

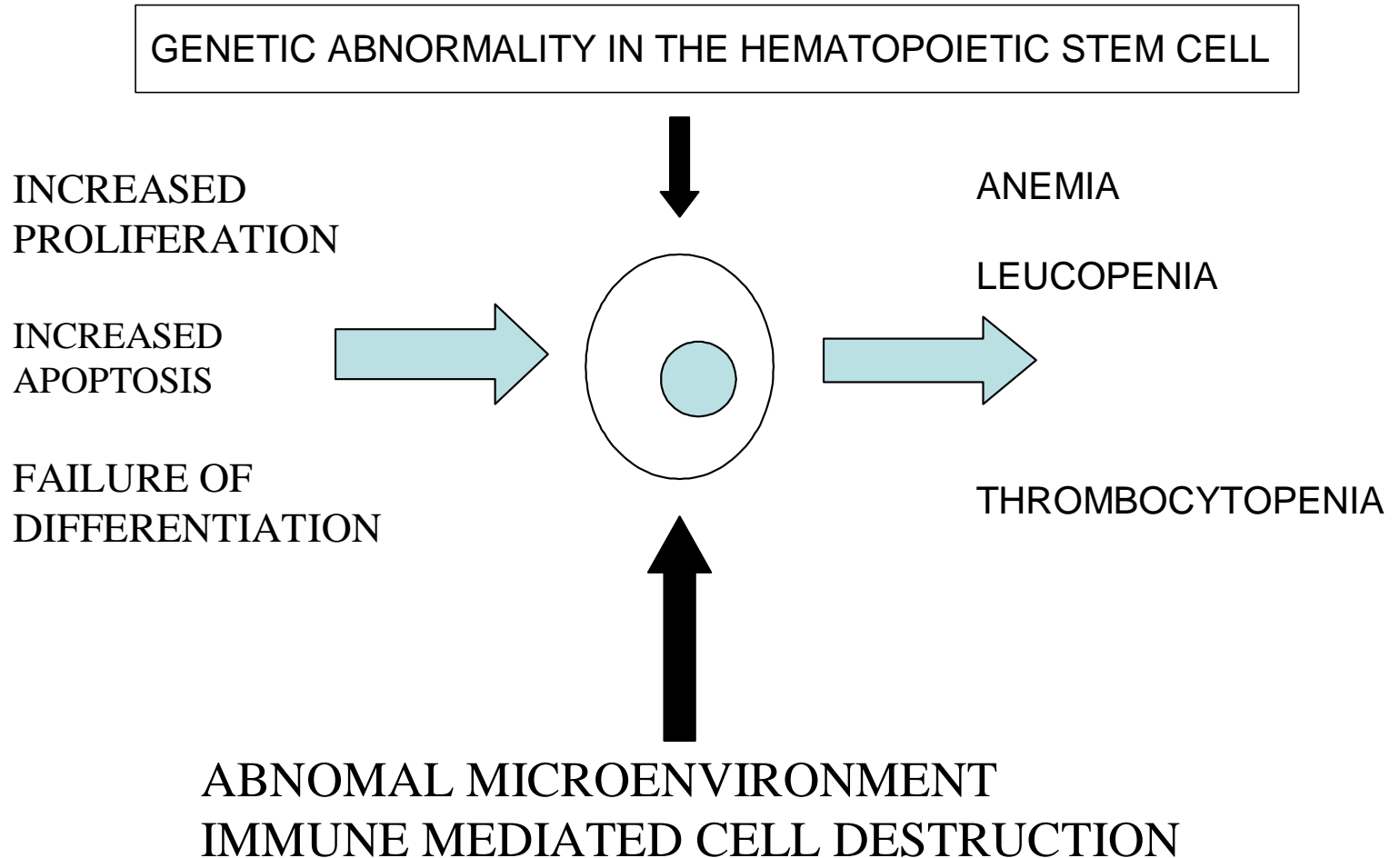


Novel Agents in the treatment of MDS

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**THE INAUGURAL ASEAN FEDERATION OF HAEMATOLOGY SCIENTIFIC MEETING AND
THE VIIITH MALAYSIAN NATIONAL HAEMATOLOGY SCIENTIFIC MEETING
- SHANGRILA HOTEL KUALA LUMPUR, 22-24 APRIL 2010**

PATHOGENESIS OF MYELOYDYSPLASIA-1

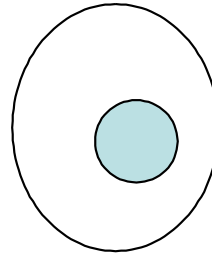


PATHOGENESIS OF MYELOYDYSPLASIA-2

GENETIC ABNORMALITY IN THE HEMATOPOIETIC STEM CELL

**INCREASED
PROLIFERATION**

INCREASED
APOPTOSIS



LEUKEMIA

**FAILURE OF
DIFFERENTIATION**



ABNOMAL MICROENVIRONMENT





MDS –The Cirrhosis of hematology

- Cell death
- Fibrosis
- Regeneration (nodular/ineffective)
- Therapeutic nihilism!



What are the genetic abnormalities in the hematopoietic stem cell in MDS?

Cytogenetic changes in MDS

- Recurrent unbalanced aberrations
 - loss of chromosome material: (5q-/-5, 7q-/-7)
 - gain of chromosome material: (+8)
- Recurrent balanced aberrations with chromosome rearrangement
 - reciprocal translocations involving chromosome bands 11q23, 21q22, 17q21 or inv(16)(p13q22).
- Normal karyotype

Frequency of cytogenetic of abnormalities in de novo and therapy-related myelodysplasia (MDS) and acute myeloid leukemia (AML).

| Type of disease | Cytogenetics | | |
|--------------------|--|---|---------------------------|
| | Unbalanced 5q-/-5, 7q-/-7, +8, % | Balanced 11q23, 21q22 17q21, 16q22, % | Normal karyotype, % |
| <i>de novo</i> MDS | 15-25 | rare | 50-60 |
| t-MDS | 50-70 | rare | 5-10 |
| <i>de novo</i> AML | 15-25 | 15-20 | 40-50 |
| t-AML | 40-50 | 15-20 | 10-15 |



Genetic Pathways in the Pathogenesis of Therapy-Related Myelodysplasia and Acute Myeloid Leukemia

Jens Pedersen-Bjergaard, Morten T. Andersen, and Mette K. Andersen

- **Class 1 Mutations:** Activating mutations of genes in the tyrosine kinase–RAS/BRAF signal transduction pathway, leading to increased cell proliferation.
- **Class 2 Mutations:** Inactivating mutations of genes encoding hematopoietic transcription factors, resulting in disturbed cell differentiation.
- **Class 3 Mutations:** Inactivating mutations of the tumor suppressor gene p53.

