5 Minute JournalClub

New Prognostic Markers in Acute Myeloid Leukemia (AML)

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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 prognostic and predictive values of several newly identified markers for AML.

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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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Inside this issue: Four interesting AML nuggets:

1. **A Phase II study** evaluating clofarabine in 112 older patients (median age 71) with AML and one or more adverse prognostic factors. Treatment was "well tolerated" and resulted in 38% CRs.

2. **A Phase II study** of the hypomethylating agent decitabine in 55 older patients (median age 74) with AML. Morphologic CR was observed in 24%; febrile neutropenia was observed in 24%.

3. **A literature review** suggesting that assays for NPM1mut and FLT3 ITDneg could be the new ER and HER2 of AML. (Ok, maybe that is an overstatement, but these are highly prognostic and predictive.)

4. **A retrospective analysis** demonstrating roughly similar results with allogeneic hematopoietic stem cell transplant in patients with AML over and under age 65.

Editor's comment: Who should treat patients with AML?

Mike Schwartz, a Memorial-trained medical oncologist practicing in Miami Beach, is one of several dozen "master clinicians" across the country who have assisted us with our CME programs. Mike's most recent contribution was helping us plan an upcoming **Satellite Symposium** that we will host in New Orleans on Friday night, December 4, preceding the ASH annual meeting.

Dr Schwartz will join four other community-based physicians as they present challenging cases of AML, MDS, CML, and myeloma from their practices to our all-star faculty. In addition to discussing these carefully selected patients, we will also reveal the results of our recent **national Patterns of Care survey** of US-based oncologists, specifically focusing on the management of the cases being presented at the meeting.

One interesting survey question that we will discuss live is "Do you treat some or most patients with AML or do you generally refer them to a tertiary center?" To my mild surprise, more than two thirds of the survey respondents generally manage these patients themselves, and that includes Mike, who will present a 59-year-old woman recently diagnosed with AML.

Our prior surveys have documented that oncologists in practice see about as many cases of breast cancer a year as breast cancer investigators, but AML is a complicated disease that occurs at less than one tenth the frequency.

Of course there is more than science required in these intense situations, as evidenced by Mike's patient, an Asian woman, who asked if she could take traditional therapeutic herbs during chemo (Mike said "No," as did 79 percent of the oncologists surveyed).

Certainly physicians who offer patients a local means to receive treatment for a very scary disease must do their best to keep up with the gradual but definite progress in AML. In New Orleans, we'll see what our faculty has to say about Mike's patient and whether they think she, like many others, can be effectively managed in the community. From my standpoint, this woman is fortunate to be receiving care from one of the many, many extraordinary clinicians working outside of academic medicine.

Next up on 5-Minute Journal Club: The final four papers highlighted in our series along with results from our Patterns of Care study documenting oncologists' management of MDS.

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New Prognostic Markers in Acute Myeloid Leukemia (AML)

Presentation discussed in this issue:

Schlenk RF et al. **Impact of prognostic markers in treatment decisions in acute myeloid leukemia.** *Curr Opin Hematol* 2009;16(2):98-104. **Abstract**

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

Introduction

- Prognostic markers are associated with a differential clinical outcome independent of the given treatment and are limited in their use for clinical decision-making.
- Pretreatment genetic aberrations in leukemic cells are powerful prognostic factors in acute myeloid leukemia (AML) (*Semin Oncol* 2008;35:346, *JCO* 2008;26:4791).
- Cautious interpretation of the prognostic value of cytogenetic aberrations, gene mutations and dysregulated genes in AML is necessary due to their evaluation mainly in retrospective studies.
- Predictive markers indicate a treatment benefit in patients that are characterized by these markers and can be used to guide clinical decision-making.
- **Purpose of review:**
  - Interpret retrospective study results and discuss novel prognostic and predictive markers in AML.

Source: Schlenk RF, Döhner K. *Curr Opin Hematol* 2009;16:98-104.

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Statistical Aspects of Interpreting Predictive and Prognostic Marker Study Results

- Selection bias
  - Patient populations in retrospective studies have been derived mostly from several combined clinical trials.
    - Main inclusion criterion has been the availability of pretreatment peripheral blood and/or bone marrow samples.
    - Leukemia specimens with low cell counts are much less likely to be included for further genetic analyses.
- Exclusion of patients with incomplete data from the analyses is not recommended as it can lead to reduced statistical power, selection bias, and overestimation of odds and hazards ratios.

Source: Schlenk RF, Döhner K. *Curr Opin Hematol* 2009;16:98-104.

