5 Minute JournalClub

Lenalidomide Activity in AML with Trisomy 13

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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 activity of lenalidomide in patients with AML with isolated trisomy 13.

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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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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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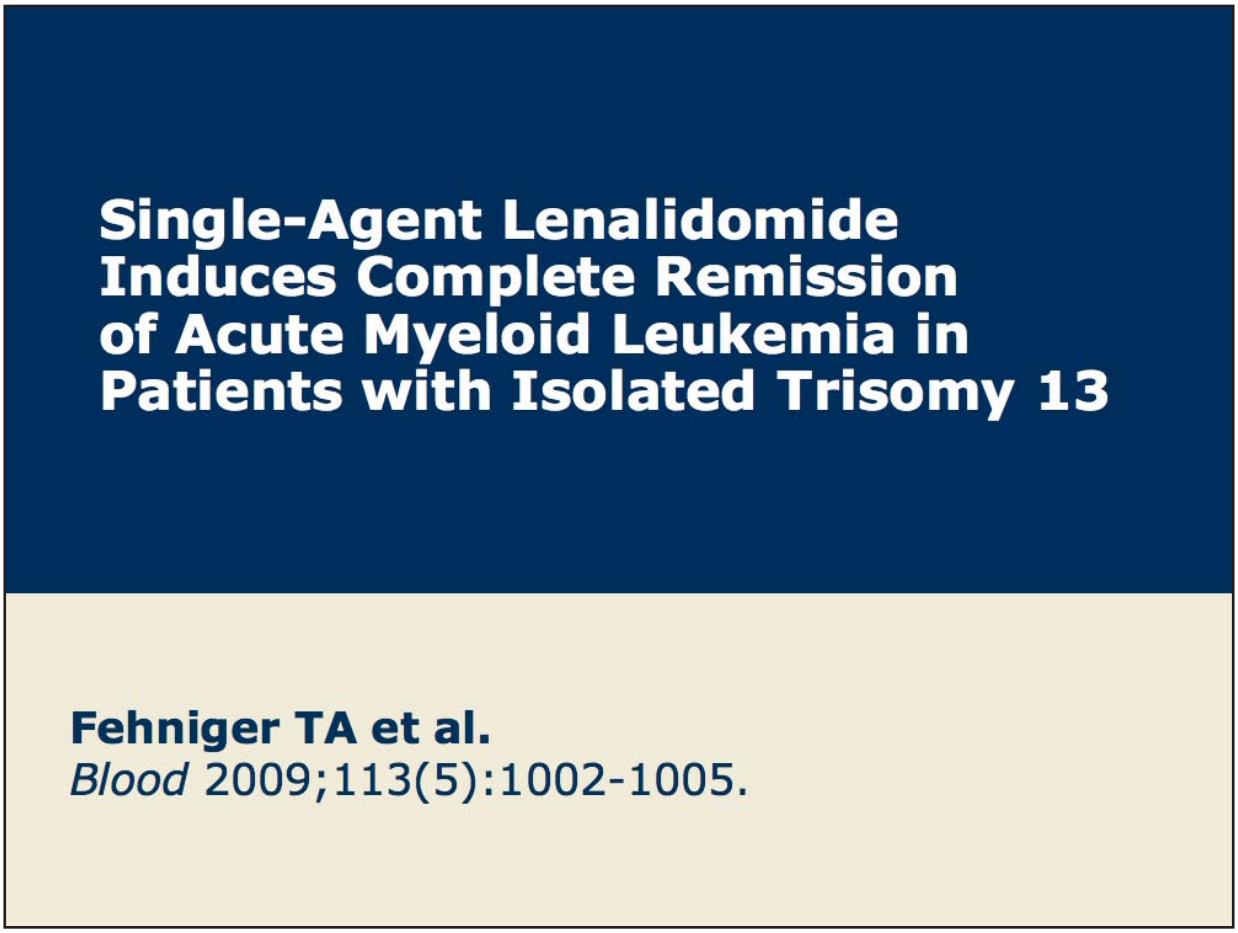
Lenalidomide Activity in AML with Trisomy 13

Presentation discussed in this issue:

Fehniger TA et al. **Single-agent lenalidomide induces complete remission of acute myeloid leukemia in patients with isolated trisomy 13.** *Blood* 2009;113(5):1002-5. **Abstract**

Slides from a journal article and transcribed comments from a recent interview with Gail J Roboz, MD (10/6/09)



