5 Minute JournalClub

Phase II Study of Maintenance Treatment with 5-Azacitidine for Patients with MDS or Post-MDS AML

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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

- Evaluate the Phase II study results of 5-azacitidine as maintenance treatment for patients with high-risk MDS or post-MDS AML.

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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:

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Lecturing Honoraria: Celgene Corporation, Cephalon Inc, Eisai Inc, Genzyme Corporation.

The following faculty (and their spouses/partners) reported no real or apparent conflicts of interest:

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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.

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Phase II Study of Maintenance Treatment with 5-Azacitidine for Patients with MDS or Post-MDS AML

Presentation discussed in this issue:

Grövdal M et al. **Maintenance treatment with 5-azacitidine for patients with high risk myelodysplastic syndrome (MDS) or acute myeloid leukemia following MDS (MDS-AML) in complete remission (CR) after induction chemotherapy.** *Blood* 2008;112;**Abstract 223**.

Slides from a presentation at ASH 2008 and transcribed comments from interviews with Gail J Roboz, MD (10/6/09) and David P Steensma, MD (12/18/08)

Introduction

- Approximately 50% of patients with high-risk MDS or MDS-AML achieve CR after administration of induction chemotherapy.
- However, the duration of CR and of overall survival (OS) is frequently short.
- **Study objectives:**
  - Assess the clinical feasibility and utility of long-term maintenance treatment with 5-azacitidine in patients with high risk MDS or MDS-AML who achieve CR after induction chemotherapy.

Source: Grövdal M et al. *Blood* 2008;112:Abstract 223.

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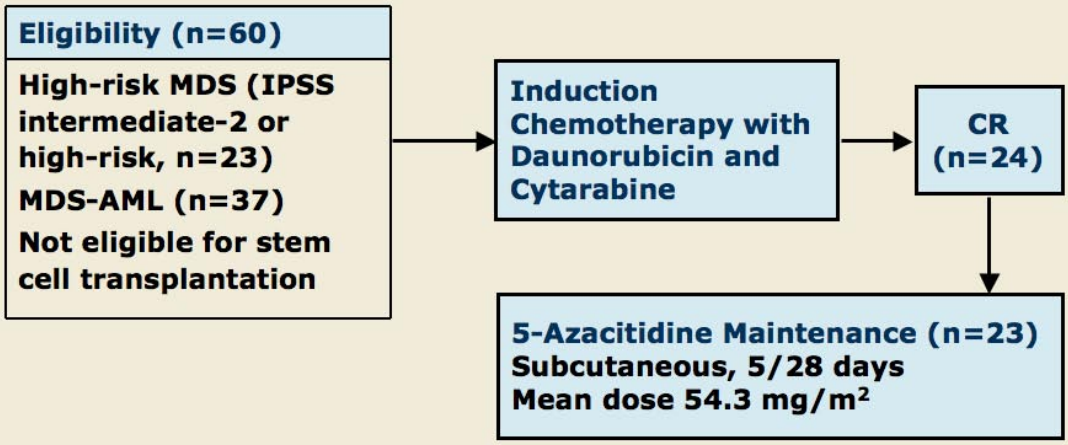
Phase II Multicenter Study of Long-Term Maintenance with 5-Azacitidine in Patients with MDS or MDS-AML



Promoter methylation status of the $P15^{ink4b}$ (P15), E-cadherin (CDH) and hypermethylated in cancer 1 (HIC) genes was assessed at study start, at CR, and for some patients during follow-up.

Source: Grövdal M et al. *Blood* 2008;112:Abstract 223.

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Results Summary

- The median CR duration in patients receiving 5-azacitidine maintenance therapy (n=23) was 13.5 months.
  - Four of 23 patients (17%) had a CR exceeding 24 months.
  - Two patients with *CDH* hypermethylation at baseline had CR durations of two and five months, respectively.
- The probability of reaching CR was negatively correlated to hypermethylation of the *CDH* promoter (p=0.008).
- The median survival was 20 months in patients receiving 5-azacitidine maintenance therapy.
- In the whole group, survival was shorter in patients with hypermethylation of the *CDH* gene (3 months vs 9 months, p=0.005).
  - Baseline methylation status of *p15* did not affect CR duration or overall survival.
- No side effects were reported in 52% of the patients receiving 5-azacitidine maintenance therapy.

Source: Grövdal M et al. *Blood* 2008;112:Abstract 223.

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Summary and Conclusions

- 5-azacitidine maintenance therapy after induction chemotherapy is feasible in patients with high-risk MDS or MDS-AML.
  - Median duration of CR was 13.5 mos.
  - Mild adverse events were reported.
- 5-azacitidine maintenance therapy, however, does not appear to prevent relapse in the majority of patients.
- Hypermethylation of multiple genes is a strong negative factor for probability of CR, duration of CR and survival.
  - The probability of achieving CR was negatively correlated to *CDH* promoter hypermethylation (p=0.008), and none of the six patients with all three genes hypermethylated achieved CR (p=0.03).
  - Two patients with baseline hypermethylation of the *CDH* gene had CR durations of only 2 and 5 months, respectively.
  - Survival was shorter in patients with hypermethylation of the *CDH* gene than in patients lacking it (9 mos vs 3 mos, p=0.005).

Source: Grövdal M et al. *Blood* 2008;112:Abstract 223.

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GAIL J ROBOZ, MD: Currently there is no known role for maintenance therapy in acute myeloid leukemia (AML). I believe this study is important because in addition to scientific rationale, the study demonstrated that it is feasible to consider azacitidine for patients with AML who are in remission. The dosing of azacitidine in maintenance for AML may be different than the approved dose for myelodysplastic syndromes. Larger cooperative group studies are ongoing and will help clarify the role of 5-azacitidine in maintenance therapy.

DAVID P STEENSMA, MD: This study addressed the common problem in MDS and in post-MDS AML of the relapse rate being very high for patients who achieve a remission. The availability now of hypomethylating agents such as azacitidine and decitabine has led to the question of whether these drugs could be used as part of a maintenance program to help keep patients in remission.

This study followed patients with high-risk MDS or post-MDS AML who were ineligible for transplant. They received a standard leukemia-like induction regimen, and the patients who achieved complete remission (CR) were maintained with a low-dose azacitidine regimen. It is hard to say what the meaning of the results are without a control arm, but I believe that it is slightly sobering that most of the patients experienced relapse and that the median CR duration was only 13.5 months. That result is within the realm of what one might expect with just induction alone in this group, perhaps slightly longer, but it is difficult to say.

The study did, however, examine the promoter methylation status of three different genes, and hypermethylation of *E-cadherin* was associated with a poor overall survival (three months) compared to those in whom the gene was not hypermethylated at baseline. No consistency was seen between methylation and durability of response or changes in methylation and outcome. This issue of how to maintain remissions still warrants further investigation.

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Dr Steensma is Attending Physician at Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.