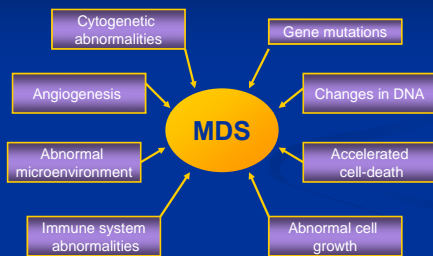


Advances in the Treatment of High-Risk Myelodysplastic Syndrome

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What's going on in the bone marrow? (don't worry, I'll explain these)



How do we treat MDS?

- Supportive Care (transfusions, antibiotics, CSFs/ESAs, iron chelation)
- Hypomethylating agents (azacitidine, decitabine)
- Immunomodulators (e.g. lenalidomide, ATG)
- Hematopoietic stem cell transplantation
- Novel Agents/Clinical trials

But, before we decide “how” to treat, we need to know...

- Why are we treating???

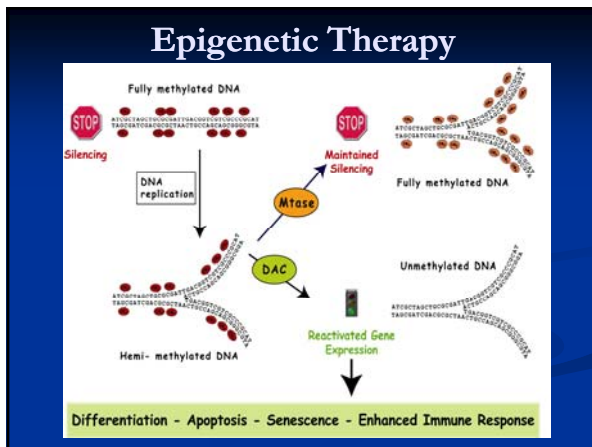
Goals of Treatment

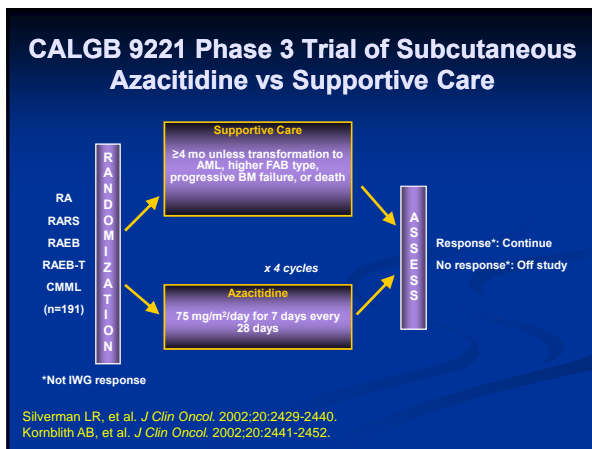
- If possible, cure me
- If you can't cure me, at least make me live longer and feel better
- If you can't make me live longer, at least make me feel better
- If you can't even make me feel better, then get me another doctor and go back to school...

**Curative therapy:
stem cell transplantation**

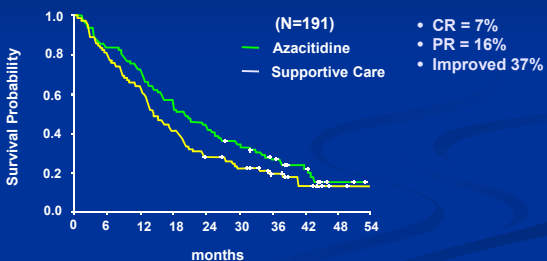
- Therapy of choice for patients < 60 years with high-risk features (increased blasts, unfavorable chromosomes)-move quickly!
- Usually not advised for lower-risk patients
- Best situations: 45-70% long-term survival
- Reduced-intensity transplants feasible for older patients, but generally higher relapse rates, need to be in remission to work
- Lots more info in Dr. Deeg's lecture

Moving along to living longer and better...





