Myelodysplastic Syndromes: Current Thinking on the Disease, Diagnosis, and Treatment

Vu H. Duong, MD, MS
Assistant Professor of Medicine
University of Maryland Greenebaum Comprehensive Cancer Center
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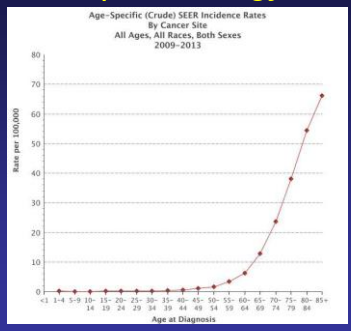
Introduction

- Group of malignant hematopoietic stem cell disorders
  - Atypical appearing cells (cytologic dysplasia)
  - Ineffective differentiation/maturation
  - Low peripheral blood counts
- Variably increased risk of progression to acute myeloid leukemia (AML)

Epidemiology



http://seer.cancer.gov/faststats/. Accessed July 1, 2016

Epidemiology

- Median Age ~70
- Age-adjusted annual incidence rate of MDS in the US: 3.3 per 100,000 people[1] (~10,000 new cases/year)
- Slight male predominance, except del(5q)
  - 25% to 30% of recently diagnosed patients with higher-risk MDS[2]
- Few RF identified: exposure to chemicals, radiation, tobacco, or chemotherapy, genetic abnormalities

1. Rollison DE, Blood. 2008
2. Sekeres MA, JNCI 2008

Signs/Symptoms

- Discovered incidentally or after a blood count is drawn due to symptoms, including:
  - fatigue (anemia)
  - infections (neutropenia)
  - bleeding (thrombocytopenia)
- Cytopenias:
  - Anemia, often macrocytic: ~85%
  - Neutropenia: ~50%
  - Thrombocytopenia: 67%[1]
    - Platelets <50 k/dL: 43%

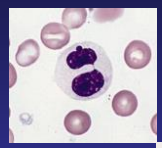
1. Kantarjian H et al, Cancer 2007;109:1705-14

Diagnosis

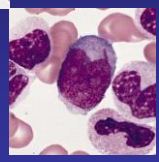
Review of peripheral blood smear can be helpful

Normal Neutrophil

Dysplastic Neutrophil



Blast with Auer Rod



library.med.utah.edu/WebPath

pathologyoutlines.com

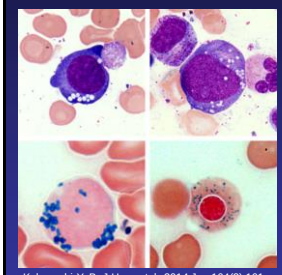
Diagnosis

* Bone marrow biopsy and aspirate is *essential* to establish the diagnosis, determine the subtype, and risk-stratify

- Morphologic evaluation
- Chromosome analysis (karyotype)
- Flow cytometry – detect cells with abnormal phenotype
- Mutational analysis

https://www.healthtap.com/

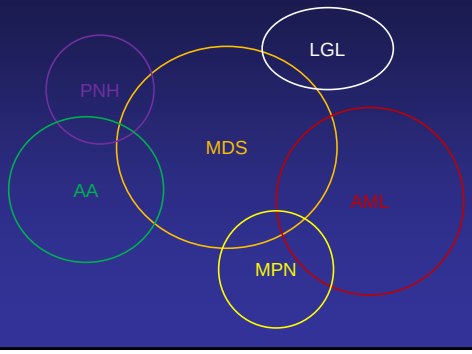
Mimics/Things to Rule Out

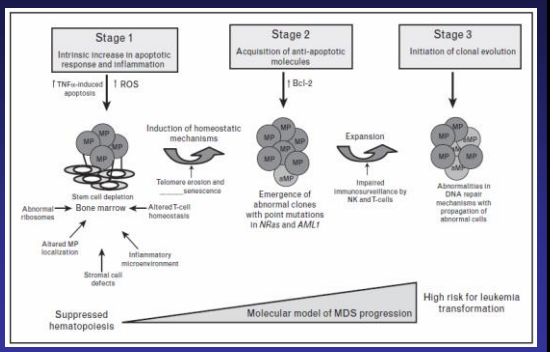


- B12/folate deficiency
- Copper deficiency
- Alcoholism
- Chemotherapy
- HIV, especially while on HAART
- Use of growth factors such as G-CSF (Neupogen)

