 mg/m ²)
Hematologic Improvement	52%	55%	65%
Erythroid Major	44%	46%	42%
Platelet Major	19%	23%	16%
Neutrophil Major	11%	14%	16%

Low, Intermediate-1 Risk Patients

- Goals of therapy = reduce transfusion needs, complications
- Low-intensity options
 - Hematopoietic growth factors
 - Lenalidomide (5q-)
 - Immunosuppressive therapy (HLA-DR +)
 - Hypomethylating agents
 - Azacitidine
 - Decitabine

Low, Intermediate-1 Risk Patients

Hematopoietic Growth Factors

- Response unlikely if serum EPO >500 mU/mL
- Objective response rates of 20 to 55%
 - Standard EPO dosing or weekly
 - Prolonged therapy needed (up to 26 weeks)
- Predictors of response: EPO <500 mU/mL, <2 U PRBCs monthly
- Improved responses rates seen combining EPO with G-CSF (1–2 mcg/kg SQ daily)
- No effect on platelet counts

EPO = erythropoietin; PRBC = packed red blood cells; G-CSF = granulocyte-colony stimulating factor.
Musto P, et al. *Br J Haematol.* 2003;122:269-71; Terpos E, et al. *Br J Haematol.* 2002;118:174-80;
Hellstrom-Lindberg E, et al. *Br J Haematol.* 1997;99:344-51.

Low, Intermediate-1 Risk Patients Hematopoietic Growth Factors

■ Darbepoetin

- Retrospective evaluation of 81 patients
 - Dosing: 75 to 300 mcg x 16 weeks
 - 150 mcg most common (65%)
 - IPSS: 55% low, 36% int-1
 - Response: 55% (30% major, 25% minor)
- High dose (300 mcg weekly), n = 62
 - Response at 12 weeks: 44/62 (34 major, 10 minor)
 - Response seen in EPO 60,000 units weekly failures (8/13)

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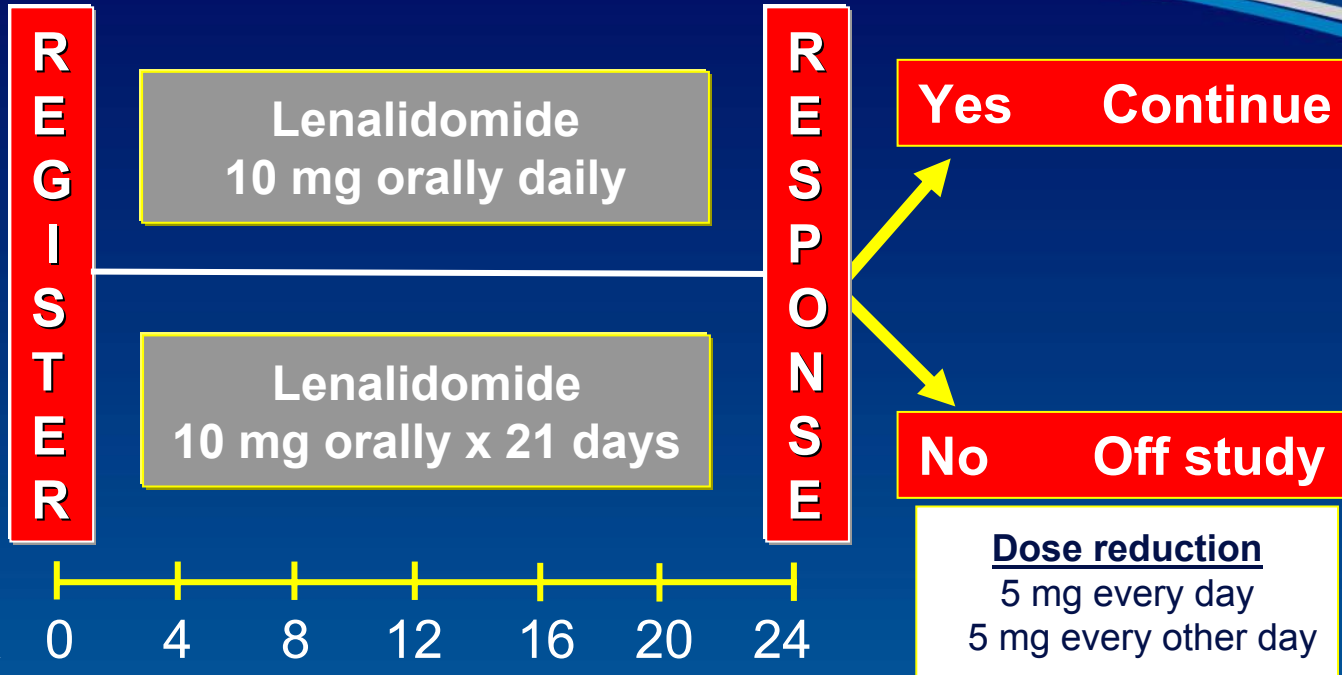
The 5q- Syndrome