Randomized Study of Azacitidine in Patients With MDS: Results



Silverman et al. *J Clin Oncol.* 2002;20:2429

Effect of Azacitidine on Quality of Life and Transfusions

Improvement in:

- Fatigue
- Dyspnea
- Physical functioning
- Positive affect
- Psychologic distress

45% became transfusion-independent

9% had a 50% reduction in transfusions

Silverman LR, et al. *J Clin Oncol.* 2002;20:2429-2440.
Kornblith AB, et al. *J Clin Oncol.* 2002;20:2441-2452.

Azacitidine vs Supportive Care: Most Frequent Adverse Events (>30%)

Adverse event	Azacitidine (n=220), %	Supportive care (n=92), %
Nausea	70.5	17.4
Anemia	69.5	64.1
Thrombocytopenia	65.5	45.7
Vomiting	54.1	5.4
Pyrexia	51.8	30.4
Leukopenia	48.2	29.3
Diarrhea	36.4	14.1
Fatigue	35.9	25
Injection site erythema	35.0	0.0
Constipation	33.6	6.5
Neutropenia	32.3	10.9
Ecchymosis	30.5	15.2

Silverman LR, et al. *J Clin Oncol.* 2002;20:2429-2440.
Kaministkas F, et al. *Clin Cancer Res.* 2005;11:3604-3608

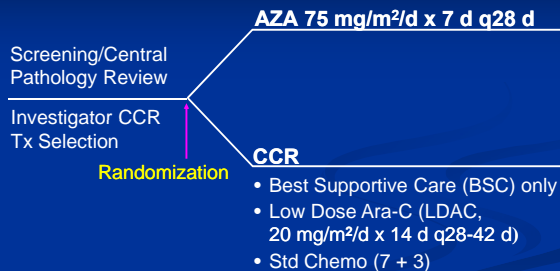
ASH 2007: Azacitidine Treatment Prolongs Overall Survival in Higher-Risk MDS Patients Compared with Conventional Care Regimens: Results of the AZA-001 Phase III Study

P Fenaux, MD, GJ Mufti, MD, V Santini, MD, C Finelli, MD, A Giagounidis, MD, R Schoch, MD, A List, MD, S Gore, MD, J Seymour, MD, E Hellstrom-Lindberg, MD, J Bennett, MD, J Byrd, MD, J Backstrom, MD, L Zimmerman, BSN, D McKenzie, MS, CL Beach, PharmD and L Silverman, MD on behalf of the International Vidaza High-Risk MDS Survival Study Group

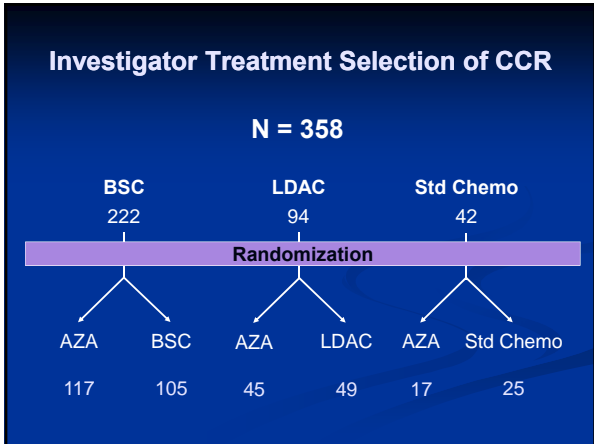
Azacitidine Survival Study: Study Design

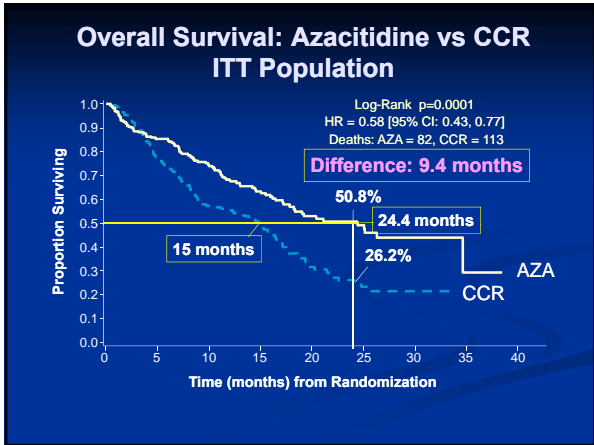
- Phase III, international, multicenter, prospective, randomized, controlled, parallel-group study
- Inclusion Criteria
 - High-Risk MDS pts:
 - RAEB, RAEB-T or CMML according to FAB
 - IPSS score of INT-2 or High