Kobayashi Y. Br J Haematol. 2014 Jan;164(2):161

Disease Overlap





Epling-Burnette PK and List AF, Curr Opin Hematol 2009 16:70-76

Case

56 yo F p/w 4-week history of fatigue, nausea, sweating and fevers. She is slightly lightheaded with some shortness of breath. She has had a poor appetite but no weight loss.

Past Medical History: Migraine headaches, hypertension, h/o dental abscess

Medications: prn Tylenol, folic acid

Family History: no full siblings

Case

Laboratory Evaluation:

White blood cells 5.9 (4.5-11 K/mcL)

Absolute neutrophil count: 3.8 (1.7-7.3 K/mcL)

Hemoglobin 8.4 (11.9-15.8 g/dL)

Hematocrit 28.8 (35-45%)

Platelets 58 (160-370 K/mcL)

HIV, Hep C, B12, folate are all negative or normal

Case

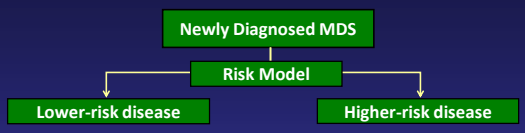
Bone marrow biopsy and aspirate:

- Hypercellular (90%) with atypical megakaryocytes and neutrophils, with no increase in blasts (<2%). Findings are consistent with myelodysplastic syndrome (refractory cytopenia with multilineage dysplasia).
- Karyotype: 47 XX, +8 [20]

WHO Classification in 2016

2008	2016
Refractory cytopenias with unilineage dysplasia (RCUD) Refractory Anemia (RA) Refractory Neutropenia (RA) Refractory Thrombocytopenia (RT)	MDS with single lineage dysplasia (MDS-SLD)
Refractory anemia with ring sideroblasts (RARS)	MDS with ring sideroblasts (MDS-RS) • MDS-RS with single lineage dysplasia (MDS-RS- SLD) • MDS-RS with multilineage dysplasia (MDS-RS-MLD)
MDS associated with isolated del(5q)	MDS with isolated del(5q)
Refractory cytopenia with multilineage dysplasia (RCMD)	MDS with multilineage dysplasia (MDS-MLD)
	MDS with excess blasts (MDS-EB)
Refractory anemia with excess blasts-1 (RAEB-1)	• MDS with excess blasts-1 (MDS-EB-1)
Refractory anemia with excess blasts-2 (RAEB-2)	• MDS with excess blasts-2 (MDS-EB-2)
MDS – unclassified (MDS-U)	MDS, unclassifiable (MDS-U)

Approach to Therapy



- Decrease transfusion burden
- Decrease symptoms
- Improve quality of life

- Alter natural history of disease
- Prevent progression to AML
- Improve overall survival

International Prognostic Scoring System

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

*Good: nl, -y, del(5q), del(20q) Poor: complex or chromosome 7 abn
Int: all others

	25% AML evolution (yrs)	Median Survival (yrs)
Low (0)	9.4	5.7
Int-1 (0.5-1)	3.3	3.5
Int-2 (1.5-2)	1.1	1.2
High (≥ 2.5)	0.2	0.4

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

WHO Classification Based System

Variable	0	1	2	3
WHO category	RA, RARS, 5q-	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	---
Tranfusion requirement	No	Regular	---	---

*Good: nl, -Y, del(5q), del(20q)
Poor: complex (≥ three abnormalities), chromosome 7 abnormalities
Intermediate: other abnormalities

	Median OS (months)	
Score: Risk Group	Learning Cohort	Validation Cohort
0: Very Low	103	141
1: Low	72	66
2: Intermediate	40	48
3-4: High	21	26
5-6: Very High	12	9

