5 Minute JournalClub

Three Alternate Dosing Schedules of Azacitidine for 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

- Consider alternative dosing schedules of azacitidine, which allow for the elimination of weekend dosing, for patients with MDS.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Steven D Gore, MD
Professor of Oncology
Johns Hopkins University
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Baltimore, Maryland

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Last review date: November 2009
Expiration date: November 2010

Click to go directly to our slides and comments on the **recent review of myelodysplastic syndromes**, **a new proposed prognostic model for MDS**, **the effect of pre-HCT azacitidine therapy on post-transplant outcomes**, **the efficacy of decitabine on survival in elderly patients with higher-risk MDS**, and a **comparison of three alternative azacitidine treatment regimens**.

As we were about to hit the send button on this, our latest e-blast, I happened to be on PubMed and stumbled across a just e-published (Nov 5) *New England Journal* **review article on myelodysplastic syndromes** (MDS). Thinking that the paper might be an important addition to this project, I quickly poured over the work. As usual, our entire clinical team loved the *NEJM* graphics (best in the business!), and the science behind this instant classic by Ayalew Tefferi and James Vardiman was spectacular. Further examination revealed only one prior (1999) *NEJM* review article on MDS, in which for example, there was but a brief mention of an initial 29 patient report of 5-azacitidine — the only reference to demethylating agents. Lenalidomide was nowhere to be found in this "ancient" document by Mark Heaney and David Golde. So at the last minute, we bypassed our usual formal faculty review and integrated this serendipitous discovery into the enclosed activity.

The concluding statements of these two review articles separated by 10 years reflect first a hopeful wish (1999): "The next decade will probably see a marked improvement in our ability to manage myelodysplasias as well as AML" and then confidence (2009): "Increasing information on the identity and nature of transformed hematopoietic stem cells and advances in biotechnology are helping to create the 'perfect storm' for breaking the current stalemate in our understanding of this disease."

So where are we today in MDS? Our faculty — Gail Roboz, Steven Gore and Hagop Kantarjian — once again comment on four papers that were identified and prioritized as important to clinical practice. The first addresses a proposed new **prognostic model for MDS** that accounts for such important factors as prior therapy and adverse cytogenetic profiles. The paper's author, Dr Kantarjian, believes this new system is superior to IPSS, but only time will tell.

Paper 2 comes out of the Moffitt Cancer Center and is a retrospective review of 54 patients receiving hematopoietic stem cell transplant (HCT) for MDS or chronic myelomonocytic leukemia (CMML). The outcomes of 30 patients receiving pre-HCT treatment with 5-azacitidine were compared to and found to be very similar to the

outcomes of 24 patients who did not receive this agent, leading the authors to conclude that 5-azacitidine can be safely and effectively used to stabilize patients prior to transplant.

The third study examines the other available demethylating agent, decitabine, and demonstrates that in spite of a 34 percent response rate, no improvement in overall survival (OS) was observed compared to supportive care in this well-conducted trial completed in Europe. While the lack of OS benefit in this study may relate to suboptimal duration of treatment, a recent US national Patterns of Care study conducted by our education group in preparation for an upcoming **ASH satellite symposium** demonstrated that 80 percent of oncologists using an up-front demethylating agent for MDS chose 5-azacitidine, perhaps reflecting the OS benefit reported with this agent.

Finally we have **a report of three alternative doses/schedules** of 5-azacitidine in MDS that through indirect comparison appear to be as effective and well tolerated as the approved day 1-7 regimen that requires weekend infusions. We may need a head-to-head trial to be fully convinced but it seems like a more patient-friendly regimen may in fact be out there.

The publications and presentations in this short series testify to significant forward momentum in MDS and AML. However, the ultimate hope is that 10 years from now, the next *NEJM* review article on MDS or AML will describe the unraveling and elimination of these diseases that have for so long resisted research progress.

Coming up next on 5-Minute Journal Club: a Phase II trial of up-front clofarabine in older patients with AML, a review of prognostic and predictive markers in AML, a trial of decitabine in older patients with AML and finally a retrospective review of more than 1,000 patients with AML and MDS receiving HCT demonstrating similar efficacy and toxicity patterns regardless of patient age, up to 78.