Molecular Effects of Chromosome Aberrations

- **5q-/-5**
 - Haploinsufficiency of RPS14
 - Haploinsufficiency of EGR
 - promoter methylation of α -catenin (*CTNNA1*)
- **-7**
 - constitutive activation of the STAT1/STAT5 signal transduction pathway
 - increased proportion of the G-CSF receptor isoform 4, which fails to internalize following G-CSF stimulation.
- **17 p13**
 - Point mutations of p53 the tumor suppressor gene

Identification of RPS14 as the 5q-Syndrome Gene by RNA Interference Screen. Plenary Session ASH 2007

- Block in the processing of pre-ribosomal RNA in RPS14-deficient cells which is functionally equivalent to the defect in Diamond–Blackfan anemia, linking the molecular pathophysiology of the 5q-syndrome to a congenital syndrome causing bone marrow failure.

RESEARCH

[The gene encoding ribosomal protein S19 is mutated in Diamond-Blackfan anaemia](#) Nature Genetics **Article (01 Feb 1999)**

An Erythroid Differentiation Signature Predicts Response to Lenalidomide in Myelodysplastic Syndrome.

- Lenalidomide is an effective new agent for the treatment of patients with myelodysplastic syndrome (MDS).
- Patients with an interstitial deletion of Chromosome 5q have a high rate of response to lenalidomide, but most MDS patients lack this deletion.
- Approximately 25% of patients without 5q deletions also benefit from lenalidomide therapy, but response in these patients cannot be predicted by any currently available diagnostic assays.
- Using gene expression profiling, we identified a molecular signature that predicts lenalidomide response.
- The response signature consisted of a cohesive set of erythroid-specific genes with decreased expression in responders, suggesting that a defect in erythroid differentiation underlies lenalidomide response.
- This will identify patients most likely to respond to the drug.

PLoS Med. 2008 Feb 12;5 (2):e35 18271621 (**P,S,E,B**)

[Benjamin L Ebert](#), [Naomi Galili](#), [Pablo Tamayo](#), [Jocelyn Bosco](#), [Raymond Mak](#), [Jennifer Pretz](#), [Shyam Tanguturi](#), [Christine Ladd-Acosta](#), [Richard Stone](#), [Todd R Golub](#), [Azra Raza](#)

Chromosome 5

- **Growth Factors**
 - **GM CSF, IL-3, IL-4, IL-5, IL-9**
- **Growth Factor receptors**
 - ***EGR-1***
- **?Tumor Suppressor Gene**
 - **critical region 5 q 31 - 2..8 mb**

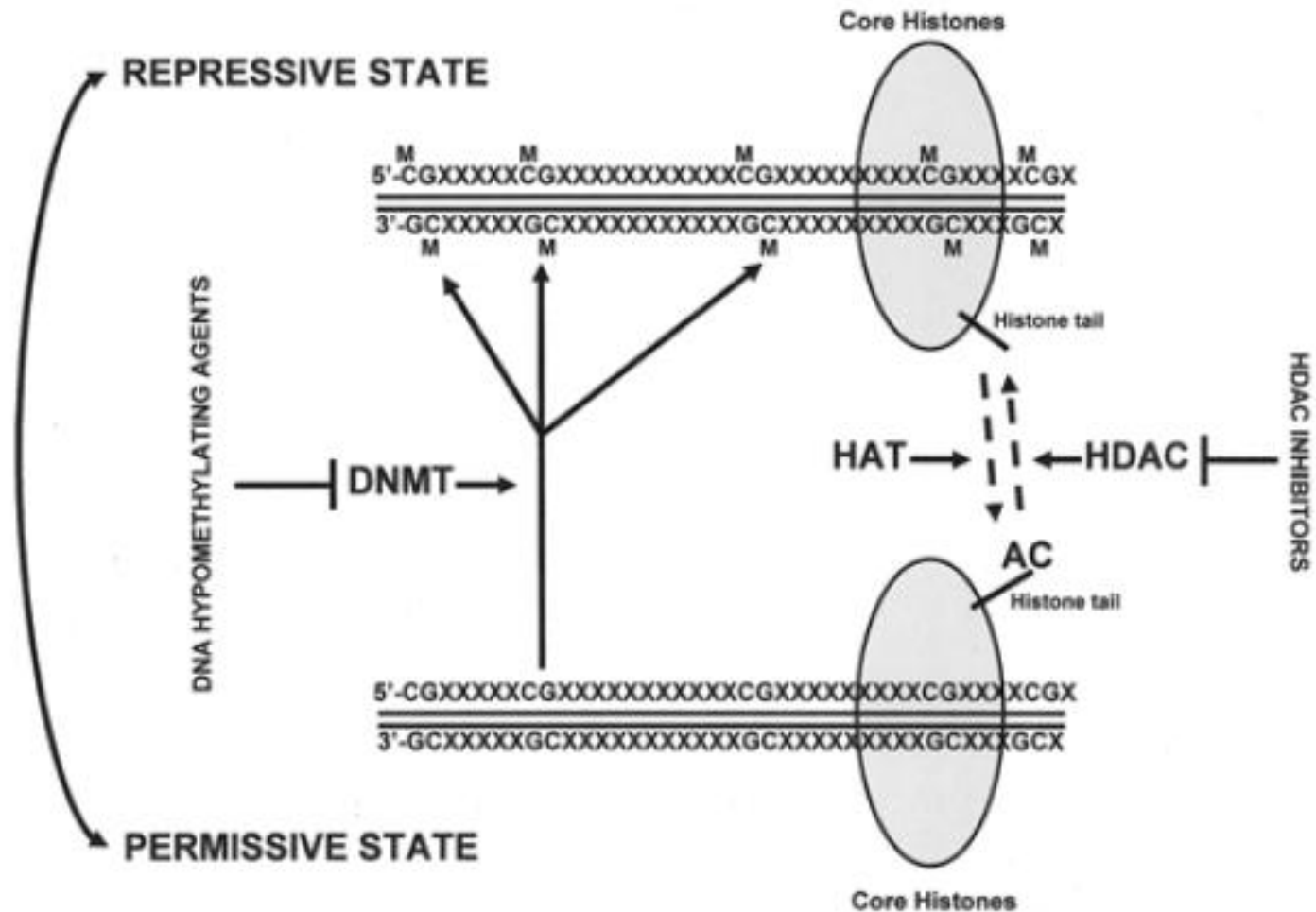
Chromosome 7

- **proto-oncogene MET mapped to 7q31**
- **genes encoding p-glycoprotein**
- **erythropoietin gene**
- **neutrophil chemotactic factor**

Epigenetic Changes in MDS

- **The term epigenetics refers to a number of biochemical modifications of chromatin that, without altering the primary sequence of DNA, have a role in genomic regulation and in particular gene expression control.**
 - **DNA level methylation**
 - **chromatin protein scaffold- histone code modifications**
- Promoter methylation of the *CTNNA1* gene in 5q-.
- Methylation of the *p15INK4B* gene in 55 of 81 patients with t-MDS or t-AML and 7q-/-7.

