5 Minute JournalClub

Studies on the Efficacy and Safety of Deferasirox for Iron Chelation in Patients with MDS: EPIC and US03

For more visit ResearchToPractice.com/5MJCMDSAML

Research To Practice®

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 efficacy and safety data from the EPIC and US03 trials of deferasirox as an iron chelator for patients with MDS.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentation, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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:

Gail J Roboz, MD
Associate Professor of Medicine
Director, Leukemia Program
Weill Medical College of Cornell University
NewYork-Presbyterian Hospital
New York, New York

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

Steven D Gore, MD
Professor of Oncology
Johns Hopkins University
The Sidney Kimmel Comprehensive Cancer Center
at Johns Hopkins
Baltimore, Maryland

Consulting Agreement and Stock Ownership: Celgene Corporation; Paid Research: Celgene Corporation, Johnson & Johnson Pharmaceuticals.

EDITOR — Neil Love: Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Centocor Ortho Biotech Services LLC, Cephalon Inc, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, GlaxoSmithKline, ImClone Systems Incorporated, Lilly USA LLC, Merck and Company Inc, Millennium Pharmaceuticals Inc, Monogram Biosciences, Novartis Pharmaceuticals Corporation, OSI Oncology, Roche Laboratories Inc, Sanofi-Aventis and Wyeth.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.

This program is supported by an educational grant from Celgene Corporation.

Last review date: November 2009
Expiration date: November 2010

Research To Practice®

5 MinuteJournalClub

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.

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates each of the five educational activities, comprised of a slide set and accompanying commentary, for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

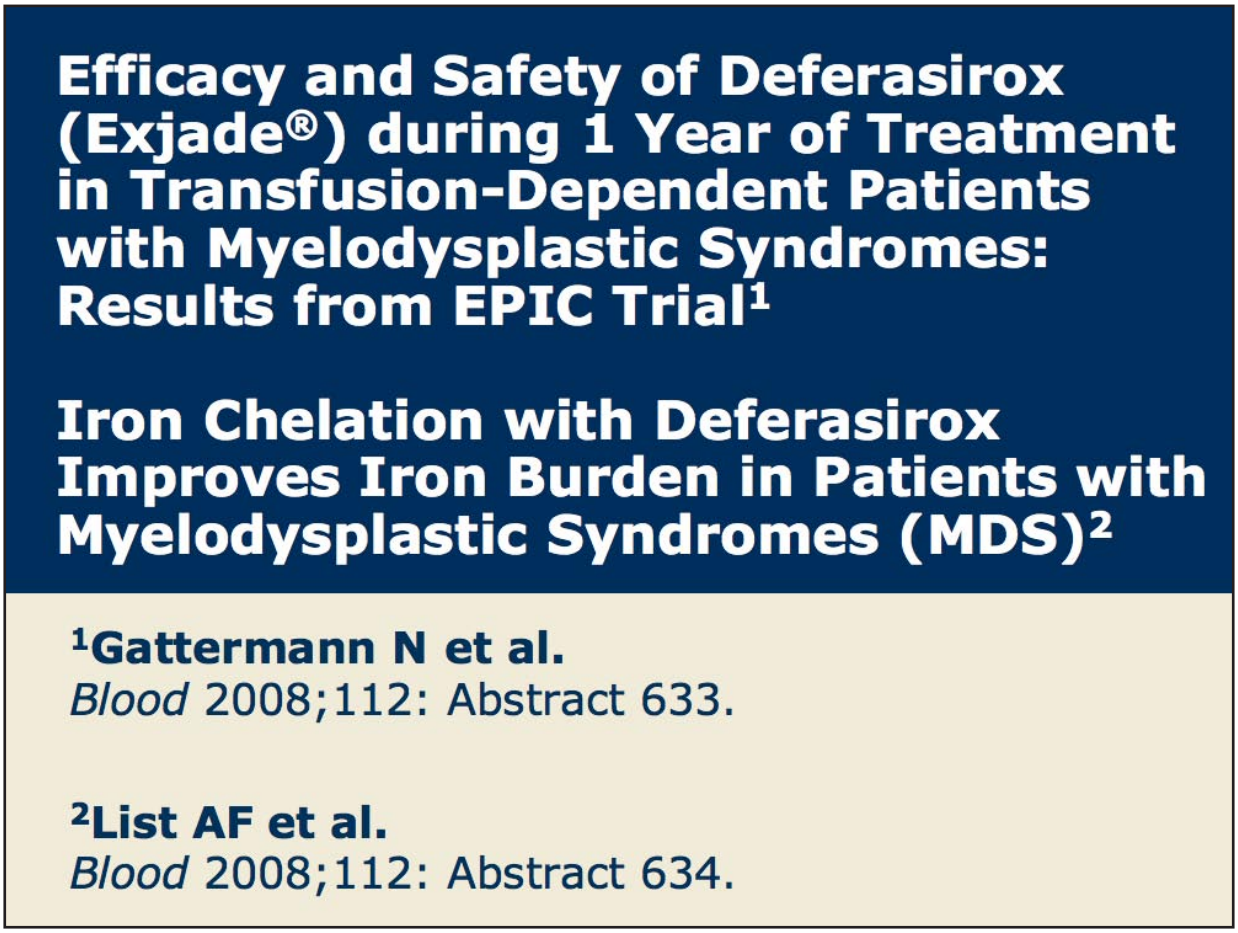
Studies on the Efficacy and Safety of Deferasirox for Iron Chelation in Patients with MDS: EPIC and US03

