5 Minute JournalClub

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

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CME INFORMATION

OVERVIEW OF ACTIVITY

Acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS) account for approximately 20 percent of all hematologic cancer and related hemopathies diagnosed on an annual basis. Emerging and continuing clinical research has resulted in an increased understanding of the heterogeneous nature of these diseases and in the availability of novel treatment strategies and options. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in AML and MDS. To bridge the gap between research and patient care, this CME activity will deliver a serial review of recent key presentations and publications and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for AML and MDS.

LEARNING OBJECTIVE

- Recognize the safety and feasibility of combination therapies with azacitidine in patients with high-risk AML or MDS.

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IN THIS ISSUE:

Two reports of combinations of biologics in MDS: First, a Phase I study of lenalidomide with 5-azacitidine. The encouraging response rate of 72 percent (39 percent CRs) and favorable tolerability profile have now resulted in the launch of a Phase II study evaluating this combination. The second paper we profile is another 5-azacitidine combination — this time with the histone deacetylase (HDAC) inhibitor valproic acid (VPA) and the differentiating agent ATRA in patients over age 70 with high-risk AML/MDS. A 29 percent response rate is reported, and further research will evaluate this interesting trifecta.

Another paper focuses on 23 patients with high- or intermediate-risk MDS or AML who received maintenance treatment with 5-azacitidine after experiencing a CR with induction daunorubicin/cytarabine. Treatment was well tolerated, and the median CR duration was 13.5 months. The probability of reaching CR was negatively correlated with hypermethylation of the *E-cadherin (CDH)* promoter.

We also pulled **two papers on the use of deferasirox** in patients with MDS requiring transfusions. Treatment was demonstrated to be effective in removing iron, although the correlation of the use of iron chelation with clinical endpoints such as reduced incidence of cardiac or hepatic dysfunction remains to be documented.

Finally, an interesting **case report** of two patients with AML and isolated trisomy 13 who both experienced sustained morphologic and cytogenetic remission after treatment with lenalidomide, in a manner similar to responses observed with the same agent in MDS and chromosome 5q deletion. While this condition is rare, the authors are hopeful that understanding the unique biology of this observation will further unravel the mysteries of myeloid leukemogenesis.

EDITOR'S NOTE: ROUNDS WITH THE INVESTIGATORS

One of the techniques we frequently employ in creating a diverse array of enduring and live education activities is inviting community-based medical oncologists to present actual cases from their practices to clinical investigators with an expertise in a specific tumor type — our so-called *Meet The Professors* programs. The objective of this approach — as with a lot of our work — is to explore the vast subtleties of applying clinical research data to individuals with cancer.

This Friday night in New Orleans, prior to the ASH Annual Meeting, we will once again host an event utilizing this type of "oncology improv" format. In addition to myeloma

and CML, we will also delve into MDS and AML, the focus of this special four-part email/web series.

As with all of these case-based adventures, I met by phone with each oncologist to better understand the issues they would most like to see discussed and to select actual patients from their practices to present to the faculty. To prepare for the "show," we also randomly recruited 100 US-based oncologists to take our most recent **Patterns of Care** survey, which included a number of queries directly related to the cases being discussed Friday night.

While many of the most pressing issues relate to MDS, I heard about a number of very challenging cases of AML, as discussed in our **last email program**. Dr Bob Moss from Fountain Valley, California told me about an 81-year-old man who ten years previously had declined medical care for asymptomatic pancytopenia. The patient returned to Dr Moss a few months ago with full-blown AML. He finds the management of elderly patients with this disease "trickier than younger patients" and is curious how investigators approach octo- and nonagenarians.

In contrast, Dr Margaret Deutsch of Raleigh, North Carolina told me about a 45-year-old woman who recently attended her son's wedding during a second remission after conventional treatment for AML. The next day the patient developed fever and chills and was found to have Proteus sepsis and circulating blasts. Dr Deutsch asks in desperation if there are any new options for such a patient, and if there is a role for stem cell transplant in this population?