Targets of Epigenetic therapy



Immune mechanisms in the pathogenesis of MDS

- Clonal amplification of T lymphocytes is demonstrable in up to 50% of patients with MDS, with suppression of hematopoiesis through CD8+ cytotoxic T lymphocytes.
- Phase 2 trials using antithymocyte globulin with or without cyclosporine have yielded hematologic improvement in approximately one-third of patients with MDS.
- Among hematologic responders, clonal CD8+ T cells have been shown to contribute to MHC class I-mediated suppression of colony-forming unit-granulocyte macrophage (CFU-GM), in isolated cases, balanced by immunologic recovery with a polyclonal T-cell population confirmed by T-cell receptor variable beta chain (TCR-V β) profile.

Pretreatment variables linked to response to immunosuppressive therapy

- **UNIVARIATE ANALYSIS**
- age (≤ 60 years)
- short duration of RBC transfusion requirement (< 6 months)
- hypocellular marrow, and presence of a paroxysmal nocturnal hemoglobinuria (PNH) clone
- (HLA)-DR15 phenotype
- **MULTIVARIATE ANALYSIS**
- Age
- transfusion duration
- presence of HLADR15



MDS- Risk Stratification

MDS- International prognostic Scoring System

| | SCORE | | | | |
|---------------------|-------|------|-----|-------|-------|
| PROGNOSTIC VARIABLE | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| BONE MARROW BLAST | <5 | 5-10 | --- | 11-20 | 21-30 |
| KARYOTYPE | G | I | P | | |
| CYTOPENIA | 0/1 | 2/3 | | | |

| PROGNOSTIC SCORE | IPSS SCORE | MEDIAN AML TRANS | MEDIAN SURVIVAL |
|------------------|----------------|------------------|-----------------|
| 0 | LOW | 9.4 | 5.7 |
| 0.5-1.0 | INTERMEDIATE 1 | 3.3 | 3.5 |
| 1.5-2.0 | INTERMEDIATE 2 | 1.1 | 1.2 |
| >2.5 | HIGH | 0.2 | 0.4 |

