5 Minute JournalClub

Outcome of Myelodysplastic Syndrome (MDS) with and without Chromosome 5 Abnormalities

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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 variability in prognosis of MDS based on the presence or absence of cytogenetic abnormalities and how these may affect treatment response to lenalidomide.

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Oncologists who partake in our **audio series** while they drive in their cars, run on their treadmills or work in their gardens seem to enjoy the often prolonged and Talmudic discussions with master clinical investigators who dissect every corner of medical oncology, but those of you out here in Web World are far more constrained by time, and to that end we offer another iteration of our 5-Minute Journal Club. This latest installment consists of a series of four emails sent at weekly intervals that will highlight approximately 20 recently published journal articles and meeting presentations on MDS/AML deemed by our faculty of Drs Steve Gore and Gail Roboz to be of great relevance to busy physicians in practice. The emails will introduce a specific set of papers and provide links to quickly access slides and faculty comments further explaining the findings from each report.

My favorite out of this first set is the ***JCO* paper by Gardner and colleagues** of a recent trial of 153 patients with newly diagnosed AML receiving induction treatment in a protected environment who were randomly assigned to a cooked (neutropenic) versus an uncooked diet. This fascinating study reveals that the prior belief, upheld by many, that uncooked foods would increase the rates of major infections or death in these patients was unfounded, and while this paper does not bring us any closer to a cure for this dreadful disease, it does provide some solace that those enduring the terrifying experience of induction therapy can enjoy a crispy apple or some grapes while they await the next step in their difficult journey.

Clearly the most practice- and paradigm-changing study profiled herein is the ***Lancet Oncology* paper by Fenaux and colleagues** demonstrating the most important advance in MDS in a long time, specifically that the use of the hypomethylating agent 5-azacitidine was associated with an impressive improvement in overall survival from 15 to 24.5 months in patients with high-risk disease. At a recent CME meeting we hosted in Naples, Florida, Dr Hagop Kantarjian commented that he believes the key to the efficacy of this intriguing agent is the ability to deliver multiple treatment cycles, which was more important than achieving a complete clinical response. He suggested that unlike ARA-C in AML, 5-azacitidine should be continued in MDS even if response is not observed in the first one or two treatment cycles.

Another critical MDS paper included here is a study by Dr Kantarjian examining MD Anderson's rich experience with patients with MDS and chromosome 5 abnormalities. The paper clearly demonstrates the heterogeneity within this uncommon patient subset, in which lenalidomide is often used. Interestingly, in his Naples presentation,

Dr K noted that he thinks this fascinating immunomodulatory agent is also a rational consideration in some patients with MDS *without* chromosome 5 abnormalities, specifically those with low-risk disease and transfusion dependence. In that setting, he believes, lenalidomide results in a transfusion independence rate of about 25 percent.

Finally, we have **an AML paper** that somehow escaped Dan Haller's *JCO* clutch and slipped into the *New England Journal* — a study demonstrating more CRs and better survival in patients receiving 90-mg/m^2 of daunorubicin than those receiving 45-mg/m^2. Dr Roboz questions the relevance of these findings because of the 45-mg/m^2 control arm, as she believes most physicians are using the 60-mg/m^2 dose.

Stay tuned for our next journal club, in which we review yet another paper by the prolific Dr Kantarjian proposing a new prognostic model for MDS, an MDS study evaluating the impact of pretransplant 5-azacitidine on the risk of post-transplant relapse, a study of decitabine in older patients with MDS and another paper on 5-azacitidine in MDS evaluating three different doses/schedules.

