Safety and Efficacy of Combination Therapies with Azacitidine in Elderly Patients with AML or MDS

Presentations discussed in this issue:

Sekeres MA et al. **Final results from a Phase I combination study of lenalidomide and azacitidine in patients with higher-risk myelodysplastic syndrome.** *Blood* 2008;112;**Abstract 221**.

Raffoux E et al. **Epigenetic therapy with azacitidine, valproic acid, and ATRA in patients with high risk AML or MDS: Results of the French VIVEDEP Phase II study.** *Blood* 2008;112;**Abstract 763**.

Slides from presentations at ASH 2008

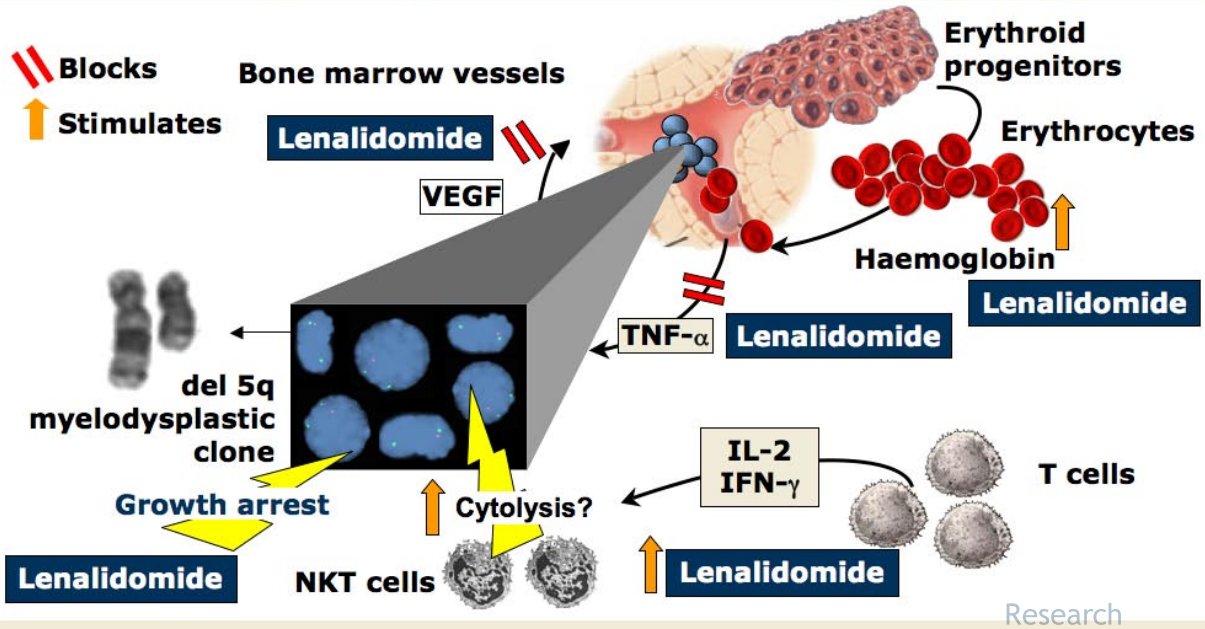
Introduction

- Current standard therapy for IPSS intermediate-1-, intermediate-2-, and high-risk MDS is single agent hypomethylating agent such as azacitidine.
- Lenalidomide is the standard of care for del (5q) MDS.
- Lenalidomide also has activity in non-del (5q) MDS (*Blood* 2008;111:86)
- Combining azacitidine and lenalidomide has potential to improve outcomes in higher risk MDS when compared to either agent alone.
- **Study objectives:**
  - Safety of combination therapy with lenalidomide and azacitidine in patients with higher risk MDS
  - Efficacy of combination therapy with lenalidomide and azacitidine in patients with higher risk MDS

Source: Sekeres MA et al. *Blood* 2008;112:Abstract 221.

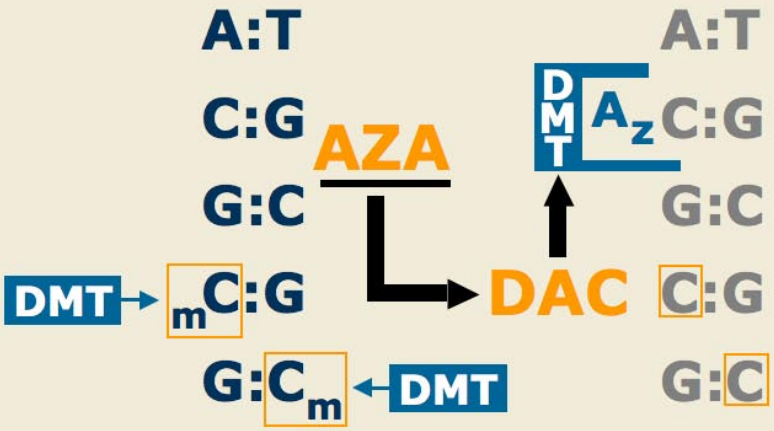
Mechanism of Action of Lenalidomide in MDS

Lenalidomide targets malignant cells in the bone marrow microenvironment



Source: With permission from Sekeres MA et al. *Blood* 2008;112:Abstract 221.