Neil Love, MD
Research To Practice
Miami, Florida

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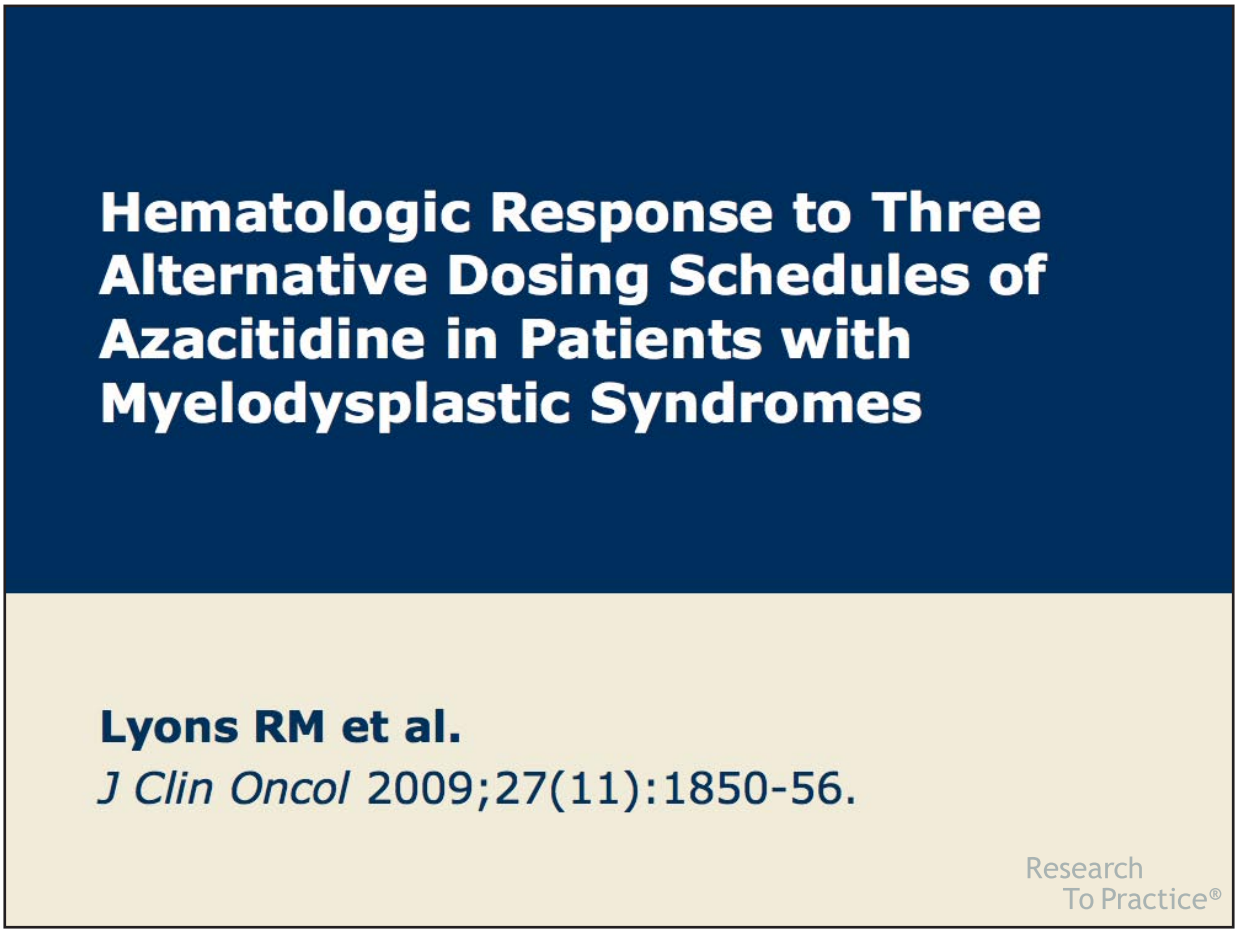
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Three Alternate Dosing Schedules of Azacitidine for MDS

Presentation discussed in this issue:

Lyons RM et al. **Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes.** *J Clin Oncol* 2009;27(11):1850-6. **Abstract**

Slides from the journal article and transcribed comments from a recent interview with Steven D Gore, MD (10/8/09) below



Introduction

- Azacitidine has been shown to alter the natural history of myelodysplastic syndromes (MDS) (*J Clin Oncol* 2002;20:2429; *Lancet Oncol* 2009;10(3):223; *J Clin Oncol* 2002;20:2441)
  - Significant prolonged survival in higher-risk MDS and trend toward prolonged survival in all French-American-British (FAB) MDS subtypes; decreased risk of transformation to AML
  - Significant reduction in transfusion dependence in higher- and lower-risk MDS (*J Clin Oncol* 2002;20:2429; *J Clin Oncol* 2006;24:3895)
- The approved AZA regimen is 75 mg/m^2/d administered subcutaneously or intravenously for 7 days every 28 days and includes weekend dosing
- **Study Objective:**
  - Assess safety and efficacy, based on hematologic improvement and transfusion independence rates, of three azacitidine dosing schedule alternatives that eliminate weekend dosing, in a multicenter, community-based open-label study

Source: Lyons RM et al. *J Clin Oncol* 2009;27:1850-56.