The most common questions about patients with MDS surround the use of hypomethylating agents, and as usual, the survey yielded interesting data but also generated more questions. For example, while we predictably demonstrated that physicians were more likely to begin "hypomethylation" with 5-azacitidine as opposed to decitabine because of the available survival data, we did not ask how often physicians utilize the other agent on disease progression. On a recent audio program, Dr Allen Yang commented that he has observed useful responses to a second demethylator — a somewhat anecdotal finding at this point, but it reminded me of similar observations with the VEGF TKIs in kidney cancer.

For MDS, Ken Hoffman, who practices in Teaneck, New Jersey, told me about a 69-year-old woman he treated for breast cancer as a first-year oncology fellow 20 years ago. At the time, the patient received six cycles of adjuvant CMFVP without complication on a CALGB protocol, and for all intents and purposes was cured. Unfortunately, two decades later, she presented to her gynecologist with fatigue, and workup revealed anemia, which proved to be from MDS.

Somehow fate sent the patient back to Ken, who isn't sure if his prior chemo caused the MDS or if it was just bad luck. Either way, after several months of frequent transfusions, 5-azacitidine was started, and the patient is now transfusion independent and doing well. Dr Hoffman's main question for investigators is whether it's reasonable

to skip the weekends with this agent (as discussed in our **last issue**), and just give treatment on days one through five. Ken — a former hospice director and true patient champion — feels strongly that the non-FDA-approved weekday schedule "makes the patient's life a whole lot easier."

Bill Harwin of Fort Myers, Florida has another patient with MDS doing well on 5-azacitidine but questions how long treatment needs to be continued. This 68-year-old woman also has mild Alzheimer's disease, and she became transfusion independent after four treatment cycles yet remains on therapy after 11 courses. Dr Harwin questions whether treatment needs to be indefinite or until progression as in the survival study reported in Lancet Oncology. His patient is on cycle 11, compared to a mean of 12 in the study. According to Bill, even if he stretches out the treatment interval to every five or six weeks, "Patients get sick of it after a while."

Bob Moss is treating a 93-year-old man who had received 28 units of packed red cells from another oncologist for a presumed diagnosis of MDS, but the prior treating oncologists did not perform a bone marrow exam because of the patient's age. Bob did the procedure and found MDS with a chromosome 5q deletion. After two weeks of lenalidomide 10 milligrams daily, the man's platelets dropped from 109,000 to 13,000 and his WBC count dropped from 7,100 to an ANC less than 200. Our Patterns of Care survey shows that 74 percent of physicians would do what Bob did, which was to hold treatment until the counts recovered and then restart lenalidomide at five milligrams daily. A year later, the patient is still on treatment, doing well and transfusion independent — another victory for quality of life.

This email marks the end of our four-part snapshot on AML/MDS. However, at ASH and well into the foreseeable future we will continue to vigorously pursue this increasingly interesting topic in order to provide you with the most current data and perspectives on these very challenging diseases.