Introduction

- Most patients with AML are elderly (≥ 60 years), and the prognosis is poor
  - Cytogenetic abnormalities remain one of the most important prognostic factors.
  - AML with trisomy 13 is rare (3% of all cases) and associated with very poor prognosis (*Blood* 2006;108:63; *Blood* 1990;76:1614)
- Lenalidomide is active in del (5q) MDS, and is administered at low dose (10mg/day) due to myelosuppression at higher doses
- Two independent trials (NCT00466895; NCT00546897) explored higher doses of lenalidomide in older patients with AML and activity is reported in two patients harboring trisomy 13 as the sole cytogenetic abnormality

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 1

- A 71-year-old man with no history of MDS presented with dyspnea and pancytopenia
- Bone marrow (BM) biopsy revealed undifferentiated AML with 90% myeloblasts expressing CD34, CD33, CD13 and CD117 with trisomy 13 in 5/20 metaphase cells as the sole chromosome abnormality by metaphase cytogenetics and FISH studies
- Therapy on clinical trial NCT00546897 consisted of lenalidomide, 50 mg/day for 14 days → 30 days off → lenalidomide, 50 mg/day for 21 days. Low-dose lenalidomide (10mg/day) was begun 30 days after completion of the 2nd high-dose cycle.

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 1: Treatment Outcomes

Treatment	Outcomes
high-dose L, 50 mg/day, cycle 1 (days 1-14)	Day 14: Peripheral blood AML blasts cleared
off drug (days 15-44) high-dose L, 50 mg/day cycle 2 (days 45-65) off drug (days 66-95)	Day 30: 25% cellularity with 72% blasts on BM biopsy; *FLT3-ITD*-positive
	Day 66: Aplasia, <10% cellularity, blasts present on BM biopsy; transfusion dependent

L = lenalidomide

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 1: Treatment Outcomes (Cont.)

Treatment	Outcomes
low-dose L, 10 mg/day (days 96-395)	Day 116: Blood cell counts normalized without transfusion or growth factors
	Day 124: 60% cellularity, <5% blasts on BM biopsy; no clonal abnormalities; *FLT3-ITD* negative. Two subsequent biopsies 6 and 14 weeks later confirmed this cytogenetic complete remission (CRc)
	Day 395: Relapse following low-dose lenalidomide for 10 months (CRc = 9 months)

L = lenalidomide

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 2

- A 68-year-old man with relapsed AML presented with marked pancytopenia
- Initial diagnosis of AML was 3.5 years earlier, with normal karyotype, and was preceded by MDS. Remission was achieved upon his initial AML diagnosis with induction fludarabine/cytarabine/G-CSF (FLAG), which was the regimen chosen because of his underlying cardiomyopathy and other comorbidities, and this was followed by consolidation with one cycle of cytarabine (1.5 g/m^2 x 6 doses)
- At current relapse, BM biopsy showed 40% myeloblasts and FAB M2 AML; Metaphase cytogenetics revealed a clone with trisomy for chromosome 13
- Therapy on NCT00466895 study:Lenalidomide, 35 mg/day for 21 of repeated 28 day cycles

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 2: Treatment Outcomes

Treatment	Outcomes
high-dose L, 35 mg/day (days 1-21) off drug (days 22-28)	Day 28: WBC=1200/µl, ANC=10/µl, RBC/platelet transfusion-dependent; 16% blasts on BM biopsy; 8/20 metaphase cells with persistent disease
high-dose L (days 29-31) off drug (days 32-78)	Day 32: lenalidomide held for fever, hypoxemia and pneumonia which resolved with medical treatment

L = lenalidomide

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 2: Treatment Outcomes (Cont.)

Treatment	Outcomes
off drug (days 32-78) high-dose L, 35 mg/day (days 79-99) off drug (days 100-106) high-dose L, 35 mg/day (days 107-127)	Day 60: lenalidomide still held, blood counts recovered without G-CSF support; Day 78: CR on BM biopsy, normal male karyotype in 20/20 metaphase cells; FISH was negative. CRc was confirmed 5 weeks later on repeat BM biopsy.
low-dose L, 10 mg/day (x 21 days q28 days from day 128 until relapse)	Day 422: Relapse (CRc = 9 months)

L = lenalidomide

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Discussion

- Lenalidomide has clinical activity in the poor-risk subset of AML with trisomy 13
- In two older patients with AML with isolated trisomy 13, sustained morphologic and cytogenetic remission were achieved with intermittent high-dose lenalidomide. In both patients, remission occurred after a prolonged delay (124 and 78 days, respectively) from initiation of this treatment.
- Further analysis of lenalidomide activity in additional patients with AML with trisomy 13 may lead to better understanding of myeloid leukemogenesis and aid in the development of new targeted therapeutic approaches for AML.

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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GAIL J ROBOZ, MD: Patients with acute myeloid leukemia with isolated trisomy 13 are rare. This was a nice paper with case reports to read because the accompanying data were complete. It is important to remember and think of if you happen to have a patient with isolated trisomy 13.

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.