Methyltransferase Inhibitor (MTI) Induced DNA Hypomethylation and Gene Activation



Azacitidine (AZA) and decitabine (DAC) are incorporated into DNA *in lieu* of cytosine residue
Inactivates DNA methyltransferase (DMT)
Leads to formation of newly synthesized DNA with unmethylated cytosine residues
Results in hypomethylation and transcription of previously quiescent genes

Source: With permission from Sekeres MA et al. *Blood* 2008;112:Abstract 221.

Trial Design

- Standard 3+3 Phase I design
- Patients with higher risk MDS as defined below were eligible:
  - IPSS score ≥ 1.5 (Int-2 risk or high risk)
  - FAB subtype RAEB-1 or RAEB-2
- Six cohorts predefined in the trial

Source: Sekeres MA et al. *Blood* 2008;112:Abstract 221.

Lenalidomide + Azacitidine: Dosing Table

Dose Level	Azacitidine Schedule	Lenalidomide Schedule
1	75 mg/m^2 SC days 1-5	5 mg PO days 1-14
2	75 mg/m^2 SC days 1-5	5 mg PO days 1-21
3	75 mg/m^2 SC days 1-5	10 mg PO days 1-21
4	50 mg/m^2 SC days 1-5, 8-12	5 mg PO days 1-14
5	50 mg/m^2 SC days 1-5, 8-12	5 mg PO days 1-21
6	50 mg/m^2 SC days 1-5, 8-12	10 mg PO days 1-21

Source: Sekeres MA et al. *Blood* 2008;112:Abstract 221.

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Lenalidomide + Azacitidine: Baseline Characteristics

Characteristic	Median (range), n=18
Age	68 years (52-78)
Female/Male (n)	6/12
Time from Diagnosis	5 weeks (2-106)
Baseline: Hemoglobin (g/dL) Platelets (/mm^3) Absolute neutrophil count (/mm^3) Erythropoietin (IU/L) Bone marrow blast count (%)	 9.9 69,000 832 95 11
IPSS (n): Intermediate-1 risk Intermediate-2 risk High risk	 3 9 6

Source: Sekeres MA et al. *Blood* 2008;112:Abstract 221.

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Lenalidomide + Azacitidine: Toxicity Results

- No dose-limiting toxicities were reached in all the dosing cohorts.
- Median absolute neutrophil count decreased 26% within the first 8 weeks.
- Median platelet count decrease was 0% (mean=24%) within the first 8 weeks.
- Cycle 2 was delayed for five patients (≤9 days) for recovery of counts or "other" reasons.

Source: Sekeres MA et al. *Blood* 2008;112:Abstract 221.

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Lenalidomide + Azacitidine: Efficacy Results

Clinical Response (n=18)	% (n)
Overall response rate	72% (13)
Complete response (CR)	39% (7)
Partial response (PR)	6% (1)
Hematologic improvement (HI)	17% (3)
Bone marrow complete response	11% (2)

Source: Sekeres MA et al. *Blood* 2008;112:Abstract 221.

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Lenalidomide + Azacitidine: Go Forward Dose for Phase II Study

Dosing Cohort	Aza Dose	Len Dose	IPSS Risk Group	Grade 3/4 Non-Heme Toxicities	Maximum Response
1	75 mg/m² SC days 1-5	5 mg PO days 1-14	1 Int-1 2 Int-2	1	2 CR 1 progression
2	75 mg/m² SC days 1-5	5 mg PO days 1-21	2 Int-2 1 High	2	1 CR 1 PR, 1 HI
3	**75 mg/m² SC days 1-5**	**10 mg PO days 1-21**	**1 Int-2 2 High**	**0**	**2 CR 1 SD**
4	50 mg/m² SC days 1-5, 8-12	5 mg PO days 1-14	1 Int-1 2 Int-2	2	2 CR 1 SD
5	50 mg/m² SC days 1-5, 8-12	5 mg PO days 1-21	2 Int-2 1 High	2	1 HI, 1 SD 1 progression
6	50 mg/m² SC days 1-5, 8-12	10 mg PO days 1-21	1 Int-1 1 Int-2 1 High	2	1 HI 2 bone marrow CR

Source: Sekeres MA et al. *Blood* 2008;112:Abstract 221.

