5 Minute JournalClub

Efficacy of Azacitidine in Higher-Risk Myelodysplastic Syndrome (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

- Identify the benefits and risks of azacitidine for patients with higher-risk MDS and chronic myelomonocytic leukemia.

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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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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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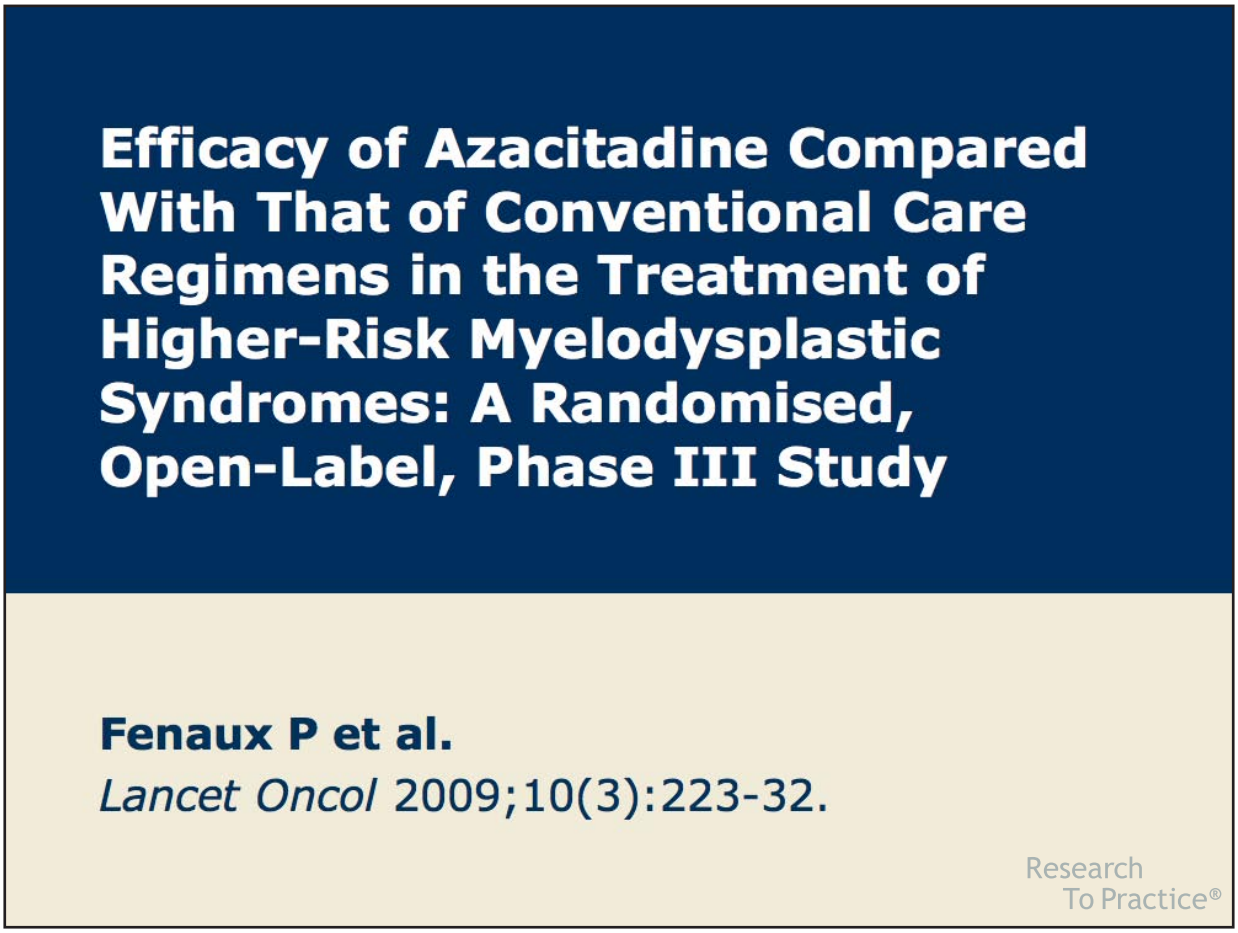
Efficacy of Azacitidine in Higher-Risk Myelodysplastic Syndrome (MDS)