Neil Love, MD
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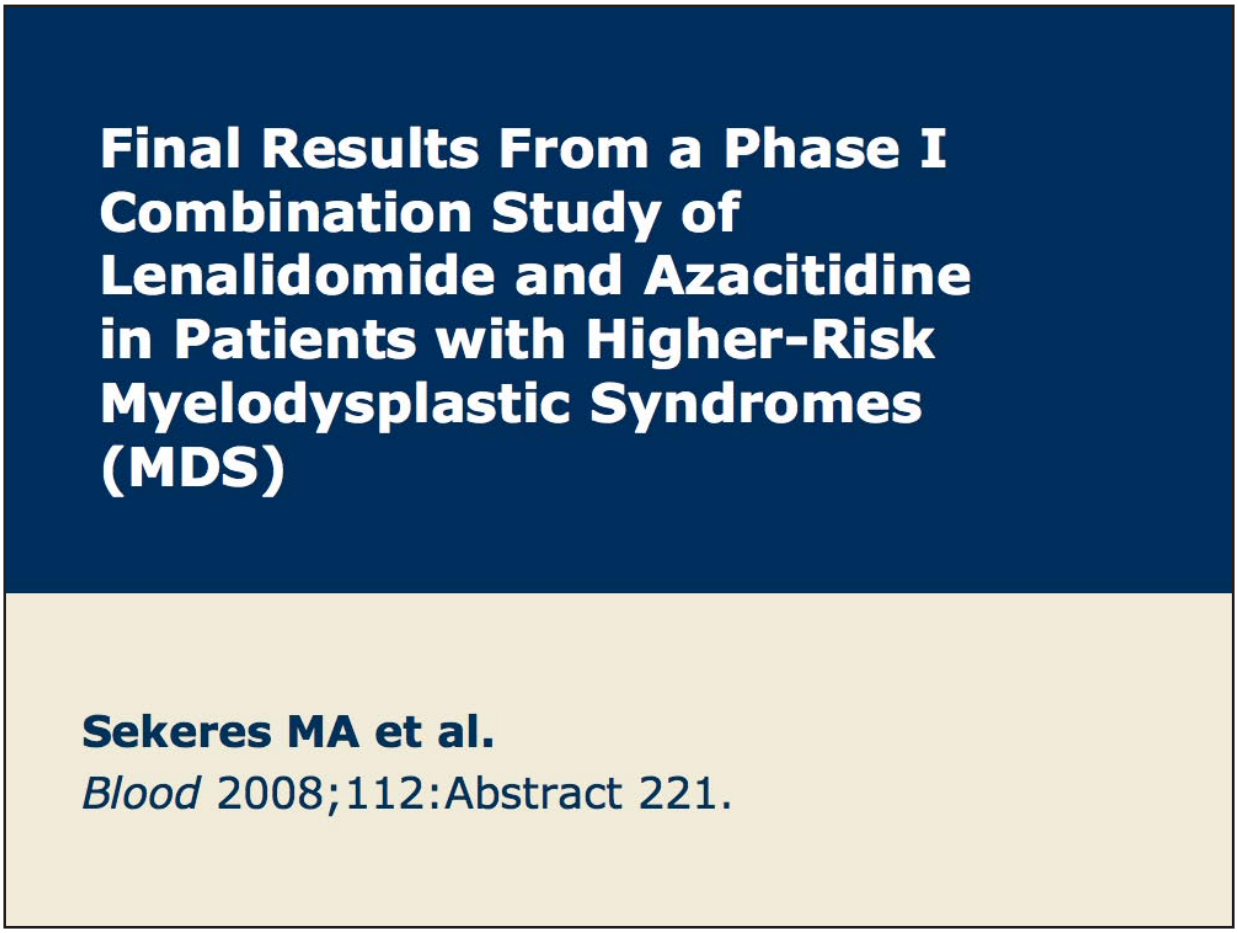
Safety and Efficacy of Combination Therapies with Azacitidine in Elderly Patients with AML or MDS

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 and transcribed comments from interviews with Gail J Roboz, MD (11/20/09), Steven D Gore, MD (10/8/09) and Allen SR Yang MD, PhD (7/30/09)



