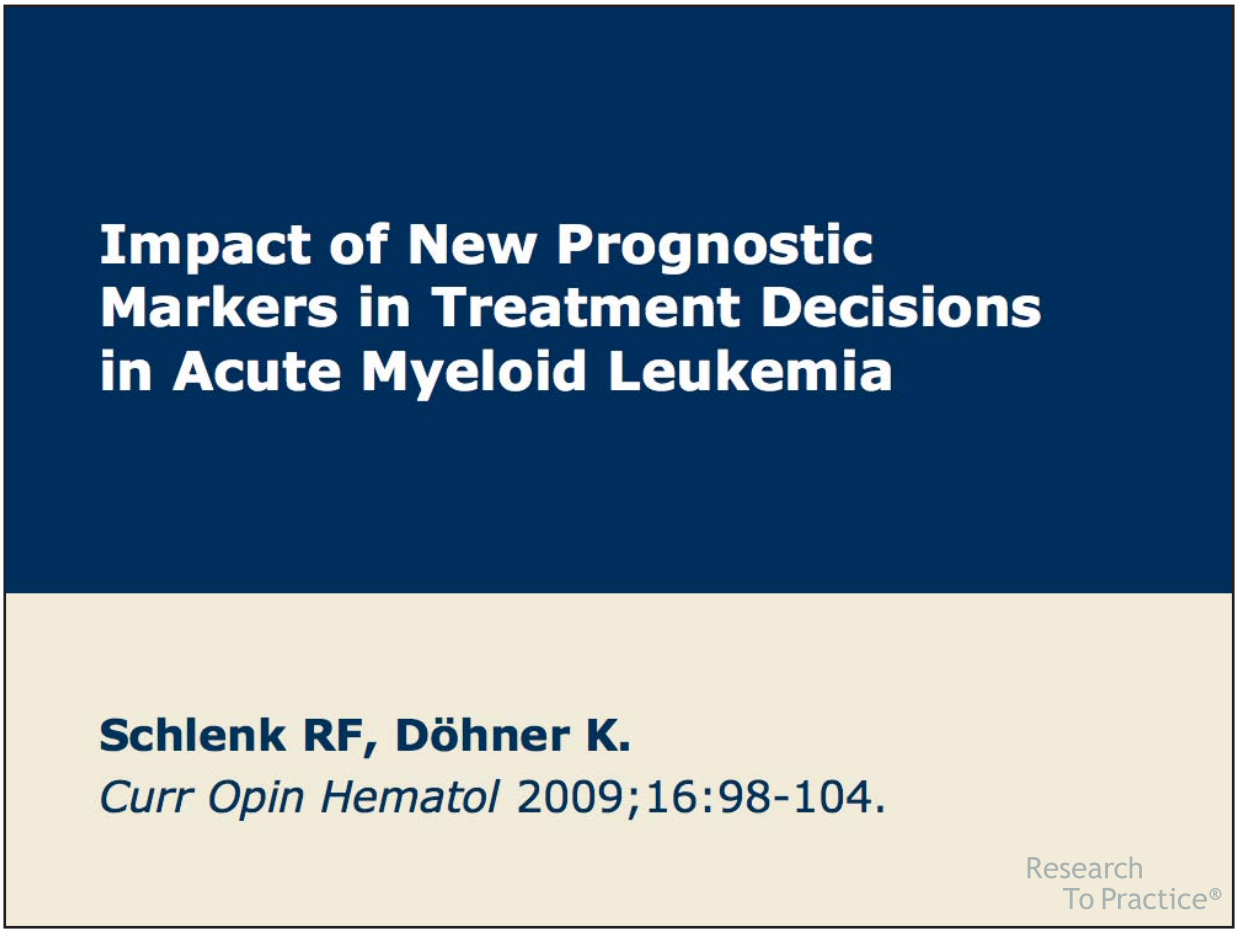
New Prognostic Markers in Acute Myeloid Leukemia (AML)

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



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.

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.

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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Summary and Conclusions

- Novel molecular markers of prognostic and predictive significance for AML have been discovered.
- In young adults with AML, the *NPM1*^{mut}/*FLT3*-ITD^{neg} genotype is a prognostic marker for a favorable outcome independent of treatment received.
- FLT3-ITD^{pos} as a single marker or the *NPM1*^{WT}/*FLT3*-ITD^{neg} genotype is predictive for decreased risk of relapse or death after allogeneic stem cell transplantation in young adults with AML.

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

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