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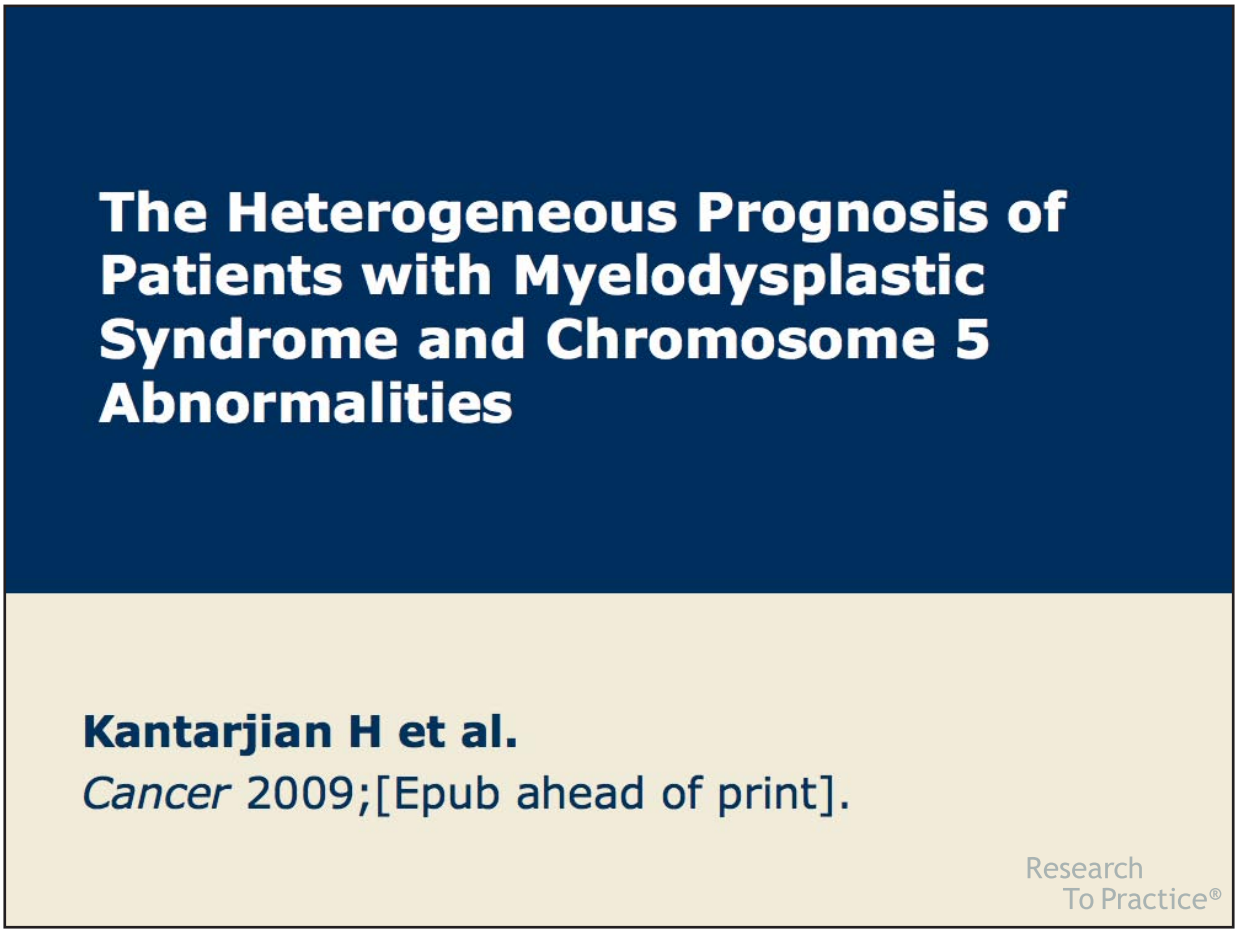
Outcome of Myelodysplastic Syndrome (MDS) with and without Chromosome 5 Abnormalities

Presentations discussed in this issue:

Kantarjian H et al. **The heterogeneous prognosis of patients with myelodysplastic syndrome and chromosome 5 abnormalities: How does it relate to the original lenalidomide experience in MDS?** *Cancer* 2009;[Epub ahead of print]. **Abstract**

Raza A et al. **Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q.** *Blood* 2008;111(1):86-93. **Abstract**

Slides from the journal articles and transcribed comments from recent interviews with Gail J Roboz, MD (10/6/09), Steven D Gore, MD (10/8/09) and Hagop M Kantarjian, MD (10/17/09) below



Introduction

- Lenalidomide has demonstrated clinical benefit in patients with lower-risk MDS (IPSS low or intermediate-1), transfusion dependence and with deletion 5q (del 5q) (*NEJM* 2006;355:1456).
- Hematologic and cytogenetic response rates were similar in response to lenalidomide therapy in patients with del 5q with or without additional chromosomal abnormalities, and across IPSS risk groups and a range of percent marrow blasts (*NEJM* 2006;355:1456).
  - Perception has arisen that lenalidomide is equally active in all MDS subsets and in all MDS subsets with del 5q.

Source: Kantarjian et al. *Cancer* 2009;[Epub ahead of print].

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Introduction (continued)

- To establish the potential benefit of lenalidomide in patients with MDS and del 5q, randomized trials would be required or historical databases could be used to establish baseline expectations against which the benefit of lenalidomide could be compared.
- **Current study objectives:**
  - Using a historical database, define prognosis and establish baseline expectations of patients that have MDS and deletion 5q with or without other cytogenetic abnormalities.

Source: Kantarjian et al. *Cancer* 2009;[Epub ahead of print].