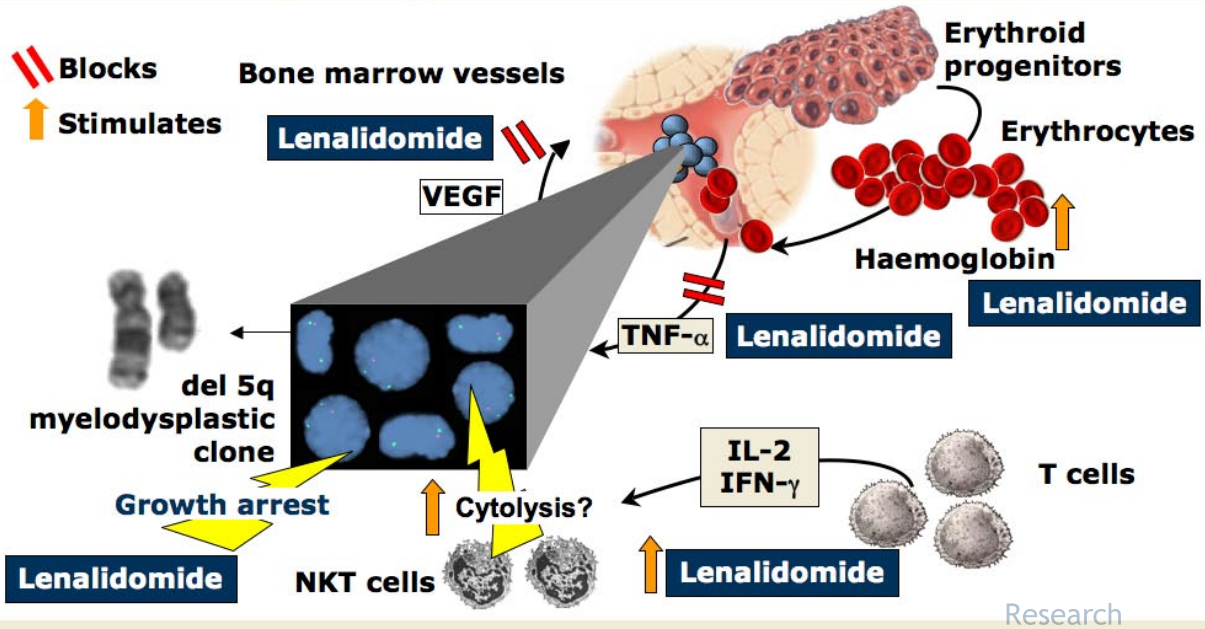
Introduction

- 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.

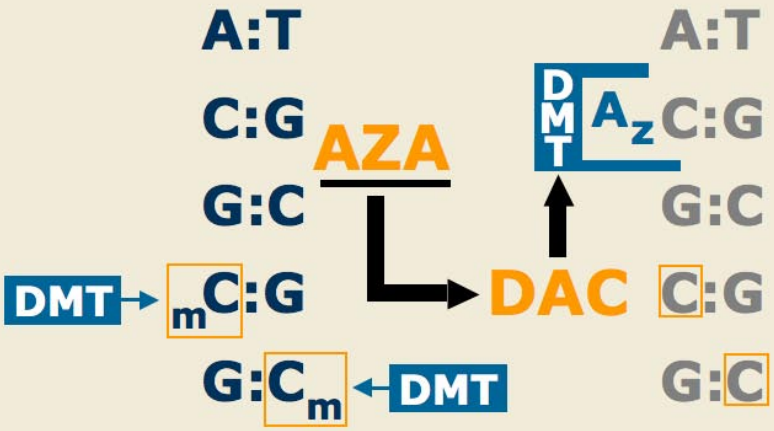
Mechanism of Action of Lenalidomide in MDS

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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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.

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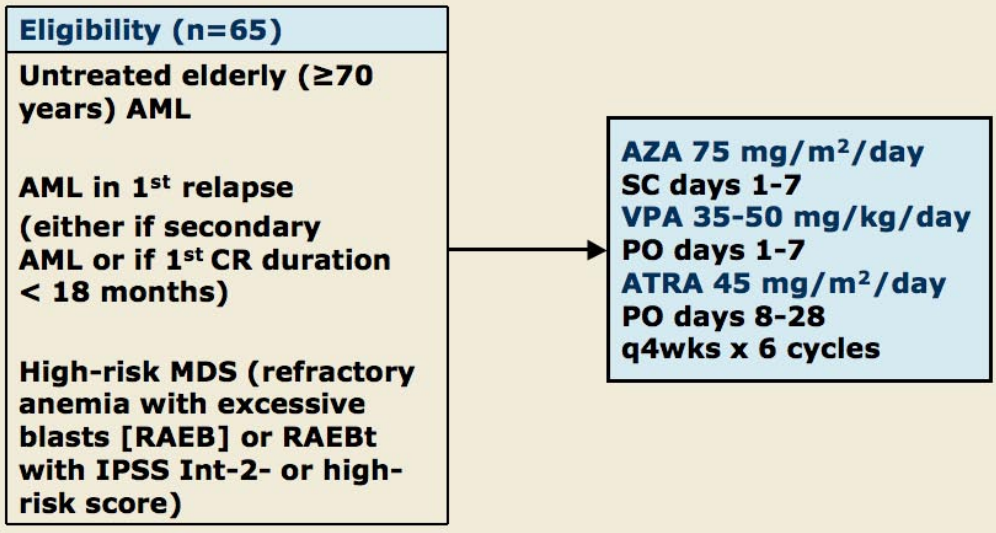
Phase II Multicenter Study of Combined AZA, VPA and ATRA Treatment in Patients with Higher-Risk AML or MDS



