5 Minute JournalClub

A Prognostic Model for MDS that Accounts for Events Not Considered by the International Prognostic Scoring System (IPSS)

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

- Identify the utility of the prognostic model for risk-stratifying patients with MDS regardless of prior therapy received.

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

Click to go directly to our slides and comments on the **recent review of myelodysplastic syndromes**, **a new proposed prognostic model for MDS**, **the effect of pre-HCT azacitidine therapy on post-transplant outcomes**, **the efficacy of decitabine on survival in elderly patients with higher-risk MDS**, and a **comparison of three alternative azacitidine treatment regimens**.

As we were about to hit the send button on this, our latest e-blast, I happened to be on PubMed and stumbled across a just e-published (Nov 5) *New England Journal* **review article on myelodysplastic syndromes** (MDS). Thinking that the paper might be an important addition to this project, I quickly poured over the work. As usual, our entire clinical team loved the *NEJM* graphics (best in the business!), and the science behind this instant classic by Ayalew Tefferi and James Vardiman was spectacular. Further examination revealed only one prior (1999) *NEJM* review article on MDS, in which for example, there was but a brief mention of an initial 29 patient report of 5-azacitidine — the only reference to demethylating agents. Lenalidomide was nowhere to be found in this "ancient" document by Mark Heaney and David Golde. So at the last minute, we bypassed our usual formal faculty review and integrated this serendipitous discovery into the enclosed activity.

The concluding statements of these two review articles separated by 10 years reflect first a hopeful wish (1999): "The next decade will probably see a marked improvement in our ability to manage myelodysplasias as well as AML" and then confidence (2009): "Increasing information on the identity and nature of transformed hematopoietic stem cells and advances in biotechnology are helping to create the 'perfect storm' for breaking the current stalemate in our understanding of this disease."

So where are we today in MDS? Our faculty — Gail Roboz, Steven Gore and Hagop Kantarjian — once again comment on four papers that were identified and prioritized as important to clinical practice. The first addresses a proposed new **prognostic model for MDS** that accounts for such important factors as prior therapy and adverse cytogenetic profiles. The paper's author, Dr Kantarjian, believes this new system is superior to IPSS, but only time will tell.

Paper 2 comes out of the Moffitt Cancer Center and is a retrospective review of 54 patients receiving hematopoietic stem cell transplant (HCT) for MDS or chronic myelomonocytic leukemia (CMML). The outcomes of 30 patients receiving pre-HCT treatment with 5-azacitidine were compared to and found to be very similar to the

outcomes of 24 patients who did not receive this agent, leading the authors to conclude that 5-azacitidine can be safely and effectively used to stabilize patients prior to transplant.

The third study examines the other available demethylating agent, decitabine, and demonstrates that in spite of a 34 percent response rate, no improvement in overall survival (OS) was observed compared to supportive care in this well-conducted trial completed in Europe. While the lack of OS benefit in this study may relate to suboptimal duration of treatment, a recent US national Patterns of Care study conducted by our education group in preparation for an upcoming **ASH satellite symposium** demonstrated that 80 percent of oncologists using an up-front demethylating agent for MDS chose 5-azacitidine, perhaps reflecting the OS benefit reported with this agent.

Finally we have **a report of three alternative doses/schedules** of 5-azacitidine in MDS that through indirect comparison appear to be as effective and well tolerated as the approved day 1-7 regimen that requires weekend infusions. We may need a head-to-head trial to be fully convinced but it seems like a more patient-friendly regimen may in fact be out there.

The publications and presentations in this short series testify to significant forward momentum in MDS and AML. However, the ultimate hope is that 10 years from now, the next *NEJM* review article on MDS or AML will describe the unraveling and elimination of these diseases that have for so long resisted research progress.

Coming up next on 5-Minute Journal Club: a Phase II trial of up-front clofarabine in older patients with AML, a review of prognostic and predictive markers in AML, a trial of decitabine in older patients with AML and finally a retrospective review of more than 1,000 patients with AML and MDS receiving HCT demonstrating similar efficacy and toxicity patterns regardless of patient age, up to 78.