Azacitidine Survival Study



BSC was included with each arm
Tx continued until unacceptable toxicity or AML transformation or disease progression





- ### Secondary Endpoints
- Time to AML or death
 - 13 mos with AZA vs 7.6 mos with CCR, p=0.003
 - Time to AML
 - 26.1 mos with AZA vs 12.4 with CCR, p=0.004
 - RBC Transfusion Independence
 - 45% with AZA vs 11% with CCR, p<0.0001
 - Infections Requiring IV Antimicrobials
 - Reduced by 33% with AZA vs CCR
- Fenaux et al. Lancet Oncol:2009,Mar10(3), 223-32.

ASCO 2008
Azacitidine extends overall survival (OS) in higher-risk MDS without the necessity for complete remission

Alan List, Pierre Fenaux, Ghulam Mufti, Eva Hellstrom-Lindberg, Steven Gore, John Bennett, Lewis Silverman, Jay Backstrom and CL Beach on behalf of the International Vidaza High-Risk MDS Survival Study Group

Conclusions, List et al.

- IWG response of HI, PR or CR associated with improved survival with azacitidine
- Authors suggest continuation of aza even in absence of CR

ASCO 2008
The Effects of Continued Azacitidine Treatment Cycles on Response in Higher-Risk Patients with Myelodysplastic Syndromes

Lewis R. Silverman, MD; Pierre Fenaux, MD, PhD; Ghulam J. Mufti, MBBS, DM, FRCP; Valeria Santini, MD; Eva Hellström-Lindberg, MD, PhD; Norbert Gattermann, MD; Guillermo Sanz, MD, PhD; Alan F. List, MD; Steven D. Gore, MD; John F. Seymour, MBBS, PhD, FRACP; Jay Backstrom, MD, MPH; David McKenzie, MS; and CL Beach, PharmD

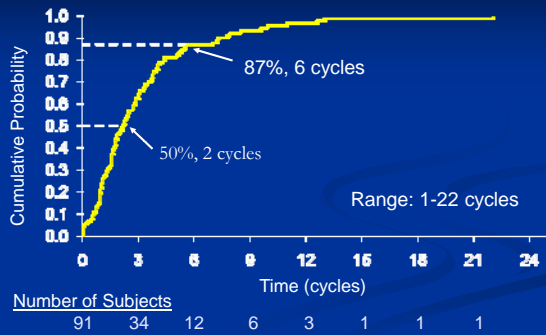
AZA Treatment Cycles Received by Patients Achieving a Response

IWG 2000 Response	AZA Cycles	
	Median	Range
Overall (n=91)	14.0	2-30
CR (n=30)	16.5	5-30
PR (n=21)	14.0	2-27
HI (n=40)	11.5	3-25

Of 179 patients who received AZA, 91 (51%) achieved an IWG 2000 response (CR, PR, or HI)

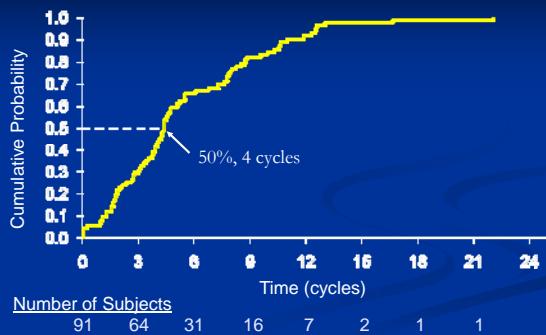
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Time to First Response (CR, PR, or HI)