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Mutations in the Nucleophosmin (*Npm1*) Gene

- Mutations in the *Npm1* gene (*NPM1*^{mut}) are the most frequent genetic aberration in adult AML and are detected in 24-35% of all cases and in 43-62% of cases with a normal karyotype.
- More than 85% of *NPM1*^{mut} occur in cytogenetically normal (CN)-AML patients (*NEJM* 2008;358:1909).
- The incidence of *NPM1*^{mut} in childhood AML is lower than in adult AML (*Blood* 2007;110:979).
- *NPM1*^{mut} is associated with:
  - Female gender
  - High bone marrow blast percentages, high WBC and platelet counts, and high levels of lactate dehydrogenase
  - High levels of CD33
- Cooperating mutations in the FMS-like tyrosine kinase 3 gene (*FLT-3*) influence the clinical characteristics of *NPM1*^{mut} (*Blood* 2005;106:3740).

Source: Schlenk RF, Döhner K. *Curr Opin Hematol* 2009;16:98-104.

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Mutations in the *FLT3* Gene

- *FLT3* mutations occur in two functional domains:
  - Internal tandem duplications (ITDs) occur in the juxtamembrane domain in 28-34% of CN-AML cases (*Blood* 2001;98:1752, *Blood* 2002;100:4372).
  - Mutations in the tyrosine kinase domain (TKD) are found in 11-14% of patients with CN-AML (*Blood* 2007;110:1262, *Blood* 2002;100:4372).
- Patients with AML having a *FLT3*-ITD are characterized by several pretreatment features (*Blood* 2002;100:4372):
  - Increased WBC count
  - Higher percentages of blood and bone marrow blasts
  - More frequent diagnosis of *de novo* instead of secondary AML

Source: Schlenk RF, Döhner K. *Curr Opin Hematol* 2009;16:98-104.

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Prognostic and Predictive Value of the *NPM1/FLT3* Genotype

- Young adult patients with the *NPM1*^{mut}/*FLT3*-ITD^{neg} genotype have favorable outcomes (relapse-free survival [RFS] and overall survival [OS]) regardless of whether they received intensive consolidation chemotherapy or autologous/allogeneic stem cell transplantation (*NEJM* 2008;358:1909).
- In elderly patients with nonacute promyelocytic (non-APL) AML, the *NPM1*^{mut}/*FLT3*-ITD^{neg} genotype predicts a significantly improved outcome if all-*trans*-retinoic acid was added to intensive chemotherapy (*Haematologica* 2009;94:54).
- For patients with either wild-type *NPM1* or *FLT3*-ITD^{pos}, prognosis is predicted by the treatment received.
  - Patients receiving allogeneic transplantation had a 40% reduction in the risk of relapse or death.

Source: Schlenk RF, Döhner K. *Curr Opin Hematol* 2009;16:98-104.

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Prognostic and Predictive Value of the *NPM1/FLT3* Genotype (continued)

- The FLT3-ITD^{pos} genotype is an unfavorable prognostic marker for RFS and OS (*Blood* 2008;111:2776).
  - It is unclear whether other molecular markers, such as *NPM1*^{mut}, add to prognostication in *FLT3*-ITD^{pos} AML (*NEJM* 2008;358:1909).
- The prognostic significance of *FLT3*-TKD^{mut} is controversial.

Source: Schlenk RF, Döhner K. *Curr Opin Hematol* 2009;16:98-104.

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Mutations in the CCAAT Enhancer-Binding Protein Alpha Gene (*CEBPA*)

- There are two major types of CEBPA mutations:
  - Nonsense mutations in the N-terminal region
  - In-frame mutations in the C-terminal region
- N- and C-terminal mutations often occur simultaneously and may affect the same (monoallelic) or different (biallelic) gene alleles.
- CEBPA mutations (*CEBPA*^{mut}) have been associated with a favorable prognosis in patients with intermediate-risk cytogenetics and those with normal cytogenetics.
- *CEBPA*^{mut} retain their prognostic importance for RFS and OS in the context of other molecular markers (*NEJM* 2008;358:1909).
- *CEBPA*^{mut} have prognostic but not predictive properties.

Source: Schlenk RF, Döhner K. *Curr Opin Hematol* 2009;16:98-104.

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Other Gene Mutations

- Myeloid/lymphoid or mixed lineage leukemia gene (*MLL*)
  - Partial tandem duplication (PTD) of the *MLL* gene has been mainly found in CN-AML (5-11% of cases).
  - There are no distinguishing clinical features between *MLL*-PTD^{pos} and *MLL*-WT patients (*JCO* 2002;20:3254).
  - Overall clinical outcome does not differ between *MLL*-PTD^{pos} and *MLL*-WT patients (*Blood* 2007;109:5164).
- *RAS* oncogenes and Wilms' tumor suppressor 1 gene (*WT1*)
  - *RAS* mutations have been detected in 10.3-13.6% of adult patients with AML, but no prognostic impact has been determined (*Blood* 2006;107:3847, *Blood* 2005;106:2113).
  - *WT1* mutations have an incidence of 10-12.6% in CN-AML (*Blood* 2009;113:4505), but inconsistent results have been reported as to its prognostic impact.