Malcovati L, et al. JCO 2007;25:3503-3510

Global MD Anderson Risk Model

Prognostic Factor	Points
Performance Status	
≥ 2	2
Age, y	
60-64	1
≥ 65	2
Platelets, x 10^9/L	
<30	3
30-49	2
50-199	1
Hemoglobin < 12 g/dL	2
Bone Marrow Blasts, %	
5-10	1
11-29	3
WBC > 20 x 10^9/L	2
Karyotype: Chromosome 7 abn or complex (≥ 3 abn)	3
Prior Transfusion, yes	1

Score	Median OS, months
Low: 0-4	54
Int-1: 5-6	25
Int-2: 7-8	14
High: ≥ 9	6

Kantarjian H. Cancer 2008; 113:1351-61

Revised IPSS

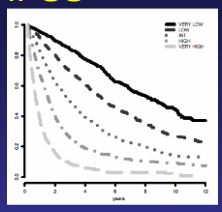
Prognostic Subgroup	Cytogenetic Abnormality	Median Survival, y
Very Good	-Y, del(11q)	5.4
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/ del(7q), complex: 3 abnormalities	1.5
Very Poor	Complex: > 3 abnormalities	0.7

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	--	Good	--	Int	Poor	Very Poor
BM blast, %	≤ 2	--	>2 - <5	--	5 - 10	>10	--
Hemoglobin	≥ 10	--	8 - <10	< 8	--	--	--
Platelets	≥ 100	50 - <100	< 50	--	--	--	--
ANC	≥ 0.8	< 0.8	--	--	--	--	--

Greenberg P. Blood 2012;120: 2454-2465

Revised IPSS

Category	Score
Very Low	≤ 1.5
Low	> 1.5 – 3
Intermediate	> 3 – 4.5
High	> 4.5 – 6
Very High	> 6

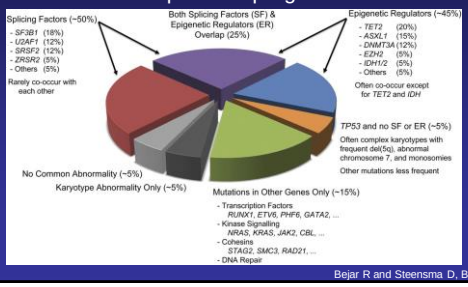


	OS, y	HR for OS	AML 25%, y	HR for AML
Very Low	8.8	0.5	NR	0.5
Low	5.3	1.0	10.8	1.0
Intermediate	3.0	2.0	3.2	3.0
High	1.6	3.2	1.4	6.2
Very High	0.8	8.0	0.73	12.7

Greenberg P, et al. Blood. 2012;120(12): 2454-2465

Point Mutations in MDS

- >90% of patients with MDS have at least 1 somatic mutation
- Some have independent prognostic value



Bejar R and Steensma D, Blood 2014

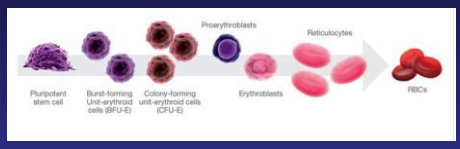
Lower-Risk Disease

- Observation
- Growth Factors
- Immunosuppressive Therapy
- Lenalidomide
- Hypomethylating Agents
- Clinical Trial

Observation

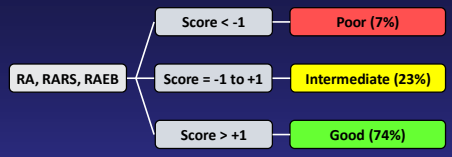
- Not all patients need active therapy for MDS
  - Mild peripheral blood abnormalities
  - No need for transfusions
  - Asymptomatic
- Treating lower-risk patients early has not been shown to improve outcomes

Erythropoiesis Stimulating Agents ± G-CSF



- 30-40% response rates in various studies
- Epoetin alfa and darbepoetin are likely as effective

Growth Factors



Serum EPO (U/l)	<100	+2
	100-500	+1
	>500	-3
RBC Transfusions	<2 units/m	+2
	≥ 2 units/m	-2