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 with or without 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.

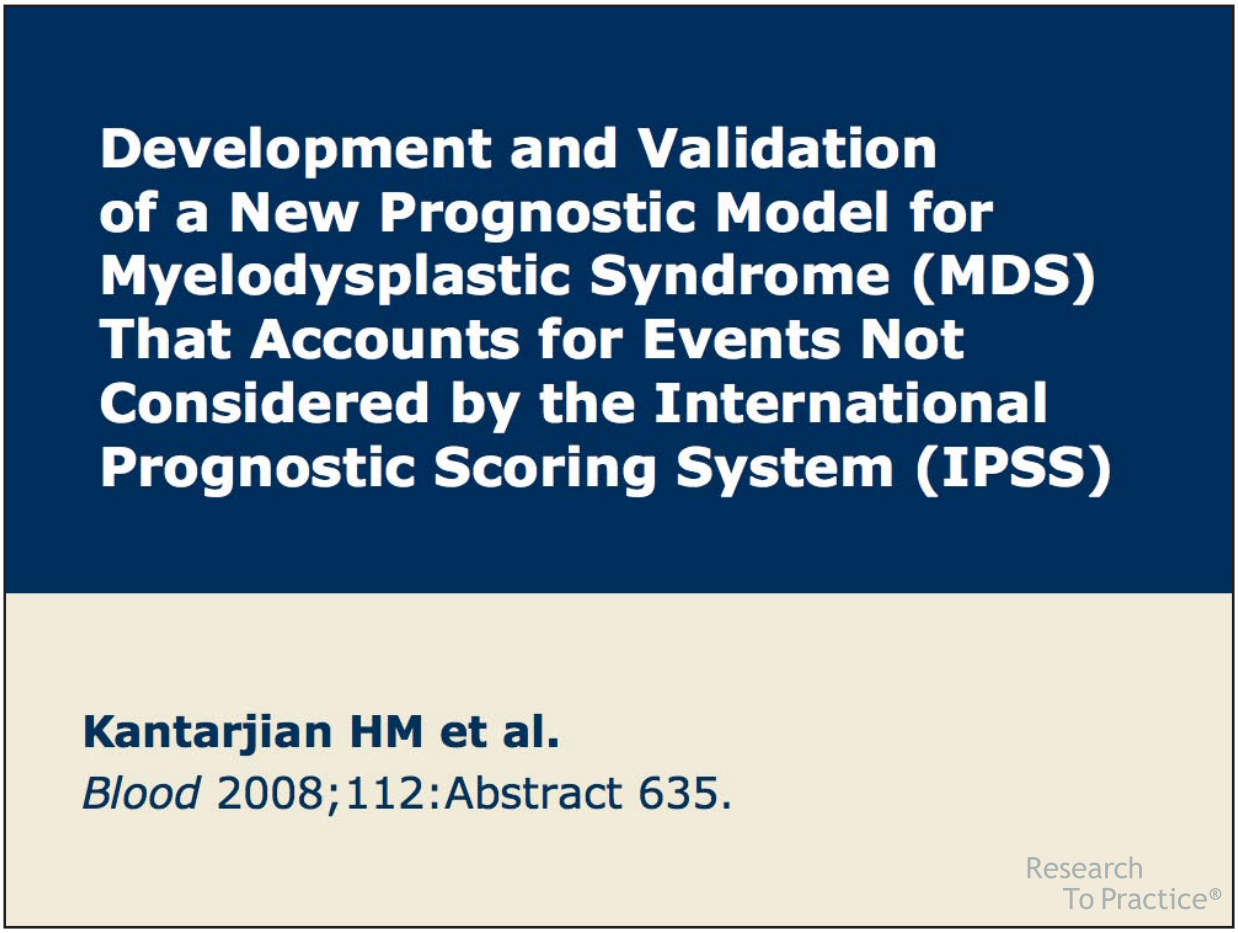
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