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Summary and Conclusions

- The combination of azacitidine and lenalidomide has acceptable toxicity with good response rates.
- The go forward dose was established for Phase II studies.

Source: Sekeres MA et al. *Blood* 2008;112:Abstract 221.

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Epigenetic Therapy With 5-Azacytidine, Valproic Acid, and ATRA in Patients With High-Risk AML or MDS: Results of the French VIVEDEP Phase II Study

Raffoux E et al.

Blood 2008;112:Abstract 763.

Introduction

- Azacytidine (AZA) is a validated therapy in patients with high-risk MDS, including patients with 20-30% marrow blasts.
- There is no clear standard therapy for elderly patients with AML, who are unfit to receive standard induction chemotherapy.
- Histone deacetylase (HDAC) inhibitors, including valproic acid, have shown activity in AML/MDS.
- Synergy of hypomethylating agents and HDAC inhibitors is supported by in vitro data.
- ATRA is a differentiating agent, and sensitivity to ATRA may be restored in non-APL cells through epigenetic mechanisms.
- **Study objectives:**
  - To assess the efficacy and safety of AZA and valproic acid (VPA) followed by ATRA treatment in patients with high-risk AML or MDS.

Source: Raffoux E et al. *Blood* 2008;112:Abstract 763.

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Phase II Multicenter Study of Combined AZA, VPA and ATRA Treatment in Patients with Higher-Risk AML or MDS

Eligibility (n=65)

Untreated elderly (≥70 years) AML

AML in 1st relapse (either if secondary AML or if 1st CR duration < 18 months)

High-risk MDS (refractory anemia with excessive blasts [RAEB] or RAEBt with IPSS Int-2- or high-risk score)

→

AZA 75 mg/m²/day SC days 1-7
VPA 35-50 mg/kg/day PO days 1-7
ATRA 45 mg/m²/day PO days 8-28
q4wks x 6 cycles

Source: Raffoux E et al. *Blood* 2008;112:Abstract 763.

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Patient Population (n=65)

Characteristic	
Age, median (range)	72 years (50-87)
Female/Male (n)	27/38
Diagnosis Group (n): Untreated AML Relapsed AML High-Risk MDS	 42 13 10
Median white blood cell (10^9/L)	2.3
Median platelet count (10^9/L)	43
Median marrow blasts (%)	31
Karyotype (n): Standard-risk High-risk Failure/not done	 28 30 7

Source: Raffoux E et al. *Blood* 2008;112:Abstract 763.

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Efficacy Results

Clinical Response (n=62)	
Overall response after 6 cycles	24%
Complete response	21%
Partial response	3%
Best response during study	29%
Complete response	23%
Partial response	6%

Source: Raffoux E et al. *Blood* 2008;112:Abstract 763.

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Prognostic Factors for CR/PR And Death

	CR + PR (31% at 6 mos)		Death (31% at 6 mos)	
	6 mos estimation	*P*-value	6 mos estimation	*P*-value
Age ≥ 70 years	24%	0.50	53%	**0.025**
Female	25%	0.21	47%	**0.03**
PS (WHO) ≥ 2	0%	0.10	57%	**0.008**
WBC ≥ $1.5x10^9$/L	26%	0.47	31%	0.96
Platelets < $50x10^9$/L	19%	**0.02**	39%	0.10
Marrow blasts > 30%	29%	0.44	42%	**0.05**
High-risk karyotype	24%	0.52	48%	**0.003**
Relapsed AML	31%	0.72	62%	**0.01**

Source: Raffoux E et al. *Blood* 2008;112:Abstract 763.

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Non-Hematological Adverse Events Grades 3-4

Adverse Event	N events	Mean cycle ± SD
Infections Pneumonia Septicemia Aspergillosis	76 13 17 2	2.0 ± 3.3
Confusion	33	1.7 ± 1.4
Asthenia	20	2.0 ± 1.5
Constipation	13	1.0 ± 1.1
Hemorrhage	13	2.0 ± 1.4
Somnolence	12	1.3 ± 1.4
Nausea/vomiting	10	2.5 ± 1.7
Subcutaneous puncture reaction	9	1.7 ± 1.9

Source: Raffoux E et al. *Blood* 2008;112:Abstract 763.

Summary and Conclusions

- Combination therapy with AZA, VPA and ATRA has a promising 25% to 30% response rate in patients with high risk AML/MDS.
- Response rates do not appear to differ by baseline cytogenetic risk, relapse status or percentage of marrow blasts.
- Future and larger studies are needed to better define the respective roles of these agents.

Source: Raffoux E et al. *Blood* 2008;112:Abstract 763.

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