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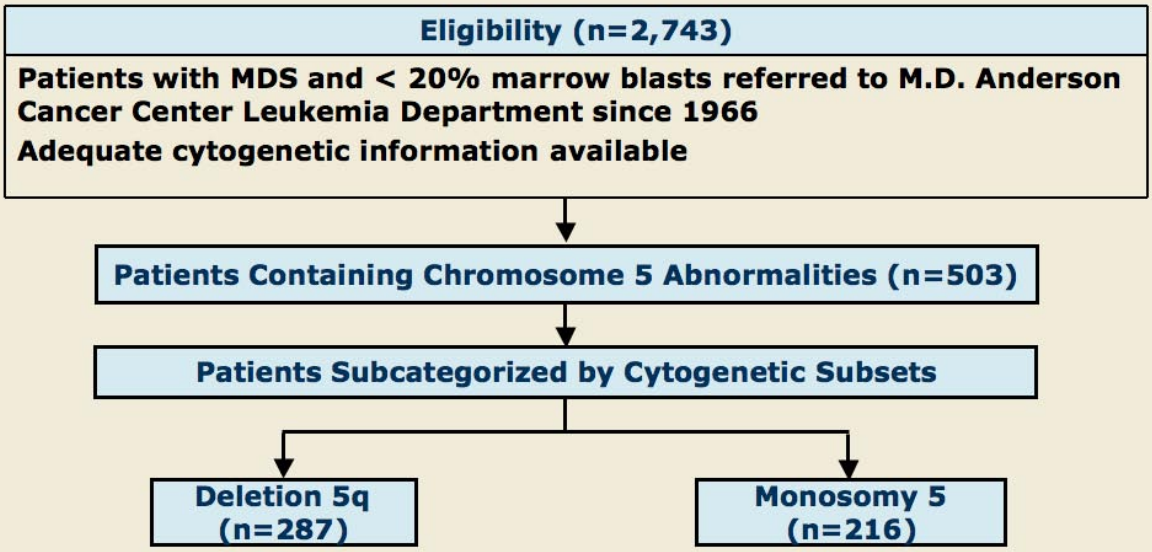
Retrospective Analysis of the Prognosis of Patients with MDS and Chromosome 5 Abnormalities



Survival measured from the date of referral to M.D. Anderson Cancer Center.

Source: Kantarjian et al. *Cancer* 2009;[Epub ahead of print].

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Survival of Patients with or without Chromosome 5 Abnormalities

Patient Group	Median Survival	2-year Survival Rate
No chromosome 5 abn. (n=2,240)	**17 mos**	**38%**
Del 5q: All patients (n=287)	**9 mos**	**23%**
Monosomy 5 (n=216)	**6 mos**	**3%**
Del 5q alone	33 mos	64%
+1 abn.	17 mos	40%
+2 abn.	12 mos	34%
+ ≥3 abn.	6 mos	0%
+ Chromosome 7 abn.	7 mos	2%

Compared to monosomy 5, deletion 5q was more frequently associated with lower IPSS risks (IPSS low and intermediate 1 risk rates of 32% vs 7%, p < 0.001) and with lower incidence of additional chromosomal abnormalities (60% vs 97%, p < 0.0001).

Abn = abnormalities

Source: Kantarjian et al. *Cancer* 2009;[Epub ahead of print].

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Survival of Patients with Lower-Risk* MDS According to Chromosome 5 Abnormalities

Patient Group	Median Survival	2-year Survival Rate
Del 5q: All patients (n=93)	**29 mos**	**60%**
Del 5q alone (n=55)	41 mos	67%
Del 5q + 1 abn. (n=19)	24 mos	48%
Del 5q + 2 abn. (n=7)	27 mos	67%
Del 5q + ≥ 3 abn. (n=6)	NR	NR
Del 5q + Chromosome 7 (n=6)	13 mos	0%

**Lower-risk MDS encompasses IPSS low and intermediate-1 risk groups.*

Source: Kantarjian et al. *Cancer* 2009;[Epub ahead of print].

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Median Survival of Patients with MDS According to % of Marrow Blasts

Patient Group	< 5% Blasts	< 10% Blasts
Del 5q: All patients (n=115, 198)	**15 mos**	**12 mos**
Del 5q alone (n=41, 53)	44 mos	41 mos
Del 5q + 1 abn. (n=15, 24)	29 mos	24 mos
Del 5q + 2 abn. (n=11, 14)	14 mos	12 mos
Del 5q + ≥ 3 abn. (n=21, 43)	5 mos	6 mos
Del 5q + Chromosome 7 (n=27, 64)	6 mos	7 mos

Source: Kantarjian et al. *Cancer* 2009;[Epub ahead of print].