Good; -Y, del5q, del20q
 Poor: complex, del7
 Intermediate: all other

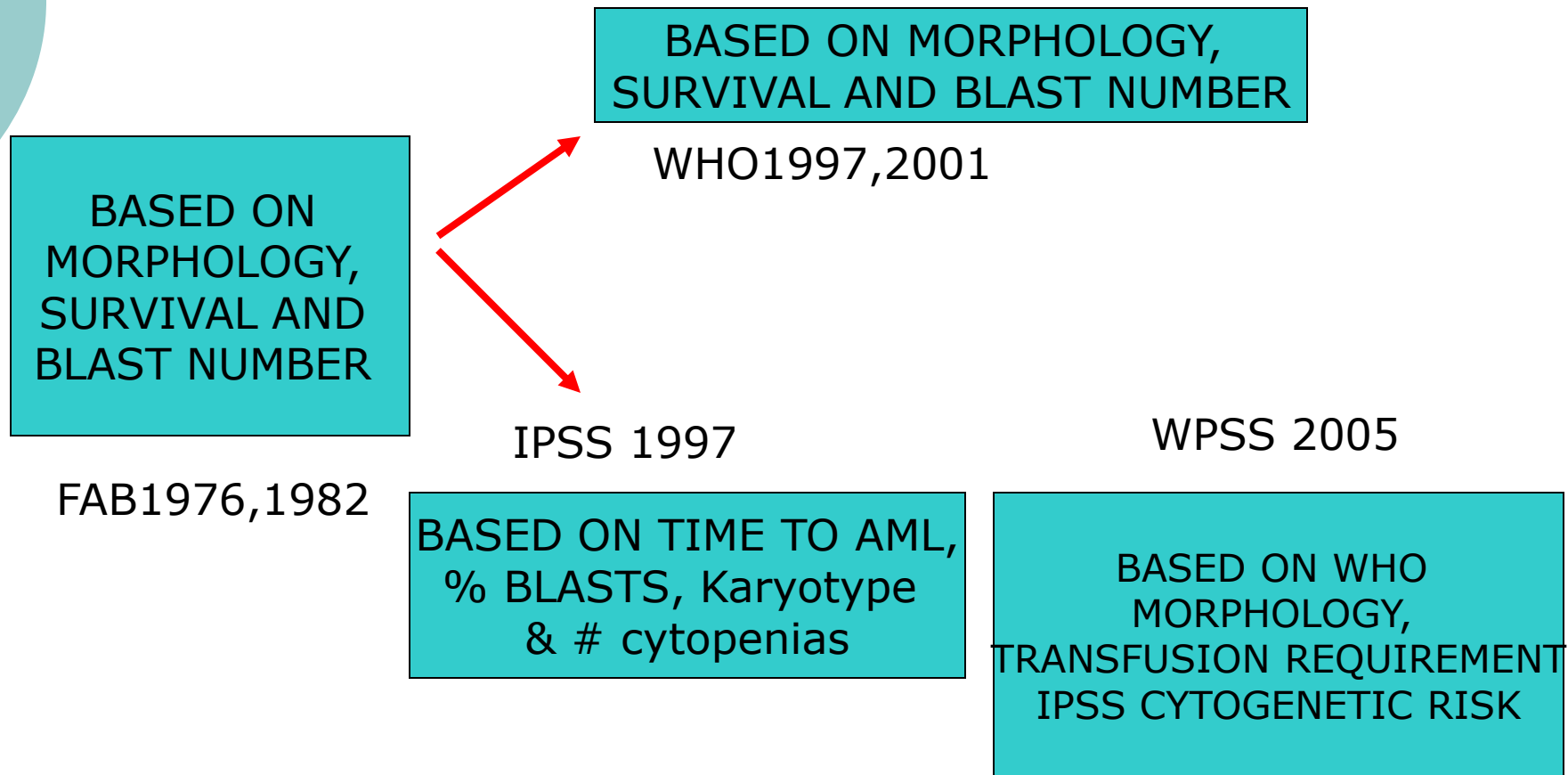
Greenberg P et al blood 1997;80:2077-

Overall IPSS Score and Survival

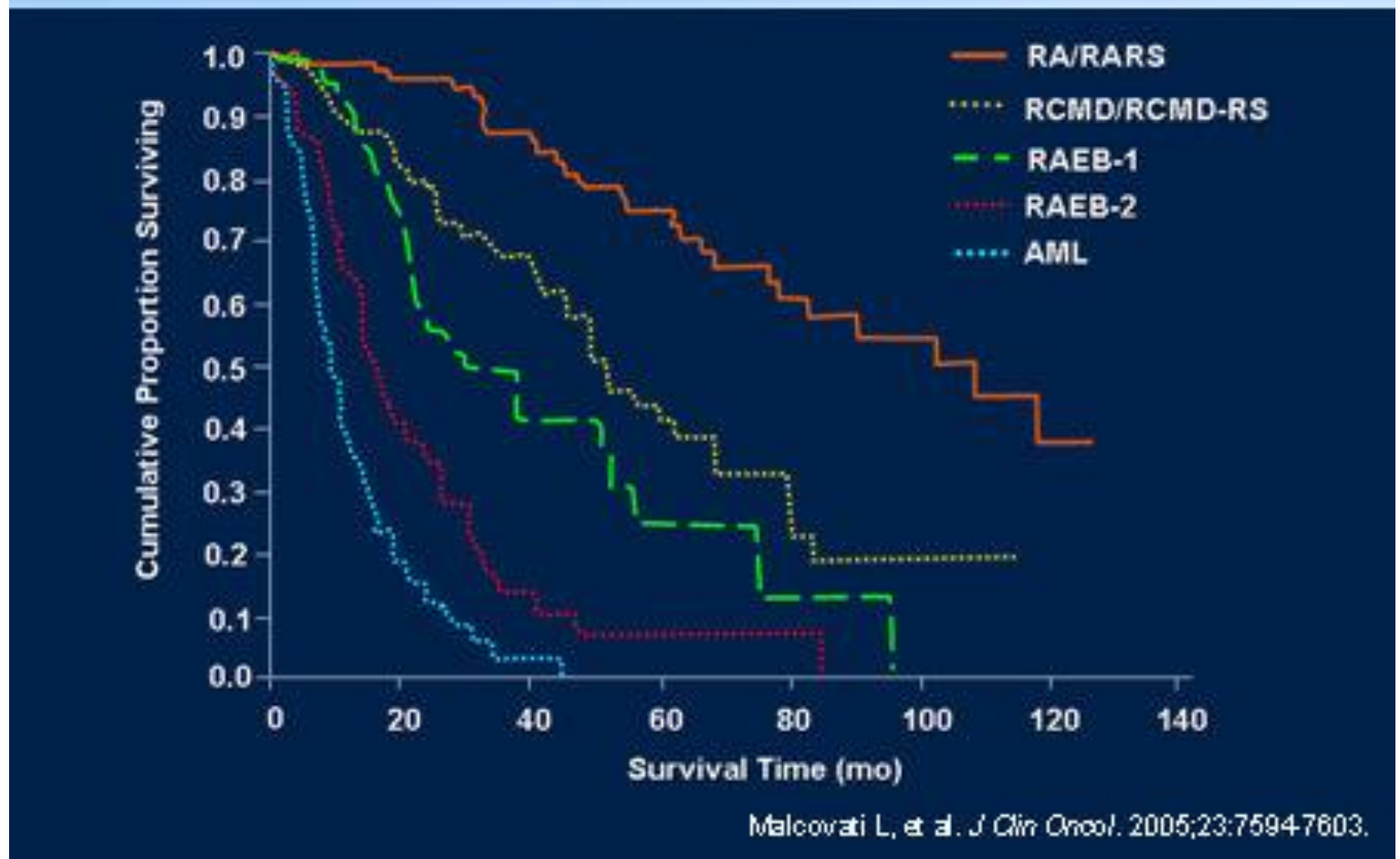
| Overall Score | Survival |
|----------------------|-----------------|
| Low (0) | 5.7 Yrs |
| Intermediate | |
| 1 (0.5 or 1.0) | 3.5 Yrs |
| 2 (1.5 or 2.0) | 1.2 Yrs |
| High (≥ 2.5) | 0.4 Yrs |