Source: Schlenk RF, Döhner K. *Curr Opin Hematol* 2009;16:98-104.

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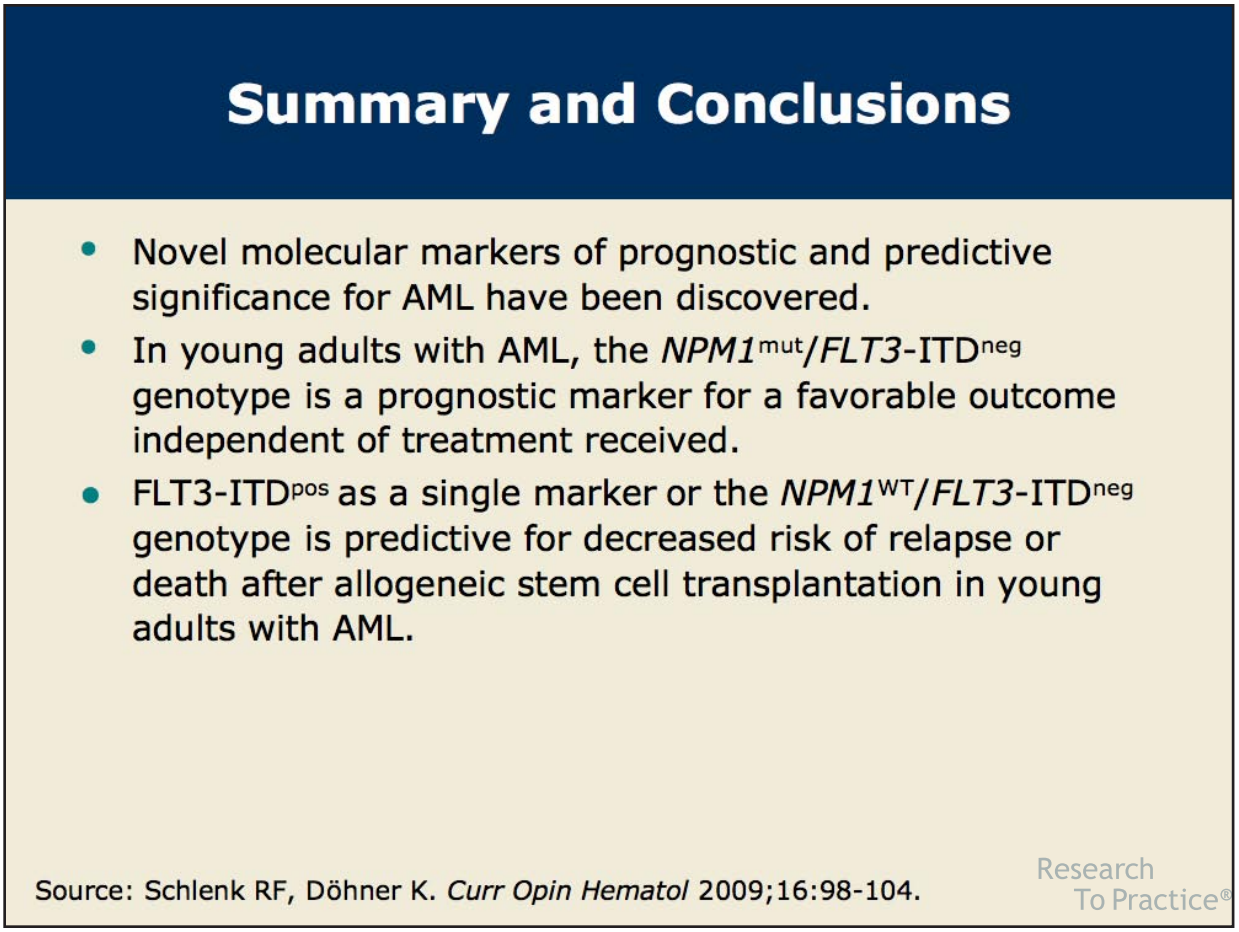

DR ROBOZ: The identification of prognostic markers in acute myelogenous leukemia (AML) is the most exciting and new area of AML that everyone should be up to date on. There has been a proliferation of new and important markers in AML. This paper summarizes beautifully what is known about the most important markers to date and, in particular, discusses the need to examine the FLT3 and NPM1 markers in the diagnostic specimens for all newly diagnosed patients. Their analysis is being incorporated more frequently into the standard treatment, and it is therefore changing clinical practice. Community oncologists should also perform this workup for patients in remission who are being referred out for consultation.

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.