Presentations discussed in this issue:

Gattermann N et al. **Efficacy and safety of deferasirox (Exjade®) during 1 year of treatment in transfusion-dependent patients with myelodysplastic syndromes: Results from EPIC trial.** *Blood* 2008;112;**Abstract 633**.

List AF et al. **Iron chelation with deferasirox (Exjade®) improves iron burden in patients with myelodysplastic syndromes (MDS).** *Blood* 2008;112;**Abstract 634**.

Slides from presentations at ASH 2008 and transcribed comments from recent interviews with Gail J Roboz, MD (11/20/09) and Steven D Gore, MD (10/8/09)



Introduction

- Many patients with myelodysplastic syndromes (MDS) are susceptible to iron overload from ongoing blood transfusions and increased dietary iron absorption.
- Deferasirox has demonstrated efficacy in maintaining or reducing body iron in patients with MDS.
- The EPIC[1] and US03[2] studies evaluated efficacy and safety of deferasirox in patients with MDS:
  - Primary endpoint: change in serum ferritin (SF) from baseline at 12 months
  - Safety was assessed by laboratory parameters and adverse events monitoring

Source: [1]Gattermann N et al. *Blood* 2008;112:Abstract 633; [2]List AF et al. *Blood* 2008;112:Abstract 634.

EPIC: Multicenter, Open-Label, Single-Arm Study of Deferasirox in Patients with Anemia, including MDS

Eligibility

- Transfusion-dependent MDS; serum ferritin (SF) ≥ 1000 ng/ml or < 1000 ng/ml and requiring >20 transfusions or 100 mL/kg blood;
- MRI-confirmed liver iron concentration >2 mg Fe/g dry weight

↓

Treatment (n=341)

- Initial dose: deferasirox, 10-30 mg/Kg/day for 12 months
- SF assessed q mo; dose adjusted according to protocol specifications in 5-10 mg/kg/d steps q 3 mo based on SF trends and safety markers

Source: Gattermann N et al. *Blood* 2008;112:Abstract 633.

US03: Multicenter, Open-Label Study of Deferasirox in Patients with MDS

Eligibility

- Transfusion-dependent Low- or Int-1 IPSS-risk MDS; serum ferritin (SF) ≥ 1000 ng/ml and requiring >20 units RBC transfusions;
- Serum creatinine (SCr) ≤ 2 x upper limit of normal (ULN)

↓

Treatment (n=176)

- Initial dose: deferasirox, 20 mg/Kg/day, increased to 40 mg/Kg/day based on tolerability and response
- SF assessed q mo and labile plasma iron (LPI) assessed quarterly

Source: List AF et al. *Blood* 2008;112:Abstract 634.

Deferasirox for MDS: Reduction in Serum Ferritin (SF) from Baseline Over 1 Year

Month	Median SF (ng/mL)	
	EPIC[1] (n=341)	US03[2] (n=176)
0 (baseline)	2730	3397
3	2358	3057
6	2210	2802
9	2076	2635
12	1904	2501

[1]EPIC: Change in median SF over one year by last observation carried forward with all patients included: -253 ng/mL (p=0.0019)
[2]US03: At 3 mos, sustained suppression of labile plasma iron (LPI) to within normal range was achieved in patients with ↑baseline levels (41% of patients had elevated LPI at baseline)

Source: [1]Gattermann N et al. *Blood* 2008;112:Abstract 633; [2]List AF et al. *Blood* 2008;112:Abstract 634.