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Summary and Conclusions

- It may not be appropriate for oncologists to consider patients with MDS and deletion 5q as one group.
  - Prognosis of patients with MDS and low-risk MDS containing chromosome 5 abnormalities is heterogeneous and is worsened by the presence of other abnormalities in addition to deletion 5q.
  - Monosomy 5 was associated less often with low-risk MDS (IPSS low and intermediate 1 risk) and more often with the presence of other adverse cytogenetic findings.
- Based on analysis of this study and on the entry criteria of the original lenalidomide study, the percentage of patients who are candidates for lenalidomide would be 2% to 3%.
  - Oncologists may be offering lenalidomide to subsets of patients with MDS in which the drug is untested in controlled trials and where it may not be effective.
- Prognosis and baseline expectation data established by this study may be used for comparative purposes with the lenalidomide experience.

Source: Kantarjian et al. *Cancer* 2009;[Epub ahead of print].

Phase 2 Study of Lenalidomide in Transfusion-Dependent, Low-Risk, and Intermediate-1-Risk Myelodysplastic Syndromes with Karyotypes Other Than Deletion 5q

Raza A et al.

Blood 2008;111(1):86-93.

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Erythroid Response to Lenalidomide in Patients Lacking 5q Deletion

	Daily dosing 10 mg/day (n=100)	21-day dosing 10 mg/day (n=114)	All patients (n=214)
Erythroid response[1]			
Total transfusion response TI + ≥ 1 g/dL Hb increase ≥ 50% ↓ no. of transfusions	42% 27% 15%	45% 25% 19%	43% 26% 17%
Median time to TI	7.4 wk	4.1 wk	4.8 wk
Hemoglobin			
Baseline, median Response, median Increase, median	7.9 g/dL 11.6 g/dL 3.3 g/dL	8.1 g/dL 11.0 g/dL 3.1 g/dL	8.0 g/dL 11.6 g/dL 3.2 g/dL

TI, transfusion independence; Hb, hemoglobin.
[1]Erythroid response measured according to modified International Working Group 2000 criteria.

Source: Raza A et al. *Blood* 2008;111(1):86-93.

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Summary and Conclusions

- A Phase II, multicenter trial (n=214) evaluating lenalidomide therapy in patients with a long-standing diagnosis of MDS (median 2.2 years) that is low- or intermediate-1-risk, with substantial RBC transfusion requirements (median 4 units/8 weeks) and without del 5q.
- In the ITT population, 26% of patients achieved transfusion independence (TI) after median 4.8 weeks of lenalidomide treatment.
  - Median TI duration was 41 weeks and 36% or responders remained transfusion-free for at least one year (median TI duration for MDS del 5q responders was > 2 years)
  - A reduction in the need for transfusion was seen in 43% of patients.
  - Median rise in hemoglobin was 3.2 g/dL from baseline
- Lenalidomide demonstrated clinically meaningful activity in patients with transfusion-dependent, low- or intermediate-1-risk MDS without deletion 5q.

Source: Raza A et al. *Blood* 2008;111(1):86-93.

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GAIL J ROBOZ, MD: The Kantarjian *Cancer* 2009 paper is a good review paper for clinicians. There's been a lot of confusion in the community about this issue and questions whether all patients with a 5q minus abnormality benefit from lenalidomide. This paper is helpful in clarifying that that may not be the case. It goes through in a clinically meaningful way what happens to these patients and which ones are likely to benefit from lenalidomide. There are patients with a dismal prognosis who carry a 5q minus, and there are patients who have prognosis that's measured in many years. It is important to recognize that all 5q minus is not the same. The Raza study showed that it is possible for some patients who do not have the 5q deletion to have a hematologic improvement in response to lenalidomide. Lenalidomide will give about a 25 percent response rate and can be considered for anemic patients at low and intermediate 1 risk with neutrophils > 500 and platelets > 50,000 who haven't responded to growth factors. Response can be assessed within about 12 weeks.

STEVEN D GORE, MD: This Kantarjian paper is useful in that it describes a spectrum of biological behaviors of patients with myelodysplastic syndrome (MDS) who have deletion of chromosome 5q or monosomy-5. It shows that there is heterogeneity in the survival outcomes of the group of patients with chromosome 5 abnormalities. The Raza study population was an unusual population of patients with transfusion-dependent MDS in that they had neutrophils of at least 500 and platelets of at least 50,000, but the study does suggest that among those patients, 25 percent will become transfusion independent in response to lenalidomide therapy. One would take this information and know that it is an option, albeit not a fabulous one, for such patients. You will find out within two or three months if the patient is going to respond.

HAGOP M KANTARJIAN, MD: The only scenario in which administering lenalidomide to patients without chromosome 5 abnormalities may work is with patients with low-risk MDS who are transfusion dependent. In that setting, usually the transfusion independence rate is about 25 percent. If you have a patient with low-risk MDS to whom you have administered growth factors for red blood cell transfusion dependence without response, you can try lenalidomide for a short period of time. I don't think it is unreasonable, and we do it quite often.

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 Kantarjian is Chairman and Professor of the Leukemia Department at The University of Texas MD Anderson Cancer Center in Houston, Texas.