Based on blast%, cytogenetics & cytopenia

Evolution of MDS Classification Systems



Overall Survival of MDS patients classified by WHO criteria

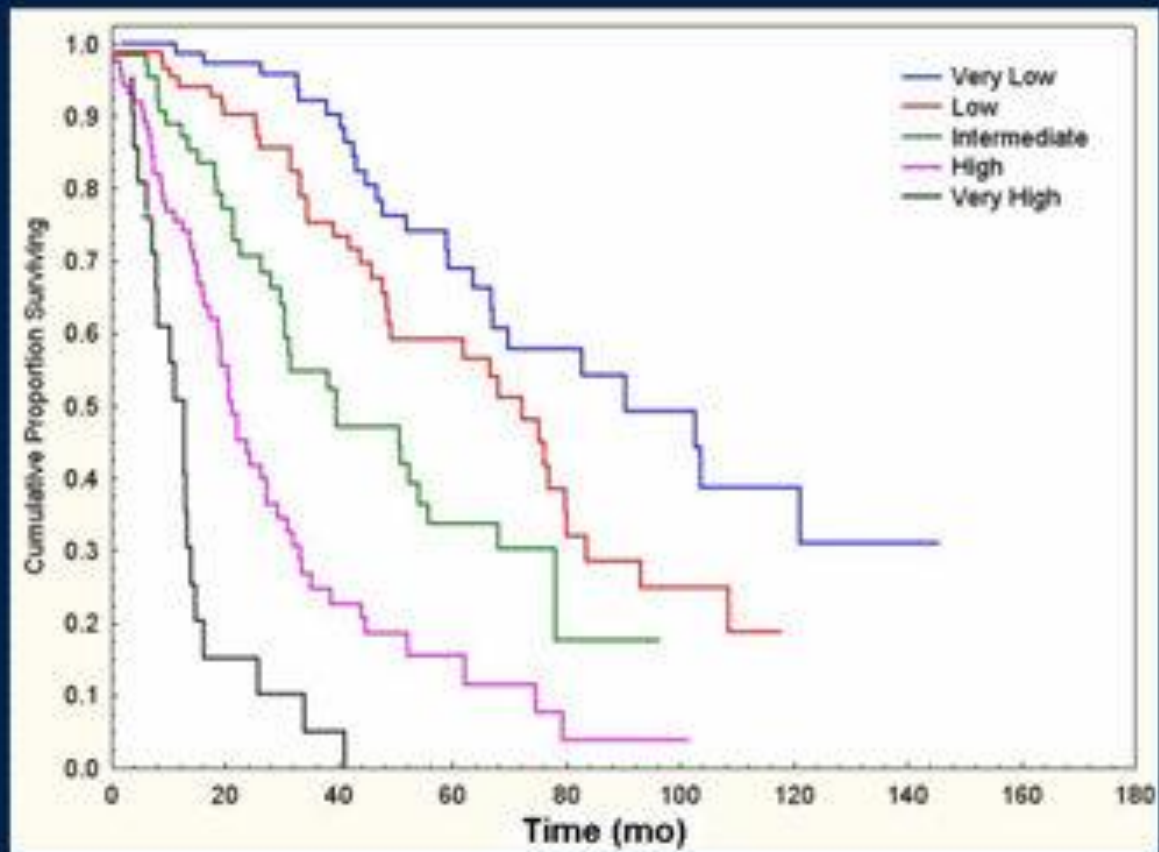


WPSS: WHO-Based Prognostic Scoring System for predicting survival in MDS

| | POINTS | | | |
|-------------------------|---------------|---------------|--------|--------|
| | 0 | 1 | 2 | 3 |
| WHO SUB-TYPE | RA, RARS, 5Q- | PRCM, RCMD-RS | RAEB-1 | RAEB-2 |
| TRANSFUSION REQUIREMENT | NONE | REGULAR | - | - |
| IPSS CYTOGENETIC RISK | GOOD | INTERMEDIATE | POOR | |

WPSS RISK SCORE: VERY LOW:0, LOW:1, INTERMEDIATE:2
HIGH:3-4, VERY HIGH: 5-6

Survival based on WPSS



MYELODYSPLASTIC SYNDROMES



Treatment of MDS: something old, something new, something borrowed...

Mikkael A. Sekeres¹

¹Department of Hematologic Oncology and Blood Disorders, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Treatment of MDS

- Supportive Care
 - Transfusion: red cells. Platelets
 - Antibiotics for infection
- Growth factors
 - Erythropoietin
 - G-CSF, GM-CSF
 - Romiplostim, Eltrombopag
- Hypomethylating agents
 - Azacytidine
 - Decitabine
- Miscellaneous agents
 - IMiDS
 - ATG, Alemtuzumab
 - Chemotherapy: intensive, cytosine, clofarabine
- Allogeneic Stem Cell transplantation



Goals of treatment in MDS

- Low Risk
 - minimizing transfusions
 - restoring effective blood cell production
 - maximizing quality of life
- High Risk
 - attaining a partial or complete remission
 - prolonging survival
 - maximizing quality of life
- Cure

Use of erythropoiesis stimulating agents (ESAs) in MDS patients.

| Study group | Study design | N | Results |
|-------------------------|--|--------------------------------|--|
| Nordic ¹⁷ | Matched cohort of ESA-treated Nordic patients to untreated Pavia patients | 121 Nordic 237 Pavia, Italy | Survival advantage for ESA-treated group (HR = .61, $P = .002$) |
| GFM ¹⁸ | Matched cohort of ESA-treated GFM patients with untreated IMRAW patients | 403 GFM | Survival advantage for ESA-treated group (HR = .43, 95% CI: .25-.72) |
| Cleveland ¹² | Systematic review of 162 trials published from 1985-2005 comparing ESA-treated patients with non-GF-treated patients | 1587 ESA 1005 Non-GF | Survival advantage for ESA-treated group at 2 years follow-up (79% vs. 68%, $P = .005$) |

J Clin Oncol. 2008; 26:3607-3613.
Blood. 2008; 111: 574-582.
Br J Haematol. 2002;118: 174-180.

Predicting response to ESA

- **GOOD RESPONSE GROUP** 74%
 - < 2 units prbc /month
 - EPO level < 500 IU
- **INTERMEDIATE RESPONSE GROUP** 24%
- **POOR RESPONSE GROUP** 7%
 - \geq 2 units pRBC / month
 - EPO >500 IU—the “poor” ESA

40,000 units/week : average response 40% reduction in transfusion

ROMIPLOSTIM- tpo receptor agonist peptibody

- Phase I/II
- 44 patients
- Weekly injections of 300, 700, 1000, or 1500 µg romiplostim
- SAE: 5 patients (11%)
- Progression to AML: 2
- transient increases in blast%: 4
- Durable platelet response: 19 patients (46%)
- Suggested dose: 700µg weekly

Lenalidomide in del (5q)MDS-1

- Phase II registration study
 - Low risk, transfusion-dependent MDS with the del(5q)
- Dose
 - 10 mg/day for a 28-day cycle
 - or 10 mg/day for 21 days of a 28 day cycle
- Number 148
- Response: 99 (67%) achieved transfusion independence
- Complete cytogenetic responses : 45%
- Median duration of RBC transfusion- independence:2.2 yrs
- one third of transfusion-independent responders remained transfusion independent after 3 years of therapy.

List A et al. N Engl J Med. 2006;355:1456-1465.

Lenalidomide in del (5q)MDS -2

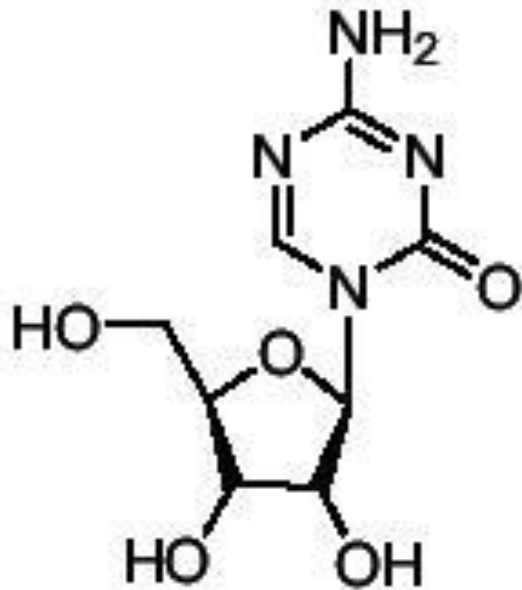
- Grade 3-4 myelosuppression : 50%
- Dose-reduction:84%.
- Response
 - younger age,
 - shorter duration of MDS
 - lower transfusion needs
 - treatment-related thrombocytopenia.
 - no baseline neutropenia,with decline in neutrophils by 75%
- All patients ultimately relapse

Lenalidomide in other MDS

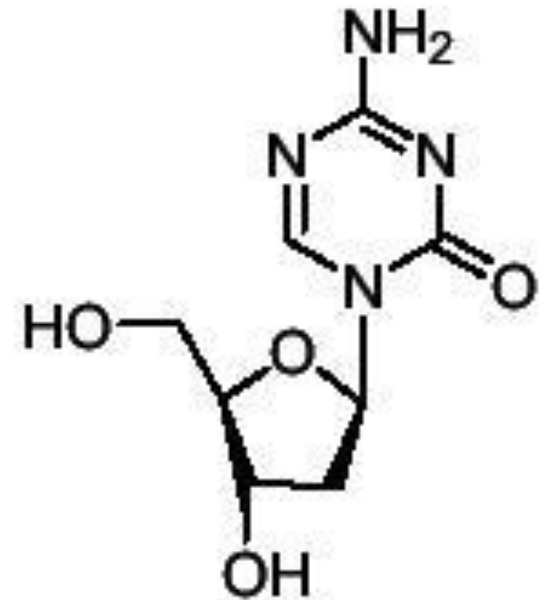
- Phase II registration study
 - Low risk, transfusion-dependent MDS with the del(5q)
- Dose
 - 10 mg/day for a 28-day cycle
 - or 10 mg/day for 21 days of a 28 day cycle
- Number 215
- Response: 56 (26%) achieved transfusion independence
- Median duration of RBC transfusion-independence: 41 weeks
- Grade III-IV Myelosuppression: 25%