Modified from: Hellstrom-Lindberg E, BJH 2003

Caution with ESAs

- In some studies in patients with solid tumors receiving chemotherapy, ESAs have been linked to increased heart attacks, stroke, blood clots, tumor growth, and death
- This HAS NOT been shown in patients with MDS

ATG & Cyclosporine

- ATG with cyclosporine vs. best supportive care
  - low- to intermediate-risk pts with < 10% blasts
  - transfusion dependent < 24 months
- Increased hematologic response rates by 6 months (29% vs. 9%)
  - Median duration of response 16.4 months

Passweg JR, JCO 2010

Immunosuppressive Therapy

Favorable factors for response:

- Age
- Immune receptor type (HLA-DR15)
- Hypocellular marrow
- PNH clones
- Low CD4:CD8 ratio

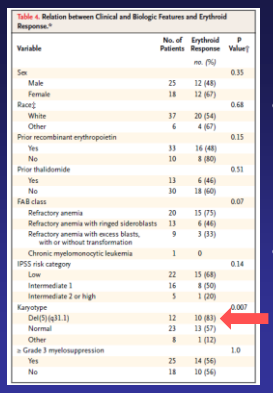


Table 4. Relation between Clinical and Biologic Features and Erythroid Response.*

Variable	No. of Patients	Erythroid Response	P Value†
		no. (%)	
Sex			0.35
Male	25	12 (48)	
Female	18	12 (67)	
Race‡			0.68
White	37	20 (54)	
Other	6	4 (67)	
Prior recombinant erythropoietin			0.15
Yes	33	16 (48)	
No	10	8 (80)	
Prior thalidomide			0.51
Yes	13	6 (46)	
No	30	18 (60)	
FAB class			0.07
Refractory anemia	20	15 (75)	
Refractory anemia with ringed sideroblasts	13	6 (46)	
Refractory anemia with excess blasts, with or without transformation	9	3 (33)	
Chronic myelomonocytic leukemia	1	0	
IPSS risk category			0.14
Low	22	15 (68)	
Intermediate 1	16	8 (50)	
Intermediate 2 or high	5	1 (20)	
Karyotype			0.007
Del(5)(q31.1)	12	10 (83)	
Normal	23	13 (57)	
Other	8	1 (12)	
‖ Grade 3 myelosuppression			1.0
Yes	25	14 (56)	
No	18	10 (56)	

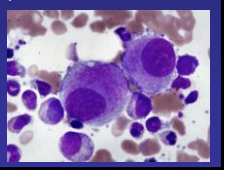
Lenalidomide – Phase I Study

- 43 patients with lower-risk MDS and symptomatic or transfusion-dependent anemia
- 24/43 patients responded (56%)
  - 10/12 patients with del5q responded (83%)

List AF et al, NEJM 2005

MDS with isolated del(5q)

- 10-15% of patients with MDS
- Presentation:
  - Normal or increased megakaryocytes in the bone marrow
  - <5% blasts in the bone marrow
  - Anemia with normal or elevated platelets in PB
- Female predominance
- Low risk of progression



Phase III study: MDS-004

- Primary endpoint: RBC-TI ≥ 26 consecutive weeks

	RBC-TI, n (%) [95% CI]		
	Placebo	Lenalidomide 5 mg	Lenalidomide 10 mg
mITT population	n = 51	n = 47	n = 41
Protocol defined (≥ 26 weeks)	3 (5.9) [1.2-16.2]	20 (42.6) [28.3-57.8]*	23 (56.1) [39.7-71.5]*
IWG 2000[13] (≥ 8 weeks)	4 (7.8) [2.2-18.9]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*
IWG 2006[14] (≥ 8 weeks)	3 (5.9) [1.2-16.2]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*

- Crossover allowed, but no improvement in survival seen

Fenaux P, Blood 2011

Lenalidomide Side Effects

- Neutropenia, thrombocytopenia – may require dose interruption/reduction
- Dry skin, rash, itching (esp. scalp)
- Diarrhea (esp. lactose intolerant patients)
- Muscle cramps
- Fatigue
- Rare: hypothyroidism, hypogonadism, deep venous thrombosis (blood clot)