Deferasirox for MDS: Most Common Drug-Related Adverse Events

Adverse Events (AE)	Patients, n (%)	
	EPIC[1] (n=341)	US03[2,3] (n=165)
Diarrhea	110 (32%)	71 (43%)
Nausea	45 (13%)	29 (18%)
Vomiting	26 (8%)	not reported
Abdominal pain[1]/distension[3]	51 (15%)	9 (6%)
Serum creatinine >ULN for ≥2 values	36 (10.6%)	26* (18%)
Rash	23 (7%)	14 (9%)
Constipation	21 (6%)	not reported

*Patients with normal baseline creatinine (n=147)

Discontinuation of drug due to drug-related AEs: 13%(EPIC)[1], 10% (US03)[2]

Source: [1]Gattermann N et al. *Blood* 2008;112:Abstract 633; [2]List AF et al. *Blood* 2008;112:Abstract 634; [3]Sekeres MA. Oncology Congress 2009 Presentation HM107.

Conclusions

- Deferasirox provided significant reduction in SF levels over 1-year of treatment with appropriate dose adjustments based on SF trends and safety markers
  - Primary Reduction in mean SF (EPIC[1]): -253 ng/mL, p=0.0019
  - Reduction in LPI levels after 3 months to normal range (US03[2])
- The adverse events reported were mild to moderate and consistent with previously reported deferasirox data in patients with MDS
  - Diarrhea (32 - 43%)
  - Increase in creatinine to >ULN for at least 2 values (EPIC[1]:10.6%; US03[2]:18%)

Source: [1]Gattermann N et al. *Blood* 2008;112:Abstract 633; [2]List AF et al. *Blood* 2008;112:Abstract 634.

GAIL J ROBOZ, MD: These two papers by Gattermann and by List suggest that the agent deferasirox is working as expected. It is removing iron from the blood serum in transfusion-dependent patients with lower-risk myelodysplastic syndromes (MDS). These studies are important because they examine iron chelation in older patients who are on multiple concomitant medications. The initial iron chelation studies were performed in children, which is a completely different patient population.

I believe that iron chelation in MDS is still controversial. There are several important questions that are being addressed by ongoing trials. First, does eliminating iron overload in patients with MDS matter clinically — does it help all patients or only patients at lower risk?

Second, what is the best way to remove iron? There are several iron chelators available currently, but what's still unknown is what's the best way to use these agents and could they be combined.

I believe most of us who deal a lot with patients with MDS are struck by the fact that rarely do we seem to see clinical complications from iron overload, especially in patients at higher risk. There seems to be something different going on in these older patients than in children. We don't know if older patients with MDS are dying from iron overload.

How iron levels should be measured is also controversial. Ferritin levels are easy and convenient to determine, but it is not completely clear if that is the best measurement to use. There are data suggesting that increased ferritin correlates with a poor outcome and decreased survival. But that does not necessarily mean that lowering ferritin levels will increase survival in these patients.

DR LOVE: What is usually the earliest clinical manifestation of iron overload in patients with MDS?

DR ROBOZ: I don't believe anyone knows that answer. Issues such as endocrinologic and sexual dysfunction are often difficult to detect in older patients. Most oncologists are concerned about cardiomyopathy, but we don't see much of that.

DR LOVE: What are the main downsides of chelation therapy?

DR ROBOZ: Expense is certainly one, in addition to potential interactions with other medications, renal complications, rash and nausea. Chelation therapy is not necessarily an easy treatment to receive as a patient. I would not encourage the random chelation of all patients.

STEVEN D GORE, MD: This treatment for iron overload is already incorporated into clinical practice, though it is not clear that iron overload is a real problem for patients with myelodysplastic syndromes (MDS). Although measurable, ferritin and various parameters associated with iron overload have not been shown to increase cardiac iron or to significantly contribute to mortality in patients with MDS. Most experts believe

that it is reasonable to use chelation for patients with low-risk MDS with ongoing transfusion needs. Deferasirox is an effective chelator, but whether chelation should be used or whether it will improve outcomes or survival is uncertain at this point.

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.