Hypomethylating agents

5-Azacytidine

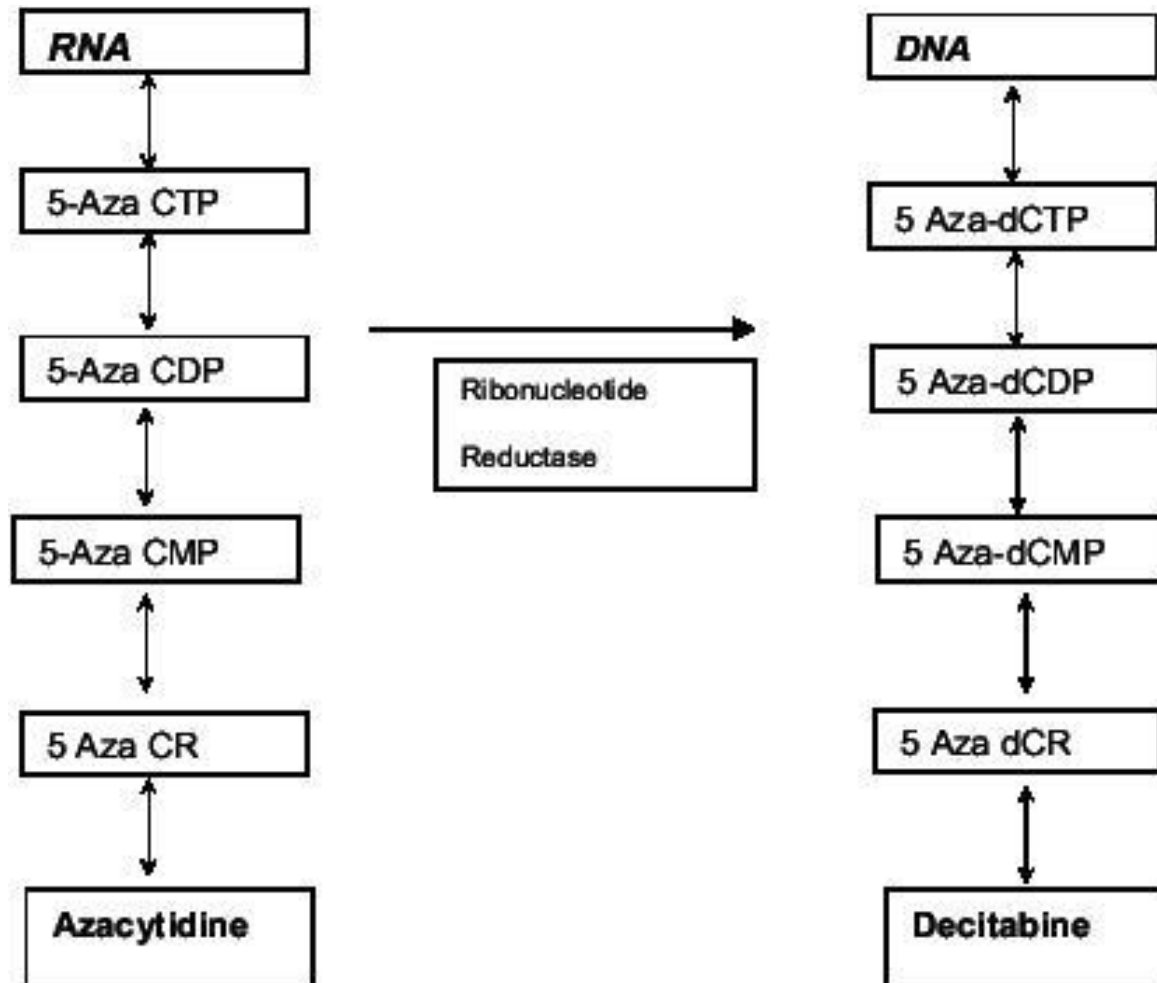


Decitabine



The ring structure of 5 Azacytidine and 5 Aza-2-deoxycytidine showing substitution of N at position 5. Azacytidine is attached to a ribose sugar whereas 5 Aza-2-deoxycytidine is attached to a deoxyribose.

Incorporation of Azacytidine into RNA and its metabolite 5 Aza 2 deoxycytidine (Decitabine) into DNA.



Azacytidine in MDS

- Phase III Randomized cross over
 - High and intermediate risk
- Dose
 - 75mg/m² x 7 days every 28 days
- Number Rx 99 Control: 92 [49 crossed over]
- CR +PR: 14%
- There was a significant delay in transformation
- to AML or death
- No significant prolongation of survival in the treatment arm.
- Major toxicity : cytopenia

Silverman LR et al CALGB. J Clin Oncol. 2006;24:3895-3903.