A Prognostic Model for MDS that Accounts for Events Not Considered by the International Prognostic Scoring System (IPSS)

Presentation discussed in this issue:

Kantarjian H et al. **Development and validation of a new prognostic model for myelodysplastic syndrome (MDS) that accounts for events not considered by the International Prognostic Scoring System (IPSS).** *Blood* 2008;112:635. **Abstract**

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



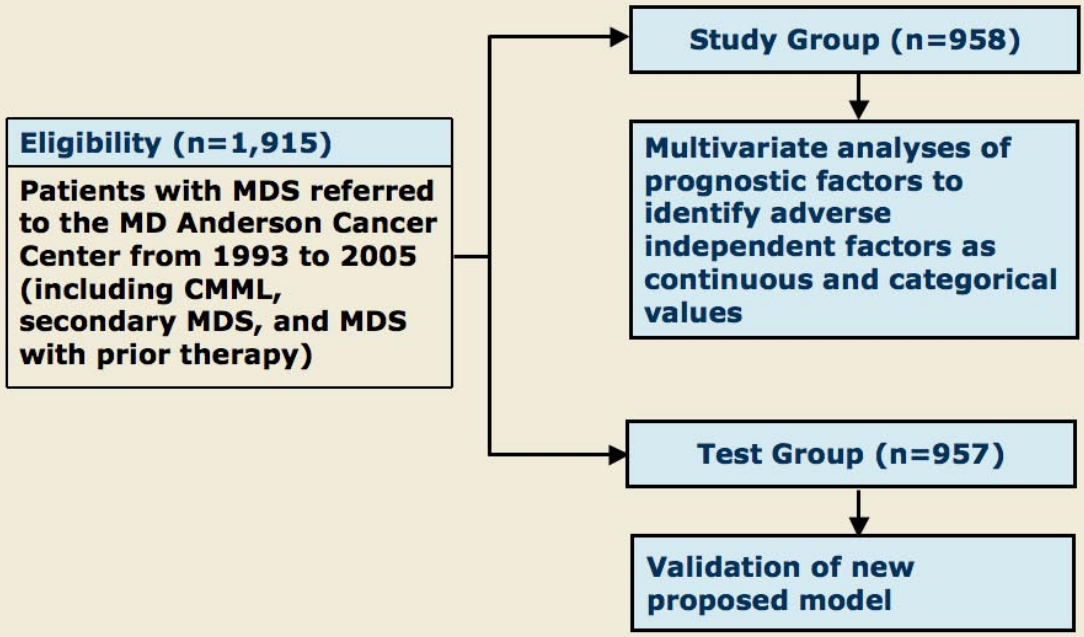
Introduction

- The IPSS risk model provides survival projections for patients with de novo MDS who are managed with supportive measures alone.
- Patients with MDS who have received investigational treatments require a prognostic stratification model that can be applied at intervals after diagnosis and adjusts for the following factors:
  - Impact of prior therapy
  - Secondary forms of disease
  - Proliferative chronic myelomonocytic leukemia (CMML)
  - Adverse cytogenetic subsets (chromosome 7 abnormalities [abn], having three cytogenetic abn)
- **Current study objectives:**
  - To develop a new MDS risk model that accounts for subsets not included in IPSS, that refines prognostic subsets, and that applies at any point during the course of MDS.

Source: Kantarjian HM et al. *Blood* 2008;112:Abstract 635.

Research To Practice®

New MDS Prognostic Model Retrospective Study Design



Source: Kantarjian HM et al. *Blood* 2008;112:Abstract 635.

Research To Practice®

Weighted Points of Prognostic Factors

Prognostic Factor	Coefficient	Score Points
Hemoglobin (g/dL) <12.0	0.274	2
Age (yrs) 60 - 64 ≥65	 0.179 0.336	 1 2
Platelets (x 10^9/L) <30 30 - 49 50 - 199	 0.418 0.270 0.184	 3 2 1
Marrow blast % 5 - 10 11 - 29	 0.222 0.260	 1 2

Source: Kantarjian HM et al. *Blood* 2008;112:Abstract 635.