All are generally manageable, most decrease with time and usually do not require permanent discontinuation

HMAs in lower-risk patients

- 151 patients (63% RA or RARS) randomly assigned to 1 of 3 different weekend-sparing AZA regimens

Table 2. HI Evaluated Using IWG 2000 Criteria

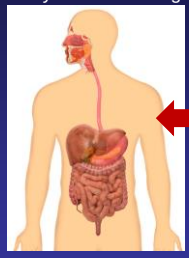
	Treatment Arm								
	AZA 5-2-2 (n = 50)			AZA 5-2-5 (n = 51)			AZA 5 (n = 50)		
HI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
HI-E									
Major	19/43	44	29 to 60	19/43	44	29 to 60	20/44	46	30 to 61
Minor	1/29	3	0.1 to 18	0		0 to 11	1/28	4	0.1 to 18
HI-P									
Major	12/28	43	25 to 63	8/30	27	12 to 46	11/22	50	28 to 72
Minor	0		0 to 11	0		0 to 10	1/27	4	0.1 to 19
HI-N									
Major	4/23	17	5 to 39	4/23	17	5 to 39	9/24	38	19 to 59
Minor	0		0 to 15	0		0 to 15	0		0 to 14
Any HI*	22/50	44	31 to 60	23/51	45	32 to 61	28/50	56	41 to 70

- Grade 3/4 toxicity: 84%, 77%, and 58%
- Marrow response and survival NOT evaluated

Lyons R et al. JCO 2009; 27:1850-1856

Iron Balance

Daily intake: 1-2 mg



~250 mg/unit

Daily losses: 1-2 mg

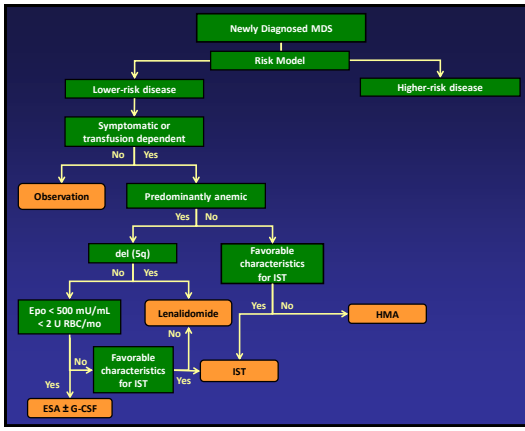
Long-term complications:

- Heart failure
- Liver disease
- Diabetes
- Skin changes
- Endocrine dysfunction

Iron Chelation Therapy

- Transfusion dependence and elevated ferritin correlate with poorer outcomes
- Deferasirox decreases serum ferritin and labile plasma iron, but high discontinuation rates (up to 80%)[1,2]
- Consider:
  - Lower-risk disease with long life expectancy
  - Serum ferritin greater than 1,000-2,500 mcg/L or other clinical evidence of iron overload

1. List AF et al. JCO 2012;30:2134-9
2. Gattermann N, et al. Leuk Res 2010;34:1143–1150



Our Patient

- Risk Score
  - IPSS: Intermediate-1
  - MDACC score: Low
  - IPSS-R: Intermediate
- Was not heavily transfusion dependent and was therefore started on darbepoetin
- Hemoglobin did not improve after 16 weeks of treatment, and she began needing more pRBC transfusions

Our Patient

White blood cells 1.9 (4.5-11 K/mcL)

- Absolute neutrophil count: 0.3 (1.7-7.3 K/mcL)
- 2% blasts

Hemoglobin 8.1 (11.9-15.8 g/dL)

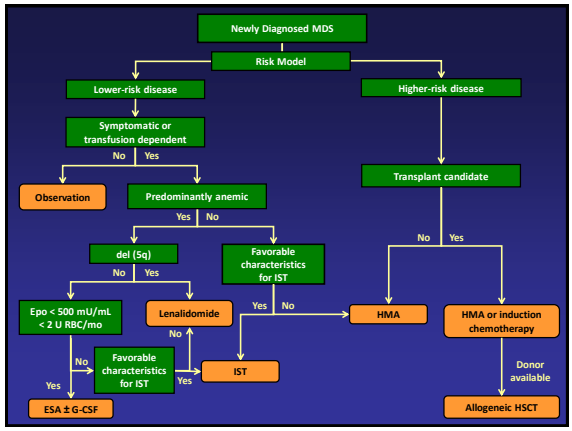
Hematocrit 28.8% (35-45%)