Azacytidine in MDS -2

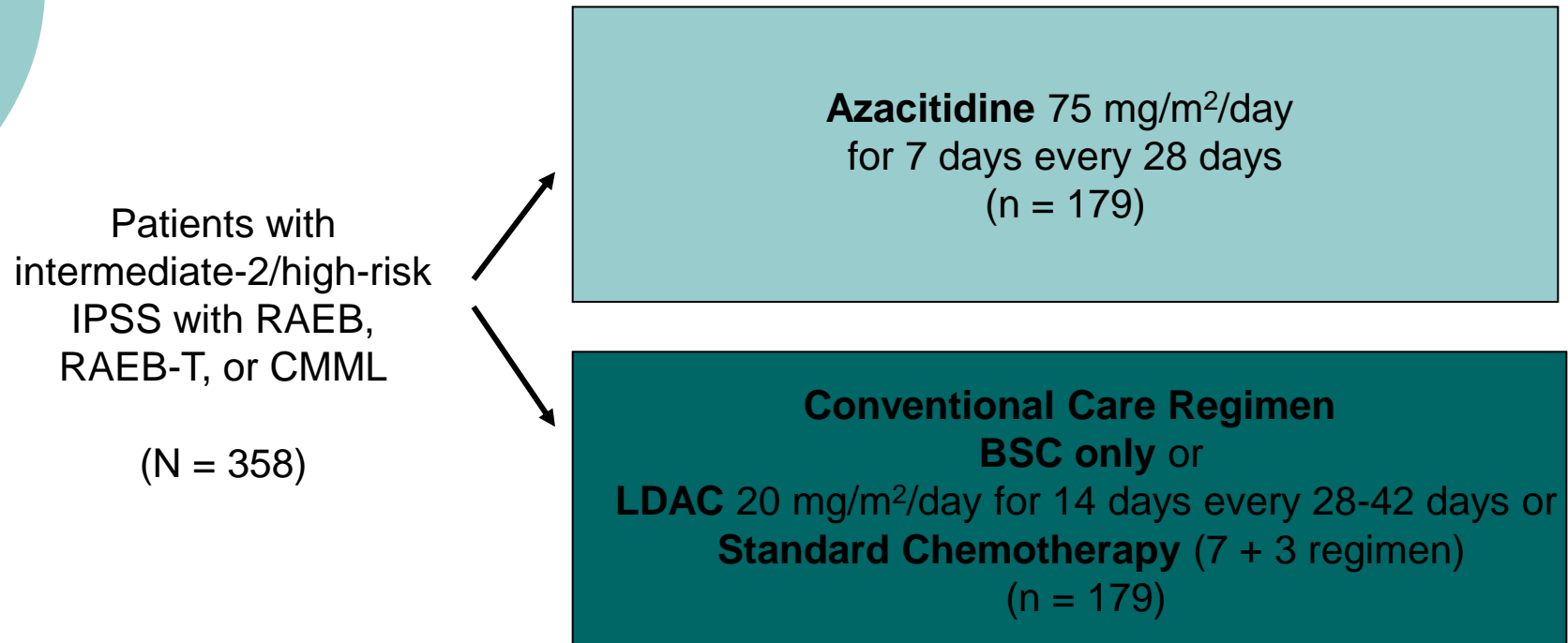
- Phase III Randomized cross over
 - High and intermediate risk
- Dose
 - 75mg/m² x 7 days every 28 days
- Number 358 Rx 179 BSC: 179
- RESPONSE

| | Rx | BSC |
|----------|-------|-----|
| ○ CR +PR | 29% | 21% |
| ○ OS | 24.5% | 15% |

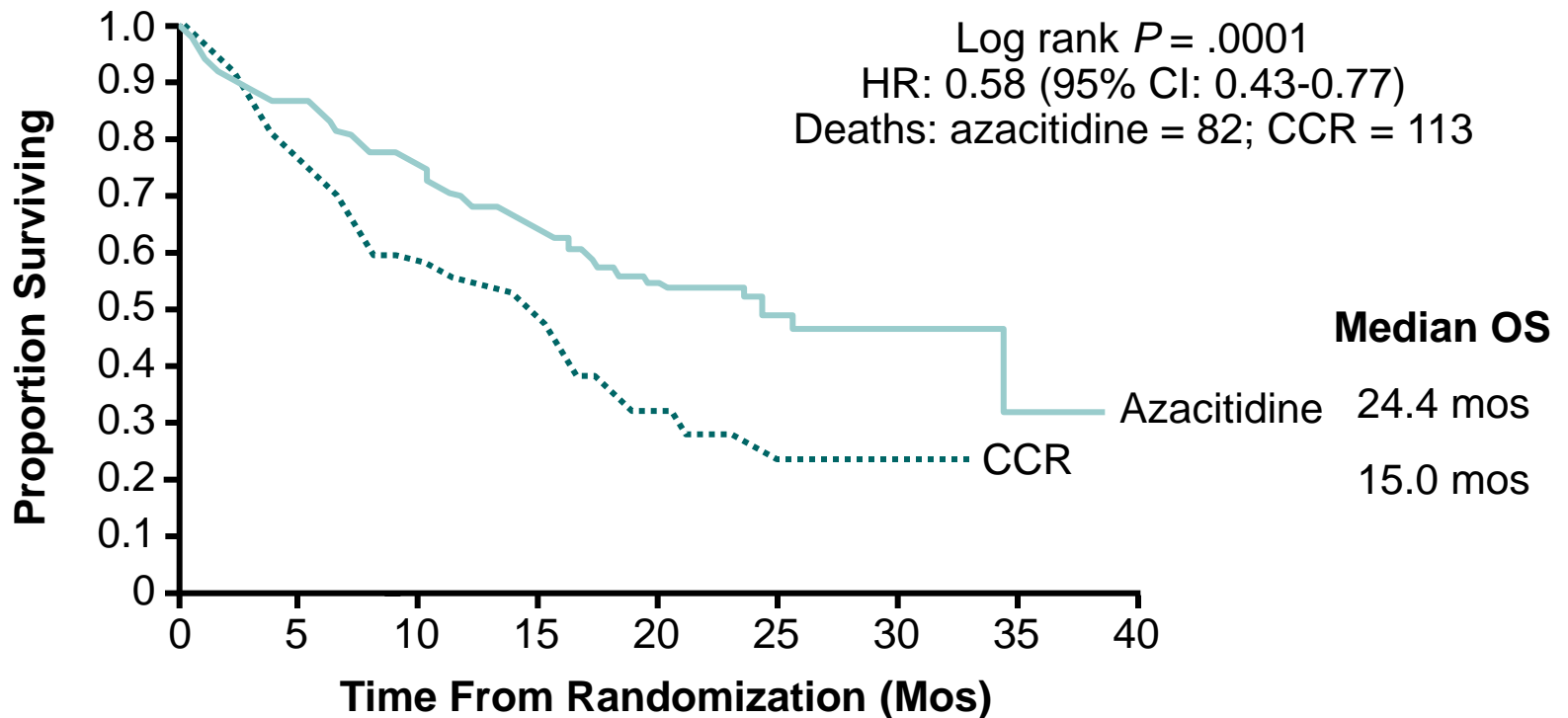
(hazard ratio .58, $P=.0001$)

Median duration of therapy: 9 months

Azacitidine for High-Risk MDS: AZA-001 Phase III Study



OS on AZA-001



Number at risk

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

Decitabine in MDS

| | | | |
|--------------------------------|---------------------------|---|--|
| Decitabine (DAC) ² | Phase III | 89 randomized to DAC 81 randomized to BSC All MDS subtypes | CR+PR rate 17% for DAC; Time to AML progression or death longer for DAC only in higher-risk group (11 vs 6 months, $P = .028$) |
| Decitabine (DAC) ³⁶ | EORTC 06011: Phase III | 119 randomized to DAC 114 randomized to BSC Higher-risk MDS | CR+PR rate 23% for DAC; median OS 10.1 months for DAC vs 8.5 months for BSC (HR = .88, $P = .38$) |

Kantarjian H, et al Blood. 2007;109:52-57.

