5 Minute JournalClub

Azacitidine Before Allogeneic Hematopoietic Cell Transplantation (AHCT) for Myelodysplasias

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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 effect of azacitidine therapy administered before AHCT on survival outcomes after transplantation in patients with higher-risk myelodysplasias.

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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.

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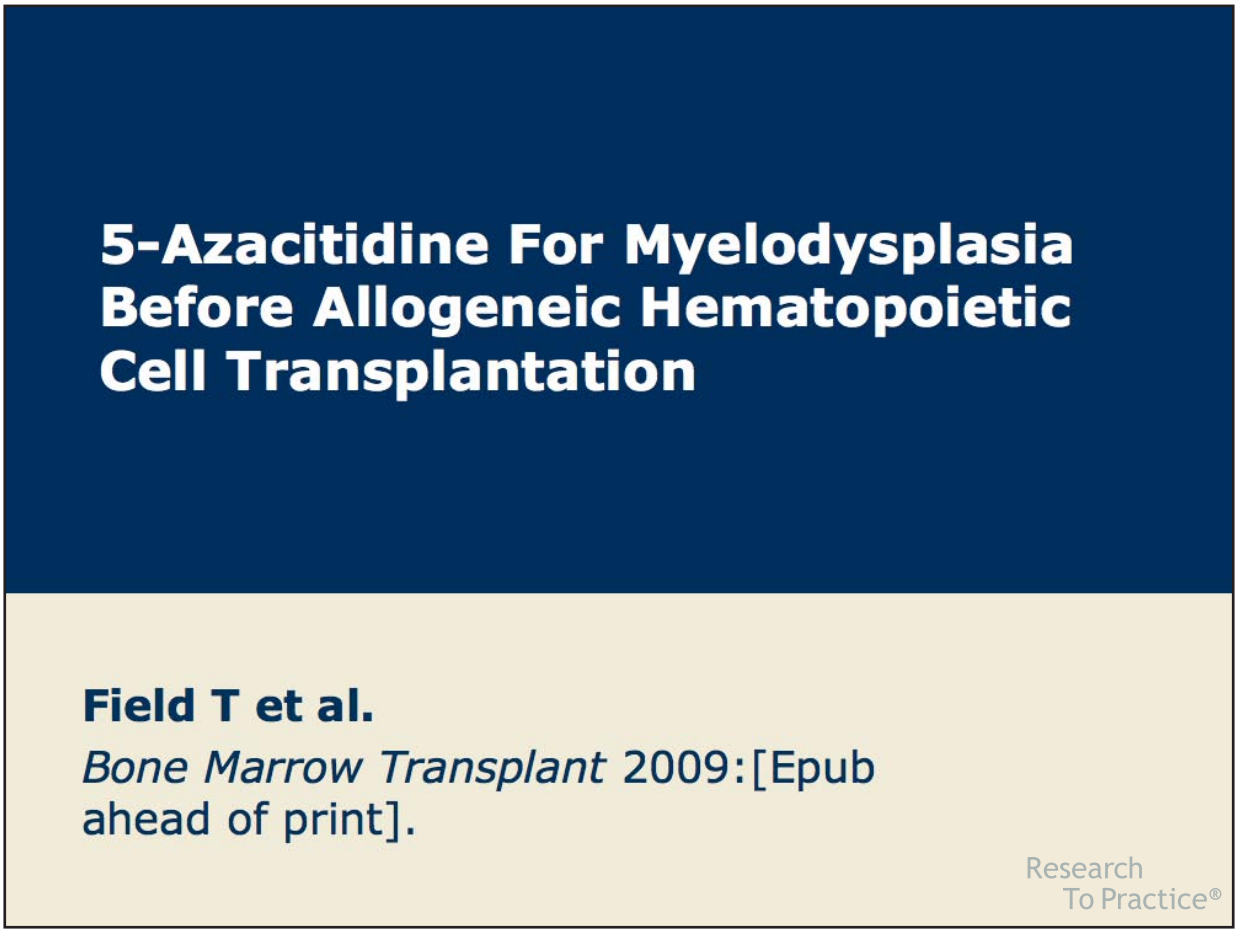
Presentation discussed in this issue:

Field T et al. **5-Azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation.** *Bone Marrow Transplant* 2009;[Epub ahead of print]. **Abstract**

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



Introduction

- Patients with intermediate- or high-risk myelodysplastic syndrome (MDS) have a significant risk of relapse after hematopoietic cell transplantation (HCT).
- The use of induction chemotherapy as pretransplant therapy can increase the risk of death or prevent proceeding to HCT because of associated toxicities.
- 5-azacitidine therapy was shown to prolong overall survival and decrease the risk of progressing to acute myelogenous leukemia versus conventional care regimens in patients with intermediate-2 and high-risk MDS (*Lancet Oncol* 2009;10:223), providing an alternative strategy to inhibit disease progression in transplant-eligible patients.
- **Current study objectives (N = 54):**
  - Assess the effect of pretransplant 5-azacitidine treatment on post-transplant outcomes using a retrospective analysis of the institutional experiences of patients with intermediate-2 and high-risk MDS.

Source: Field et al. *Bone Marrow Transplant* 2009:[Epub ahead of print].

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Retrospective Analysis of Patients with Myelodysplasia Receiving 5-Azacitidine Therapy Pre-HCT

- Medical record review of consecutive patients (n=54) with MDS or chronic myelomonocytic leukemia who received allogeneic HCT between July 2004 and December 2007 at the H Lee Moffitt Cancer Center.
- Patients were assigned to two groups based on whether they had received 5-azacitidine therapy at any time prior to transplant.
- Patient characteristics were balanced in both study arms.
  - All patients and donors received high-resolution molecular typing for HLA-DRB1 and DQB1.
  - All patients received the same conditioning regimen (*Blood* 2004:104:857).
  - All patients received similar supportive care measures, including antiseizure and graft versus host disease (GVHD) prophylaxes.

Source: Field et al. *Bone Marrow Transplant* 2009:[Epub ahead of print].

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Post-HCT Outcomes in Patients with Myelodysplasia with or without Pre-HCT 5-Azacitidine Therapy

Outcome Parameter[1]	With 5-Azacitidine (n=30)	Without 5-Azacitidine (n=24)
Overall survival rate - 1 yr	47%	60%
Relapse-free survival rate - 1 yr	41%	51%
Cumulative incidence of GVHD Grade 2-4 Grade 3-4	 79% 13%	 71% 4%
Cumulative incidence of relapse[1] 1 year 2 year	 20% 31%	 32% 36%

[1]*p-values for all outcome parameters were nonsignificant*

Multivariate analyses demonstrated that pretransplant treatment with 5-azacitidine does not appear to be a significant predictor of relapse, nonrelapse mortality, overall and relapse-free survival, and grade 2-4 acute GVHD.

Source: Field et al. *Bone Marrow Transplant* 2009:[Epub ahead of print].

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Summary and Conclusions

- Treatment of patients with high-risk MDS with 5-azacitidine prior to HCT did not significantly affect rates of remission, relapse, acute and chronic GVHD, and survival after transplant.
  - A trend toward decreased early relapse in patients who had received 5-azacitidine was observed.
- 5-azacitidine therapy may stabilize disease while patients await HCT.

Source: Field et al. *Bone Marrow Transplant* 2009:[Epub ahead of print].

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STEVEN D GORE, MD: Allogeneic stem cell transplant is the only curative therapy for myelodysplastic syndrome (MDS). However, in patients with high-risk MDS, who tend to be the individuals receiving transplants currently, the probability of disease-free outcome at three years is about 30 percent. Many clinicians therefore are interested in knowing whether the use of a DNA methyltransferase inhibitor, such as azacitidine or decitabine, prior to transplant, is a reasonable approach.

This retrospective study compared the post-transplant outcomes of patients who did or did not receive 5-azacitidine therapy prior to transplant. It demonstrated that there was no statistical difference in the outcome between the two groups, although there was a trend toward decreased early relapse in the patients who received 5-azacitidine. I believe this study shows that the approach of administering 5-azacitidine before transplantation is feasible, but a prospective study would need to be performed to confirm it.

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