Platelets 41 (160-370 K/mcL)

Our Patient

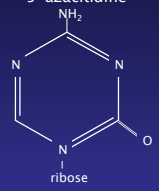
Bone marrow biopsy and aspirate:

- Hypercellular (90%) with trilineage dysplasia, with mildly increased blasts (7%), consistent with progression of MDS to refractory anemia with excess blasts-1.
- Karyotype: 47 XX, +8 [20]



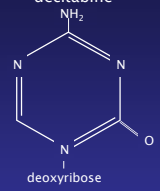
Hypomethylating Agents

5-azacitidine



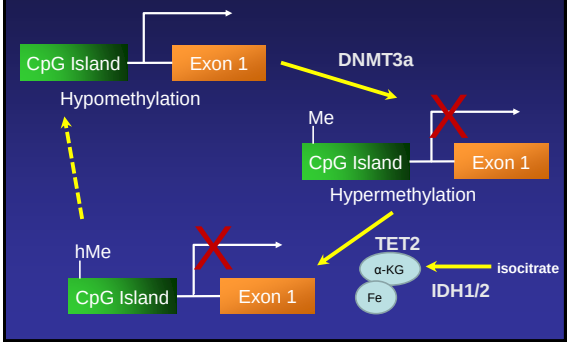
- Affects RNA metabolism and protein sythesis
- Can be converted to deoxyribonucleoside and inhibit DNA synthesis or DNA methyltransferase

decitabine



- Inhibits DNA synthesis and covalently binds to DNA-methyltransferase
- Higher demethylating activity
- Crosslinks DNA at high doses

DNA Methylation



Decitabine vs. Best Supportive Care

2 Phase III trials:

1) IPSS ≥ 0.5 (Intermediate 1 or higher)

	Decitabine, n=89	BSC, n=81	P value
Overall Response Rate	17% (9% CR)	0%	<0.001
Overall Survival	14.0 months	14.9 months	0.636

2) Elderly patients with higher-risk MDS

	Decitabine, n=119	BSC, n=114	P value
Overall Response Rate	34% (13% CR)	2%	NR
Overall Survival	10.1 months	8.5 months	0.38

Decitabine was NOT continued until disease progression

1. Kantarjian H, Cancer 2006
2. Lubbert M, JCO 2011

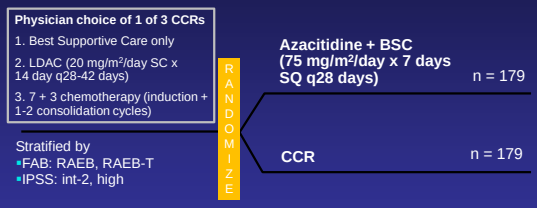
Azacitidine

- CALGB 9221: Phase III trial of Azacitadine vs. supportive care
  - Any FAB category
  - IPSS was only available for 81 patients (42%)
  - Crossover allowed after at least 4 months on supportive care arm

Endpoint	Azacitidine, n=99	BSC, n=92	P value
Overall Response Rate	60% (23% CR+PR)	5% (0 CR or PR)	<0.001
Time to AML/death	21 months	13 months	0.007
Overall Survival	20 months	14 months	0.10

Silverman LR et al, JCO 2002;20:2429-2440

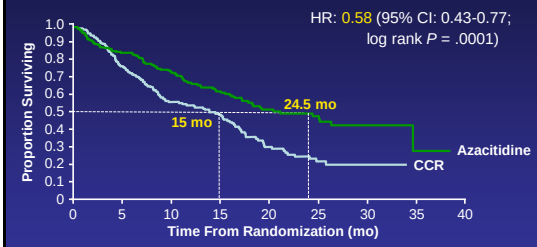
AZA-001: Azacitidine vs. CCR



Treatment continued until unacceptable toxicity or AML transformation or disease progression