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 Complete response Partial response	24% 21% 3%
Best response during study Complete response Partial response	29% 23% 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.

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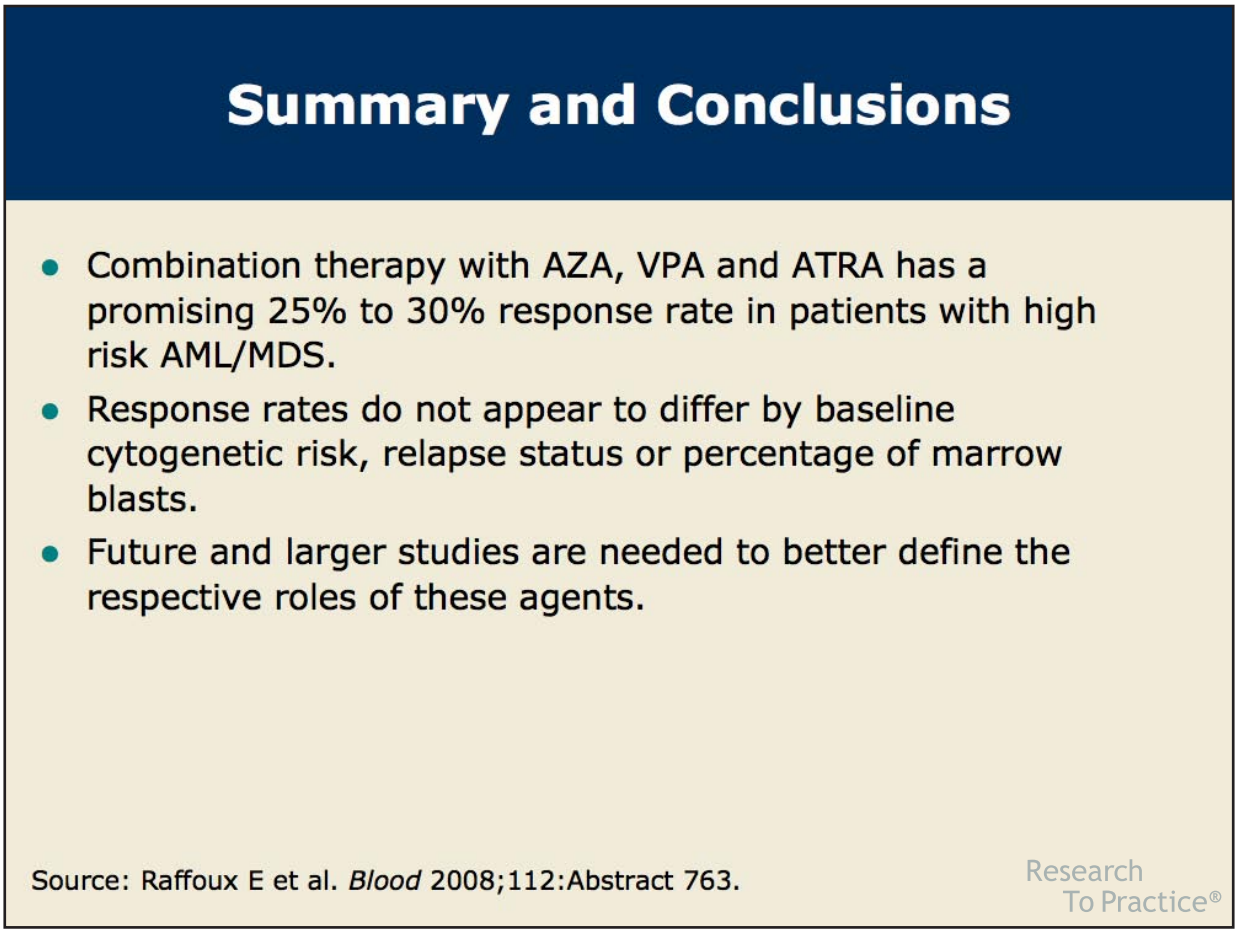