Research To Practice®

Weighted Points of Prognostic Factors (continued)

Prognostic Factor	Coefficient	Score Points
White blood cells (x 10^9/L) >20	0.258	2
Karyotype (chromosome 7 or ≥3 abn)	0.479	3
Prior transfusion Yes	0.107	1
Performance status ≥2	0.267	2

Source: Kantarjian HM et al. *Blood* 2008;112:Abstract 635.

Research To Practice®

Segregation of Patients (Pts.) into Prognostic Groups in New MDS Prognostic Model

		Study Group (n=958)		Test Group (n=957)	
Risk	Score	No. Pts.	Median Survival	No. Pts.	Median Survival
Low	0 - 4	157	54 mos	159	45 mos
Intermediate 1	5 - 6	229	25 mos	228	23 mos
Intermediate 2	7 - 8	233	14 mos	244	13 mos
High	≥9	341	6 mos	326	6 mos

Application of new model's prognostic scores within the four IPSS risk groups was highly prognostic in each. Application of IPSS scores within the four risk groups of the new model was not prognostic.

Source: Kantarjian HM et al. *Blood* 2008;112:Abstract 635.

Research To Practice®

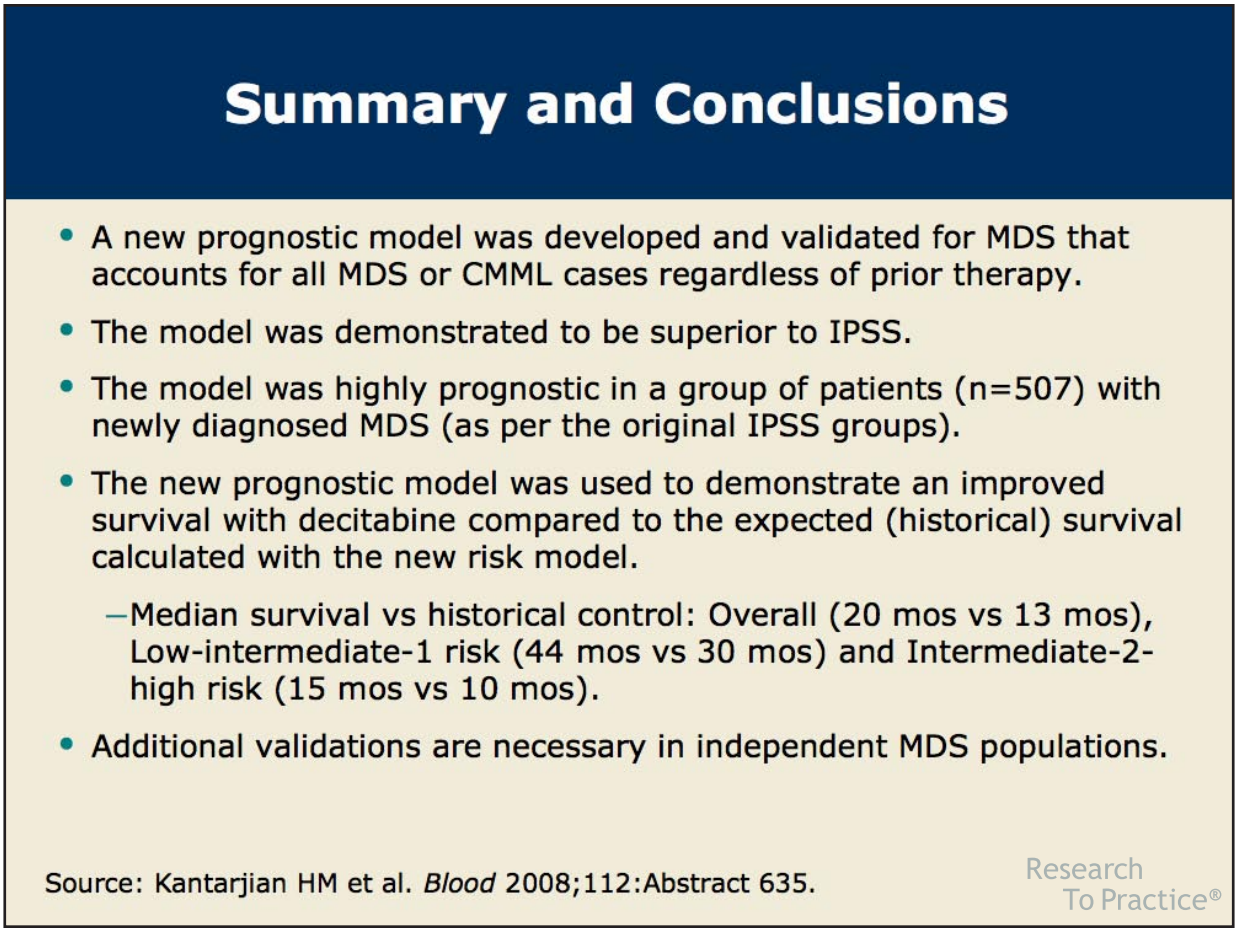
Prognosis for Patients in Multiple MDS Subsets According to the New Prognostic Model