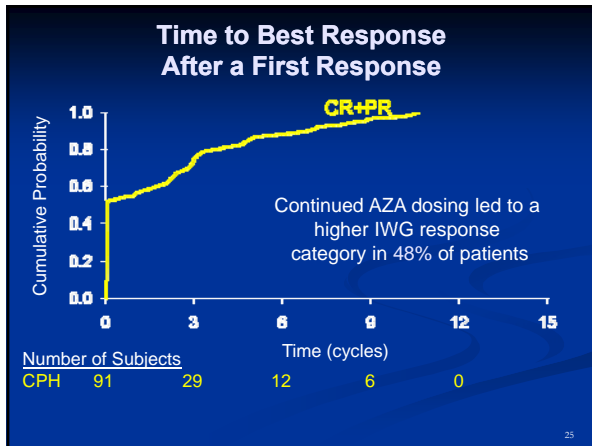


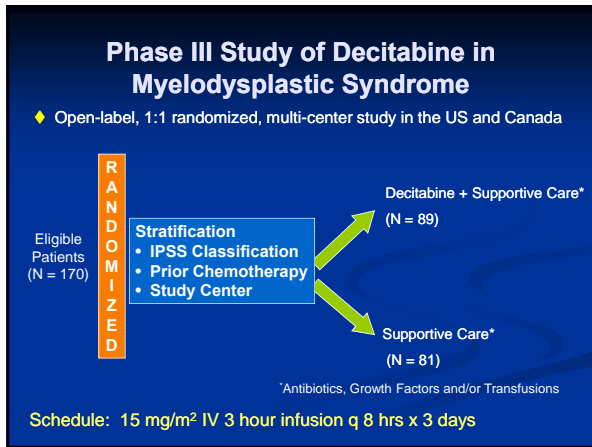
23

Time to Best Response



24





Response* to Decitabine (ITT)

IWG Response Rate, Onset & Duration	Decitabine (n = 89)	Supportive Care (n = 81)
Overall Response Rate (CR+PR)	15 (17%)**	0 (0%)
Complete Response (CR)	8 (9%)	0 (0%)
Partial Response (PR)	7 (8%)	0 (0%)
Hematologic Improvement (HI)	12 (13%)	6 (7%)

**p-value <0.001 from two-sided Fisher's Exact Test

Onset & Duration of Response (Months)	Decitabine (n = 89)	Supportive Care (n = 81)
Median time to (CR+PR) response	3.3 (2.0 - 9.7)	N/A
Median Duration of (CR+PR) response	10.3 (4.1 - 13.9)*	

*For patients with a confirmed date of progression

Best response observed after 2 cycles (median number of cycles = 3)

Kantarjian, Cancer 2006.

Study D-0007

Quality of Life (QOL)

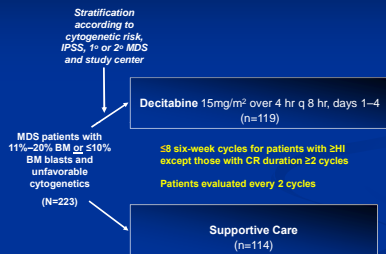
- Decitabine statistically superior to supportive care in:
 - Improvement of Global Health status
 - Physical functioning
 - Fatigue
 - Dyspnea

*Quality of Life (QOL) was measured using the European Organization for Research and Treatment of Cancer QOL scale. Kantarjian H, et al. *Cancer*. 2006;106:1794-1803.

Study D-0007

Phase III Study of Low-Dose Decitabine vs Supportive Care in Elderly Patients With Int or High Risk MDS

EORTC 06011 Randomized, Multicenter, Phase III Trial



Primary endpoint: OS

Secondary endpoints: Time to AML or death, response, PFS, and safety

Wijermans P et al. *Blood*. 2008;112:90 [abstract 226]; updated results presented at: 50th ASH Annual Meeting, December 6–9, 2008, San Francisco, CA

Some thoughts about hypomethylating agents in MDS...

- Unclear when exactly to use in lower-risk patients
- Be patient: prepare for many months of treatment and expect to “get worse before you get better”
- Aza has a survival benefit in high-risk MDS, decitabine not yet shown, but might if the right study is done
- The survival benefit with aza is only 9 mos: PARTICIPATE IN CLINICAL TRIALS!