Presentation discussed in this issue:

Fenaux P et al. **Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomized, open-label, phase III study.** *Lancet Oncol* 2009;10(3):223-32. **Abstract**

Slides from the journal article 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

- Median survival for patients with Intermediate-2 or High-Risk myelodysplastic syndrome (MDS) by IPSS is 1.2 years and 0.4 years, respectively
- Beyond allogeneic stem-cell transplantation, no treatment strategies for MDS meaningfully improves survival or rate of leukemic transformation
- In CALGB-9221, azacitidine (Aza) improved survival compared to observation but was inconclusive due to its crossover design and lack of active comparator (JCO 2002;20:2429)

Objectives of the current study:

- Assess effect of azacitidine vs conventional care regimen [CCR, best supportive care (BSC), low-dose cytarabine (LDC) or intensive chemotherapy IC)] on overall survival and time to progression to AML in patients with higher-risk MDS

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

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Phase III, International, Multicenter, Randomized, Controlled, Parallel-Group, Open-Label Trial (N = 358)

Eligibility

IPSS Intermediate-2 or High-risk MDS and FAB-defined refractory anemia with excess blasts (+/-) in transformation, or chronic myelomonocytic leukemia with ≥ 10% bone marrow blasts and WBC < 13 x 10^9 cells/L

Investigator Preselection of Conventional Care Regimens (CCR)

Best supportive care (BSC, n = 222)

Low-dose cytarabine (LDC, n = 94)

Intensive chemo (IC, n = 42)

R

Azacitidine (Aza, n = 179)

CCR* (n = 179)

*Patients randomized to CCR received the investigator preselected treatment

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

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Median Overall Survival and Time to Progression to AML: Azacitidine versus CCR (21.1 months median follow-up)

	Azacitidine (n = 179)	CCR (n =179)	Hazard Ratio	*P*-value
Overall survival	24.5 mos	15 mos	0.58	0.0001
2-year overall survival	50.8%	26.2%	NR	<0.0001
Time to transformation to AML	17.8 mos	11.5 mos	0.50	<0.0001

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

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Median Overall Survival and Time to Progression to AML According to Investigator Preselected Therapy

	BSC only (n = 222)		Low-dose cytarabine (LDC) (n = 94)		Intensive chemo (IC) (n = 42)	
	Aza (n=117)	BSC (n=105)	Aza (n =45)	LDC (n=49)	Aza (n=17)	IC (n=25)
Overall survival	21.1 mo	11.5 mo	24.5 mo	15.3 mo	25.1 mo	15.7 mo
Hazard ratio, p-value	HR = 0.58, p = 0.0045		HR = 0.36, p = 0.0006		HR = 0.76, p = 0.51	
Time to transformation to AML	15.0 mo	10.1 mo	15.0 mo	14.5 mo	23.1 mo	10.7 mo
Hazard ratio, p-value	HR = 0.41, p < 0.0001		HR = 0.55, p = 0.097		HR = 0.48, p = 0.19	

HR = Hazard ratio, adjusted for treatment, subgroup, ECOG performance status, lactate dehydrogenase, hemoglobin, number of prior red-blood-cell transfusions and presence or absence of cytogenetic-7/del(7q) abnormality

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

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Hematologic Response and Improvement: Azacitidine versus Conventional Care Regimen (CCR)

	Total ITT (n = 358)		
	Aza (n=179)	CCR (n=179)	P-value
Hematologic Response			
Any remission	29%	12%	0.0001
Complete remission	17%	8%	0.015
Partial remission	12%	4%	0.0094
Stable disease	42%	36%	0.33
Hematologic Improvement (imprvmnt)			
Any imprvmnt	49%	29%	<0.0001
Major erythroid imprvmnt	40%	11%	<0.0001
Major platelet imprvmnt	33%	14%	0.0003
Major neutrophil imprvmnt	19%	18%	0.87

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

Hematologic Response and Improvement: Azacitidine versus Investigator Preselected Therapy