Fenaux P, et al. Lancet Oncol. 2009;10:223

AZA-001: Azacitidine vs. CCR



ORR 29% (17% CR) in azacitidine arm vs. 12% (8% CR) in CCR arm

Fenaux P, et al. Lancet Onc 2009;10:223

Azacitidine – Other Issues

- Median cycles to 1st response: 2-3[1,2]
- Responders must continue treatment indefinitely
- Do NOT need a complete response to benefit[3]
  - OS benefit in AZA-001 trial was maintained even if CR patients were excluded
- Side effects: Decreased blood counts, nausea, constipation, fatigue, infections
  - Usually manageable without discontinuation of drug

1. Silverman LR, JCO 2006
2. Silverman LR, Cancer 2011
3. List AF, ASCO 2008, Abstract #7006

Our Patient

- Was started on azacitidine and referred for a transplant consultation.
- After 4 cycles her counts had not changed
- Repeat bone marrow biopsy:
  - Over 95% cellular with persistent trilineage dysplasia and increased blasts from 7% previously to 13% (RAEB-2)

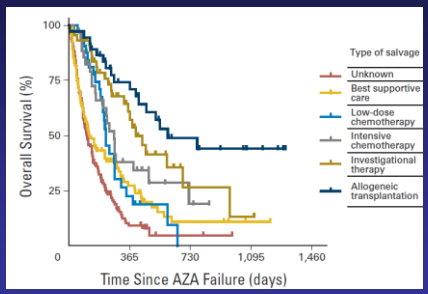
Outcomes after HMA Failure

MDS & CMML Patients

Institution	No. of Patients Treated	No. of HMA failures	AML Progression	Median OS (months)	OS at 12 months
MDACC[1]	NR	87	25 (29%)	4.3	30%
GFM[2]	435	NR	NR	5.6	29%
Moffitt[3]	151	59	12 (20.3%)	5.8	17%

1. Jabbour E et al, Cancer 2010; 116:3830
2. Prébet T et al, JCO 2011; 29:3322
3. Duong VH, Clin Lymphoma Myeloma Leuk 2013;13:711

Outcomes after HMA Failure



Prébet T et al, JCO 2011; 29:3322

Transplant in MDS

- ONLY potentially curative therapy for MDS, but is associated with significant complications

Life Expectancy (years)

IPSS Risk Group	At diagnosis	At AML progression
Low	6.51	7.21
Int-1	4.61	5.16
Int-2	4.93	2.84
High	3.2	2.75

- All patients were 60 or younger
- Myeloablative conditioning
- Matched related donors only
- Prior to HMA era

Cutler CS et al, Blood 2004;104:579-585

Transplant in MDS

- Age 60-70
- Reduced intensity conditioning

IPSS Risk Group	Early Transplant	Nontransplant strategy
Life Expectancy (months)		
Low/Int-1	38	77
Int-2/High	36	28
Quality-Adjusted Life Expectancy (months)		
Low/Int-1	35	47
Int-2/High	33	15

Koreth J et al, JCO 2013

Azacitidine Before Transplant

- Retrospective study of 265 patients who underwent alloSCT

3 yr outcomes	OS	EFS	Relapse	NRM
AZA	55%	42%	40%	19%
ICT	48%	44%	37%	20%
AZA-ICT	32%	29%	36%	35%

- No statistically significant differences

Damaj G et al, JCO 2012:4533-4540

Our Patient

- Was enrolled on a clinical trial with IV rigosertib, and achieved a bone marrow remission with hematologic improvement
- She recently received allogeneic stem cell transplantation from an unrelated donor.

Summary/Conclusions

- MDS is a complex and heterogenous group of bone marrow malignancies
- Accurate diagnosis and risk stratification of MDS are essential in determining goals of care and appropriate management
- Lower-risk disease: observation, growth factors, lenalidomide, and immunosuppressive therapy
- Higher-risk disease: hypomethylating agents, possible allogeneic stem cell transplantation
- AlloSCT offers a chance at cure, but is also associated with significant toxicity