- Defined by isolated 5q-, <5% blasts
- IPSS low or int-1
- Characteristics
 - Majority female
 - Symptomatic, macrocytic severe anemia
 - Platelets normal or elevated
 - 50% have counts >350,000/mm³
 - Up to 20% have splenomegaly
 - Median survival 53 to 146 months
 - 5 to 16% evolve to AML
 - Poor response to EPO (6-14%)

Phase 2 Studies of Lenalidomide in Low-Risk MDS

Eligibility

- IPSS: Low/Int-1
- ≥ 2 U RBC/ 8 wks
- Plts $>50,000/\mu\text{L}$
- ANC $>500/\mu\text{L}$



Primary endpoint: Transfusion independence and Hgb response
Secondary endpoints: Cytogenetic response
Safety

Erythroid Responses in 5q-

Variable	% patients (n = 148)
Erythroid Response	76%
RBC Transfusion Independence (TI)	67%
Complete Cytogenetic Response	45%
Duration of TI	Not reached at 104 weeks

Lenalidomide in Patients Without 5q-

Variable	Daily Dose N = 100	21-Day Dose N = 114	All Patients N = 214
Erythroid Response, n (%)	41 (41)	51 (45)	92 (43)
Transfusion Independence	26 (26)	30 (26)	56 (26)
Median Time to Response (wks)	6.4	3.6	4.5
Median Duration of Response (wks)	—	—	41

Most Common Adverse Events

Adverse Event	All Grades N (%)	Grade ≥ 3 N (%)
Neutropenia	60 (28)	53 (25)
Thrombocytopenia	56 (26)	43 (20)
Rash	47 (22)	9 (4)
Pruritus	45 (21)	2 (1)
Fatigue	33 (15)	8 (4)
Diarrhea	32 (15)	3 (1)
DVT	NA	2 (1)

DVT = deep vein thrombosis.

Raza A, et al. *Blood*. 2008;111:86-93.

Hypocellular MDS

- Likely due to T-cell mediated immune destruction of progenitor cells
- Characteristics
 - HLA-DR15 +
 - PNH clone positivity
 - Respond to immunosuppressive therapy (IST)
 - ATG 40 mg/kg daily x 4 + CSA
- Retrospective evaluation of 129 patients
 - Predictors of prolonged survival with IST
 - Age ≤ 60
 - Combination therapy with ATG and CSA
 - Low, int-1 IPSS

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Transfusional Iron Overload

- Each red cell unit contains approximately 200 mg of elemental iron
 - Chronic transfusion-dependent patients have an iron excess of ~0.4 to 0.5 mg/kg/day
- Total body iron stores become saturated at ~ 500 mg/kg transfused
 - Approximately 20 to 30 transfusions
- No endogenous mechanism to remove excess iron
- Marrow failure states increase iron absorption

Transfusional Iron Overload

- Laboratory evaluation
 - Ferritin
 - False positives during acute illness
 - Transferrin saturation
 - Not helpful in marrow failure states due to rapid iron recycling
 - No measure correlates with tissue iron concentrations
- Radiographic evaluation
 - MRI with R2 (hepatic), T2* (cardiac) weighting
 - Echo, RNV
- Quantitative phlebotomy
- Biopsy

Challenges of Iron Chelation in MDS

- Iron overload in MDS \neq iron overload in thalassemia, sickle cell disease
- When to initiate?
 - Ferritin ≥ 1000 to 2500 ng/mL?
 - Total RBCs received?
 - NCCN recommendation: >20 to 30
- Greater risk of toxicities due to age
- Effect of ESAs
- Effect of chelation on survival?
 - Retrospective review of 133 patients showed IPSS of low, intermediate-1 patients predicted significant improvement with iron chelation

ESA = erythropoiesis-stimulating agents.

Leitch HA, et al. *Blood*. 2006;106:Abstract 249.

Iron Chelation

	Deferoxamine	Deferiprone	Deferasirox
Route	IV, SQ	PO	PO
Half-Life	20 mins	2–3 hours	8–16 hours
Route of Iron Excretion	Urine, stool	Urine	Stool
Daily Dose	20–60 mg/kg	50–100 mg/kg	20–30 mg/kg
Toxicities	Ocular, auditory, bone	Marrow, hepatic, GI	Renal, hepatic, skin, marrow
Monitoring	Annual eye, audiometry exams	Weekly CBC	Monthly creatinine, LFTs, urinalysis, annual eye, auditory exams
Comments	Available >30 years	Not FDA approved	Dear HCP letter May 2007 – renal, marrow

GI = gastrointestinal; CBC = complete blood count; FDA = Food and Drug Administration; LFT = liver function test; HCP = health care professional.

Future Directions

- Improved allogeneic stem cell transplant options
- Further understanding of cytogenetic predictors
- New approaches
 - Angiogenesis inhibitors
 - Farnesyl transferase inhibitors
 - Arsenic trioxide
 - TNF inhibition
 - MAPK inhibitors
 - BCL-2 inhibitors
 - New combinations
- Improved supportive care
 - Thrombopoietic agents

HOPA/ISOPP 2008

Thursday, June 19

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