	BSC (n = 222)		LDC (n = 94)		IC (n = 42)	
	Aza (n=117)	BSC (n=105)	Aza (n=45)	LDC (n=49)	Aza (n=17)	IC (n=25)
Hematologic Response						
Any remission	27%*	5%	31%*	12%	29%	40%
Complete remission	12%*	1%	24%*	8%	29%	36%
Partial remission	15%*	4%	7%	4%	0%	4%
Stable disease	44%	39%	33%	37%	47%	24%
Hematologic Improvement (imprvmnt)						
Any imprvmnt	50%*	31%	53%*	25%	35%	28%
Major erythroid imprvmnt	39%*	8%	44%*	10%	29%	22%
Major platelet imprvmnt	30%*	10%	38%	19%	33%	20%
Major neutrophil imprvmnt	15%	20%	27%	11%	23%	24%

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

***p*-value < 0.05**

Deaths, Discontinuation and Grade 3/4 Hematologic Toxicity: Azacitidine versus CCR

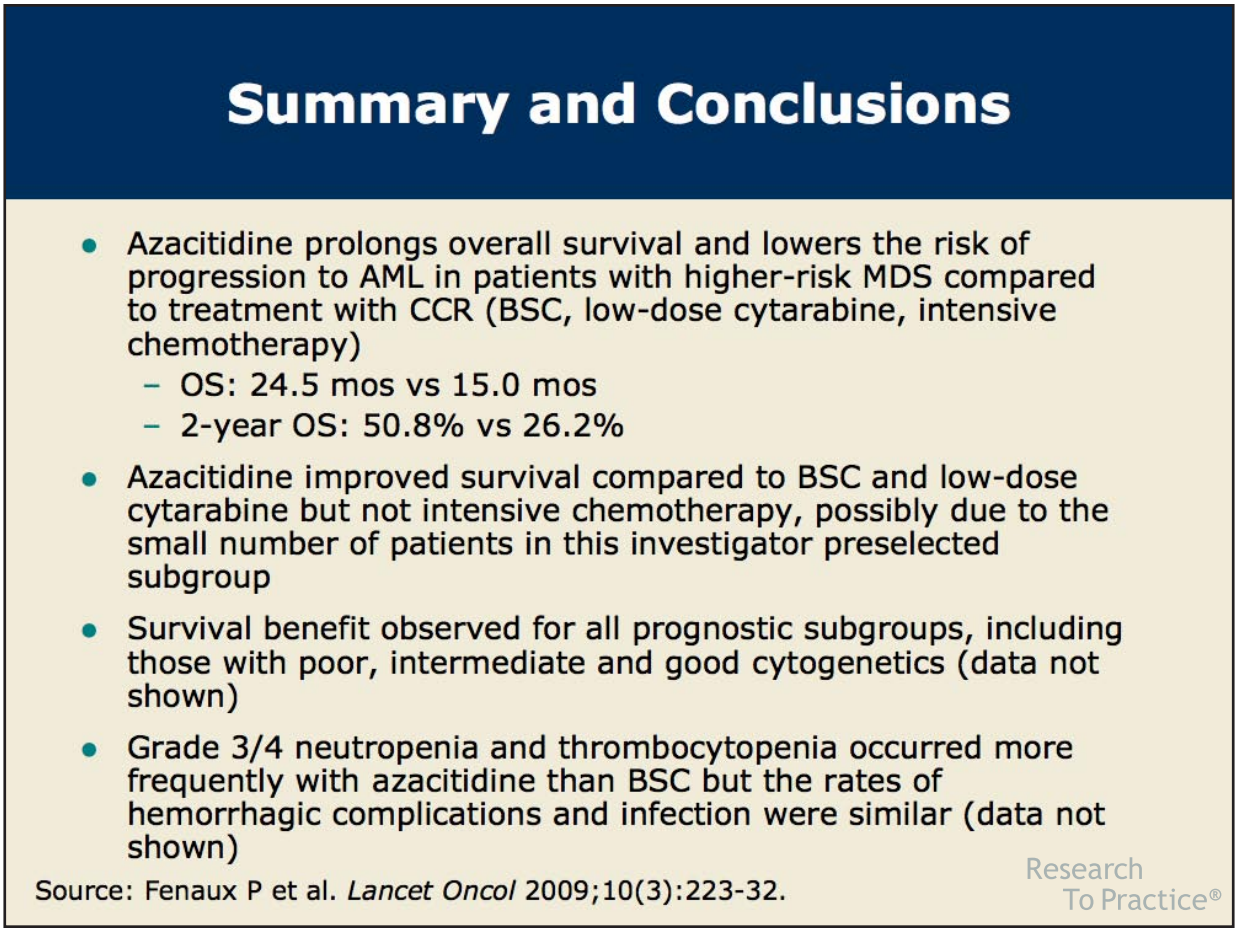
	Total ITT (n = 358)	
	Aza (n=179)	CCR (n=179)
Deaths	46%	63%
Deaths, first 3 months of treatment	11%	9%
Discontinuation before study completion due to hematol AEs	5%	2%
Grade 3/4 Hematologic Adverse Events (AEs)		
Neutropenia	91%	76%
Thrombocytopenia	85%	80%
Anemia	57%	68%
Baseline Gr 0-2 progressing to Gr 3/4 during treatment		
Neutropenia	84%	61%
Thrombocytopenia	74%	72%
Anemia	54%	64%