Steensma DP et al (MDS) [abstract]. Blood. 2007;110:1450.

WijerMans P et al [abstract]. Blood. 2008;112:226.

Miscellaneous Agents

- **Clofarabine.**
 - oral and iv
- Number:61 patients
 - higher-risk MDS or AML(45%)
 - Previous treatment with azacytidine:52%
- Response
 - CR 30% (13% in pats failing azacytidine)
- **Ezatiostat** (TLK 199), a glutathione-S transferase P1-1 inhibitor
- Phase I study :45 patients
- Dose: 200 mg to 6000 mg daily x 7 days of a 21-day cycle,
- 17 patients (38%) achieved a hematologic improvement



Supportive care and chelation therapy in MDS: are we saving lives or just lowering iron?

Heather A. Leitch¹ and Linda M. Vickers¹

¹Division of Hematology, St. Paul's Hospital and the University of British Columbia, Vancouver, BC, Canada

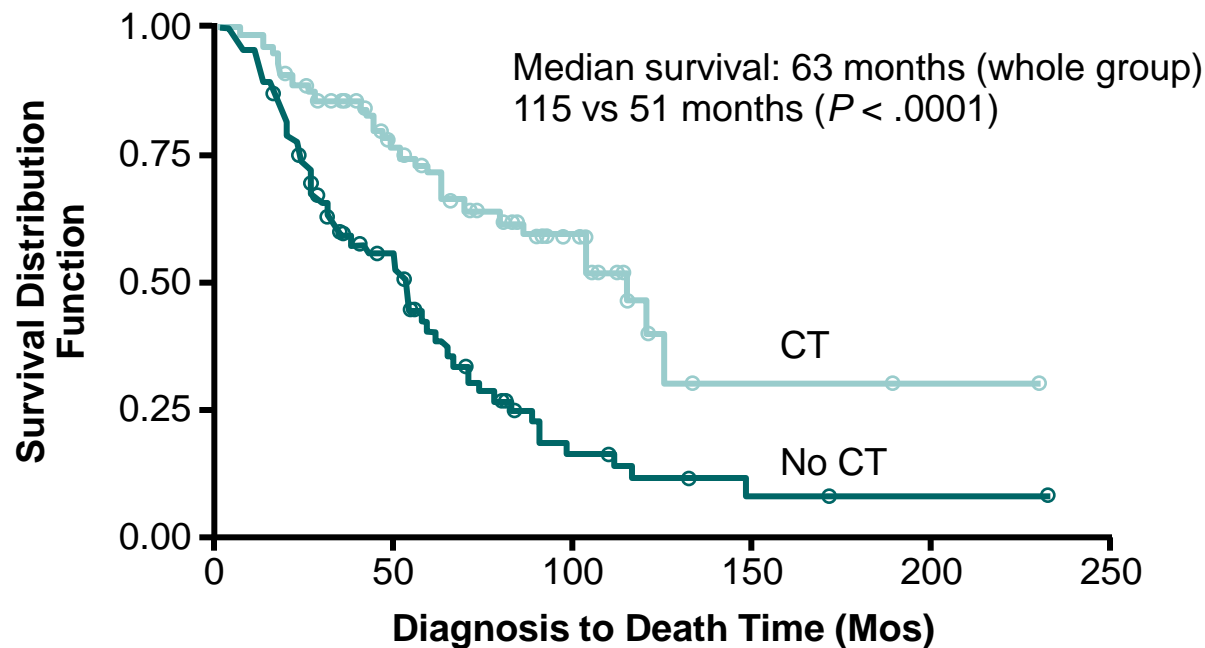
Hematology 2009

Iron Chelation Therapy and Survival in MDS

- Survey of 170 patients with MDS referred for RBC transfusion at 18 French treatment centers during 1-month period in 2005
 - Assessments: hematologic data, RBC transfusion requirement, iron chelation therapy, and iron overload
 - Cohort survival prospectively followed and reanalyzed on May 15, 2007
- Standard iron chelation therapy
 - Subcutaneous deferoxamine 40 mg/kg/day for 3-5 days/week: n = 41
 - Deferiprone 30-75 mg/kg/day: n = 5
 - Subcutaneous deferoxamine + deferiprone: n = 5
 - Deferasirox 20-30 mg/kg/day: n = 6
- Low-dose iron chelation therapy
 - Subcutaneous deferoxamine bolus 2-3 g/week: n = 12
 - Intravenous deferoxamine 50-100 mg/kg once after RBC transfusion: n = 7

Iron Chelation Therapy and Survival in MDS

- OS significantly better for patients who received iron chelation therapy
- Results consistent across all subgroups analyzed (IPSS low and intermediate-1, sex, age)





Stem Cell transplantation for Myelodysplastic Syndromes

? From the frying pan into the fire

The only curative treatment for MDS

Choosing the patient with MDS who is most likely to benefit from a transplant

- There should be no unrealistic expectations in an older patient with high risk MDS
 - 6-12 months of poor quality life before certain death versus
 - Death during transplant: 50%
 - **Cure with quality of life 25%**
 - Poor quality life with chronic graft versus host disease: 25%

Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes

Rodrigo Martino, Simona Iacobelli, Ronald Brand, Thekla Jansen, Anja van Biezen, Jürgen Finke, Andrea Bacigalupo, Dietrich Beelen, Jossy Reiffers, Agnes Devergie, Emilie Alessandrino, Ghulam J. Mufti, Renée Barge, Jorge Sierra, Tapani Ruutu, Marc Boogaerts, Michele Falda, Jean-Pierre Jouet, Dieter Niederwieser, and Theo de Witte, for the Myelodysplastic Syndrome subcommittee of the Chronic Leukemia Working Party of the European Blood and Marrow Transplantation Group

| | Conditioning (RIC) | Standard myeloablative (SMC) | |
|------------|--------------------|------------------------------|---------|
| Patient no | 215 | 621 | |
| Age >50 | 73% | 28% | |
| NRM | 22% | 32% | p=0.04 |
| Relapse | 45% | 27% | p<0.01 |
| PFS | 33% | 39% | p=0.7 |
| OS | 41% | 45% | p=0.4 |
| aGVHD | 46% | 65% | p<0.001 |

Blood. 2006;108:836-846

And a Silver Sixpence In Your Shoe

- US cost of transfusing one unit RBC: \$500 + other costs of \$450 per unit.
- The median number of RBC units/year: 11.1 (range 0-91.3)
- Cost of therapeutic agents used to treat MDS : \$63,577; when
- Agent + transfusion + Chelation: \$104,989/ year.

It is our responsibility then, as healthcare providers, to be judicious in recommending expensive therapies because of their "newness," and as researchers to develop medically and economically sound algorithms for how to rationally treat the patient with MDS.

All "p" values must be kept in perspective