	Median Survival (mos)/1 yr Survival (%)			
Disease	Low	Int. 1	Int. 2	High
CMML (n=176)	33 mos	19 mos	12 mos	8 mos
MDS - prior therapy (n=702)	38 mos	19 mos	12 mos	8 mos
MDS - no prior therapy (n=507)	56 mos	36 mos	14 mos	9 mos
Secondary MDS (n=571)	43 mos	19 mos	16 mos	6 mos
Decitabine trial 2007[1] three-arm (n=124)	Not reached[2]	42 mos	19 mos	13 mos
Postdecitabine failure (n=59) (% 1 yr survival)	100%	54%	41%	18%

[1] Kantarjian et al. *Blood* 2007;110:42 [Abstract 115].
[2] 100% at 3 years

Source: Kantarjian HM et al. *Blood* 2008;112:Abstract 635.

Research To Practice®



GAIL J ROBOZ, MD: There has been a proliferation of prognostic scoring systems for MDS recently published in the literature. For example, before the commonly used system of the International Prognostic Scoring System, or IPSS, was developed, there were several years when many papers were published suggesting a variety of laboratory and clinical features that should be incorporated into MDS prognostication.

The IPSS system that is commonly used today does not accurately classify patients with lower-risk MDS. There is a wide survival range for these patients — some patients at lower risk may only live a few years and others may survive up to 10 or 11 years. The challenge becomes how to identify the patients within that technically classified lower-risk group who are not going to fare well. Another limitation of the IPSS is that it does not include secondary disease or proliferative MDS, including chronic myelomonocytic leukemia. There have been substantial efforts to try to determine which additional factors could be added to the IPSS that will allow for the inclusion of these subset groups and that will allow us to predict more accurately the prognosis of our patients.

This proposed model from MD Anderson may not be the final development in the area of prognostic systems for MDS, but it does incorporate factors such as performance status, platelet count and transfusion history. These are factors that can be important in determining the outcome of a patient with MDS that are not included in the IPSS

prognostic system. I believe that if clinicians give their patients a score based on this new proposed system in addition to the IPSS system, they may elect to treat or to monitor very closely certain patients who in the past would have been otherwise labeled as low risk and asked to come back for follow-up after a year's time.

STEVEN D GORE, MD: I believe that this study requires additional validation. This model demonstrates median survival times that are lower for the low-risk and intermediate-1 groups than what is shown by the IPSS model. The intermediate-2 and the high-risk groups show median survival times that are similar to those reported by IPSS. The new model does incorporate platelet counts that are thought by some to be possibly important, but I am uncertain as to the usefulness of this new model with the data that we have reported to date.

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.