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

Deaths, Discontinuation and Grade 3/4 Hematologic Toxicity: Azacitidine Investigator Preselected Therapy

	BSC (n = 222)		LDC (n = 94)		IC (n = 42)	
	Aza (n=117)	BSC (n=105)	Aza (n=45)	LDC (n=49)	Aza (n=17)	IC (n=25)
Deaths	45%	63%	44%	63%	53%	64%
Deaths, first 3 mo of treatment	11%	9%	11%	14%	12%	0%
Discontinuation before study completion due to hematol AEs	3%	2%	9%	5%	6%	0%
Grade 3/4 Hematologic AEs						
Neutropenia	91%	69%	89%	89%	94%	90%
Thrombocytopenia	82%	71%	71%	93%	88%	95%
Anemia	54%	66%	66%	64%	56%	58%

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.



GAIL J ROBOZ, MD: This paper is important for clinicians in active practice to read right away. This is the first time that patients with higher-risk myelodysplastic syndrome (MDS) were shown to have a survival benefit with treatment. The azacitidine treatment was compared in an interesting way to three treatments that clinicians would routinely think about using: a low dose of regular chemotherapy, regular induction chemotherapy or supportive care. Azacitidine treatment for these patients increased their survival from a median of 15 months to about 24 months. Patients who might otherwise have been offered supportive care or low-dose ara-C are now receiving azacitidine as standard treatment.

STEVEN D GORE, MD: This is an important paper, probably the most important study that has come out in MDS for some time. Of course, I'm a co-author, so that should be taken into consideration. The study demonstrated a doubling of the two-year survival in the azacitidine-treated group compared to that of the conventional care arm. It established azacitidine at the FDA-approved dose and schedule as the treatment of choice for patients with high-risk MDS.

HAGOP M KANTARJIAN, MD: This is the first study outside the setting of allogeneic transplant that shows a disease-modifying course in MDS. The study demonstrates that it is not always necessary to achieve a complete response (CR) in order to improve survival. The CR rate with azacitidine in this study was 17 percent, and yet

azacitidine was associated with a better median survival. This result may be related to how long you can administer azacitidine therapy to a patient, and since azacitidine is a low-intensity targeted therapy, one could deliver an average of nine cycles in this study. This study also suggests that low-intensity therapy may be better than intensive chemotherapy in some of the more indolent disorders or possibly in elderly acute myelogenous leukemia (AML). A subset analysis of these study data performed by Silverman et al (*Blood* 2008;112;Abstract 227) looking at the average number of azacitidine courses necessary to achieve a first response demonstrated that about half of the patients that had an initial first response will go on to improve that response with continued azacitidine treatment. This suggests that in MDS, azacitidine treatment should be continued even though a response is not observed after one or two cycles and is in contrast to the ara-C or high-dose ara-C experience in AML. In MDS you may have to persist with your treatment before you see the full response effect.

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.