GAIL J ROBOZ, MD: The paper by Sekeres and colleagues is a Phase I study that is interesting. Two myelosuppressive drugs with cross-reacting toxicities, lenalidomide and azacitidine, were used in patients with high-risk myelodysplastic syndromes (MDS). The additive negative effect of the two drugs in combination was less than what the authors had anticipated. Patients were tolerant of the regimen. These preliminary results warrant additional studies.

The pathogenesis of MDS is multifaceted, and it seems logical to me to pursue combination therapies, because the number of changes that are going on in an MDS marrow, epigenetic, genetic and immune mediated, lend themselves to combinations. For example, we're looking at lenalidomide in combination with cyclosporine. About a quarter of patients with low-risk disease who do not have a 5q deletion have responses with lenalidomide therapy.

DR LOVE: What do we know about the response rate to lenalidomide in patients with high-risk MDS?

DR ROBOZ: There are some scattered responses in high-risk disease, and it appears that patients with multiple karyotypic abnormalities beyond 5q and patients with particularly low platelet counts do not respond well. But for some patients, mostly those with isolated 5q disease, there are responses.

DR LOVE: Are there any other particular drug combinations that you believe make a lot of sense?

DR ROBOZ: I believe the scientific rationale is the strongest for combining HDAC inhibitors with a demethylating agent such as azacitidine or decitabine. The clinical results have been a little disappointing so far in that we have not seen responses as robust as we would have liked. This may be due to our not knowing yet the correct manner to combine these drugs.

The paper by Raffoux and colleagues is an early study that combines the HDAC inhibitor valproic acid with azacitidine and with the differentiating agent ATRA. This study is using drugs that make some sense scientifically to combine together and examining the outcomes. ATRA has a long history in MDS and acute myeloid leukemia (AML), though I believe in general that the data for the use of ATRA in MDS and in nonacute progranulocytic leukemia (non-APL)-AML are weak. From a scientific standpoint, however, it seems to make sense to try to force cells that are not maturing correctly to differentiate.

STEVEN D GORE, MD: The regimen that was examined by Raffoux was developed at the MD Anderson Cancer Center. It is one of several regimens that combine a DNA methyltransferase inhibitor such as azacitidine with a histone deacetylase (HDAC) inhibitor, valproic acid. In this particular regimen, they have also added ATRA in a type of triple approach in order to have the differentiating activity of ATRA after epigenetic modulation. The study demonstrated that the combined therapy using 5-azacitidine and valproic acid followed by retinoic acid therapy results in a 25 to 30 percent response rate in patients with high-risk acute myeloid leukemia or MDS. These results are worth continuing to pursue.

ALLEN SR YANG, MD, PHD: The study presented by Mikkael Sekeres and colleagues was a Phase I study examining the combined administration of azacitidine and lenalidomide to patients with higher-risk myelodysplastic syndromes (MDS). The study demonstrates that the two drugs can be administered safely in combination and that the main toxicity appears to be myelosuppression, as would be expected. The overall response rate was 72 percent. I believe that the combination of 5-azacitidine and lenalidomide is feasible. It would be very exciting to have a benefit demonstrated in a randomized clinical trial.

Dr Roboz is Associate Professor of Medicine and Director of the Leukemia Program at Weill Medical College of Cornell University at NewYork-Presbyterian Hospital in New York, New York.

Dr Gore is Professor of Oncology at Johns Hopkins University in Baltimore, Maryland.

Dr Yang is Assistant Professor of Medicine at the University of Southern California in Los Angeles, California.