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Phase II Trial of Alternative Dosing Schedules of Azacitidine (AZA) in Patients with MDS

Eligibility

Diagnosis of MDS:

Refractory anemia (RA) or RA with ringed sideroblasts (RARS) requiring a transfusion every 28 days or with thrombocytopenia or neutropenia

RA with excess blasts (RAEB)

RA with excess blasts in transformation (RAEB-T)

Chronic myelomonocytic leukemia (CMML)

R

AZA 5-2-2 (n=50)
AZA, 75 mg/m^2 SC, d1-5 → AZA, 75 mg/m^2, d8-9 q28d x 6

AZA 5-2-5 (n=51)
AZA, 50mg/m^2 SC, d1-5 → AZA, 50 mg/m^2, d8-12 q28d x 6

AZA 5 (n=50)
AZA, 75 mg/m^2 SC, d1-5 q28d x 6

SC = subcutaneous

Source: Lyons RM et al. *J Clin Oncol* 2009;27:1850-56.

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Hematologic Improvement (HI)

	AZA 5-2-2	AZA 5-2-5	AZA 5
Major or minor HI[1] (Intent-to-treat) (n=50, 51, 50)	44%	45%	56%
Onset of HI during first two cycles	82%	56%	90%
Major or minor HI, FAB lower-risk patients (n=33, 29, 32)	49%	41%	50%
Patients with multilineage cytopenias who experienced multilineage HI (n=32, 24, 30)	34%	21%	33%

[1]HI evaluated using International Working Group 2000 criteria

Source: Lyons RM et al. *J Clin Oncol* 2009;27:1850-56.

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Achievement of RBC Transfusion Independence (TI) Among Baseline RBC Transfusion-Dependent Patients

	AZA 5-2-2	AZA 5-2-5	AZA 5
Overall (intent-to-treat) (n=24, 22, 25)	50%	55%	64%
FAB lower-risk patients (n=17, 12, 18)	53%	50%	61%
Onset of TI within first two cycles	92%	75%	75%

Absence of baseline neutropenia or thrombocytopenia and lower transfusion requirements were predictive of higher rates of RBC transfusion independence.

Source: Lyons RM et al. *J Clin Oncol* 2009;27:1850-56.

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Selected Grade 3 or 4 Adverse Events

	AZA 5-2-2 (n = 50)	AZA 5-2-5 (n = 48)	AZA 5 (n = 50)
≥ 1 grade 3 or 4 adverse events	84%	77%	58%
Hematologic disorders	66%	50%	34%
Anemia	24%	15%	10%
Febrile neutropenia	8%	8%	2%
Leukopenia	14%	8%	8%
Neutropenia	42%	31%	22%
Thrombocytopenia	26%	15%	12%
Infections	22%	29%	10%

Source: Lyons RM et al. *J Clin Oncol* 2009;27:1850-56.

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Summary and Conclusions

- These three alternate dosing regimens demonstrated good activity and tolerability
  - HI, overall (intent-to-treat): 44%-56%
  - HI, lower-risk MDS: 41%-50%
  - Achievement of TI, overall (intent-to-treat): 50%-64%
  - Achievement of TI, lower-risk MDS: 50%-61%
- In all dosing arms, the onset of TI and HI was relatively rapid, occurring in the majority of patients within the first two dosing cycles (75%-92% for TI, 56%-90% for HI)
- Grade III/IV adverse events included hematologic disorders (34%-66%) and infections (10%-29%)
- The AZA 5 dosing regimen may be a better-tolerated and more convenient dosing schedule than the other two alternative dosing regimens.

Source: Lyons RM et al. *J Clin Oncol* 2009;27:1850-56.

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STEVEN D GORE, MD: This study examined potentially more convenient, alternate azacitidine treatment regimens that do not require weekend administration in patients with low-risk myelodysplastic syndrome (MDS). These three regimens appear to be more or less comparable to each other and to the standard seven-day regimen for the palliation of cytopenias for low-risk disease.

This was a limited study, but there may be a slight difference between schedules, as patients with thrombocytopenia apparently were less likely to respond on the AZA 5-2-2 and AZA 5 treatment schedules than patients on the AZA 5-2-5 schedule. There was also a trend toward improved transfusion independence in patients on the AZA 5-2-5 schedule. The data suggest that these schedules, which exclude treatment on weekends, are reasonable for the amelioration of cytopenias in patients with low-risk MDS in the community.

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