New Prognostic Markers in Acute Myeloid Leukemia (AML)
Presentation discussed in this issue:

Slides from the journal article

Impact of New Prognostic Markers in Treatment Decisions in Acute Myeloid Leukemia

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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.


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.

Mutations in the Nucleophosmin (Npm1) Gene

- Mutations in the Npm1 gene (NPM1\textsuperscript{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\textsuperscript{mut} occur in cytogenetically normal (CN)-AML patients (NEJM 2008;358:1909).
- The incidence of NPM1\textsuperscript{mut} in childhood AML is lower than in adult AML (Blood 2007;110:979).
- NPM1\textsuperscript{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\textsuperscript{mut} (Blood 2005;106:3740).


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

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

- Young adult patients with the \(NPM1^{\text{mut}}/FLT3^{\text{ITD}^\text{neg}}\) 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 (\textit{NEJM} 2008;358:1909).
- In elderly patients with nonacute promyelocytic (non-APL) AML, the \(NPM1^{\text{mut}}/FLT3^{\text{ITD}^\text{neg}}\) genotype predicts a significantly improved outcome if all-\textit{trans}-retinoic acid was added to intensive chemotherapy (\textit{Haematologica} 2009;94:54).
- For patients with either wild-type \(NPM1\) or \(FLT3^{\text{ITD}^\text{pos}}\), prognosis is predicted by the treatment received.
  - Patients receiving allogeneic transplantation had a 40% reduction in the risk of relapse or death.


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

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

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\textsuperscript{mut}) have been associated with a favorable prognosis in patients with intermediate-risk cytogenetics and those with normal cytogenetics.
- CEBPA\textsuperscript{mut} retain their prognostic importance for RFS and OS in the context of other molecular markers (\textit{NEJM} 2008;358:1909).
- CEBPA\textsuperscript{mut} have prognostic but not predictive properties.


Other Gene Mutations

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

Summary and Conclusions

- Novel molecular markers of prognostic and predictive significance for AML have been discovered.
- In young adults with AML, the $NPM1_{\text{mut}}/FLT3-ITD_{\text{neg}}$ genotype is a prognostic marker for a favorable outcome independent of treatment received.
- FLT3-ITD$_{\text{pos}}$ as a single marker or the $NPM1_{\text{WT}}/FLT3-ITD_{\text{neg}}$ genotype is predictive for decreased risk of relapse or death after allogeneic stem cell transplantation in young adults with AML.