PROCEEDINGS ARTICLE

Prognostic markers in AML: focus on CBFL

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Acute myeloid leukemia (AML) is a heterogeneous disease increasing in frequency owing to an aging population. Decisions on intensive induction treatments, intensification and allografting rely on the ability to divide an apparently homogeneous group according to risk. A wide range of clinical, cytogenetic and molecular variables may be used to inform this task; here we examine those variables useful in assessing prognosis for a patient with non-acute promyelocytic AML focusing on core binding factor leukemia. In clinical practice, when counseling an individual patient with AML, a range of well-known clinical variables (age, performance status and tumor burden) and genetic variables (cytogenetic and gene mutation) must be considered to better define the prognostic risk.

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CLINICAL VARIABLES

Age and performance status

It has been repeatedly demonstrated that prognosis worsens with increasing age in acute myeloid leukemia (AML). This may reflect concurrent comorbidities in addition to different disease biology such as multidrug-resistance protein positivity, prior myelodysplastic-related changes or stem cell phenotype, adversely affecting both attainment of remission and refractory relapse risk. The increasing incidence of adverse versus favorable cytogenetic abnormalities with increasing age contributes to the poorer outcome of AML in older adults. Comorbidity scores have been designed to predict survival in older patients receiving standard induction therapy, as well as outcome following allotransplantation.¹

Tumor burden

A high peripheral white blood cell (WBC) count together with a raised serum LDH, the presence of epatosplenomegaly and extramedullary leukemia (EML) may reflect an increased tumor burden in AML even in the setting of 'good-risk' acute leukemias, such as acute promyelocytic leukemia or core binding factor leukemia (CBFL).¹

GENETIC VARIABLES

Cytogenetic

The karyotype of the leukemic cells is the strongest prognostic factor for response to induction therapy and for survival. Younger adult patients are commonly categorized into three risk groups: favorable, intermediate and adverse. Complex karyotype, which has been defined as the presence of three or more chromosome abnormalities in the absence of t(8;21), inv(16) or t(16;16) and t(15;17), has consistently been associated with a very poor outcome. Approximately two-thirds of these cases are associated with loss of 17p and/or *TP53* gene mutation, and with a high prevalence of high-level DNA amplifications. AML with monosomal karyotype has been identified by several groups as a

cytogenetic category that distinguishes cases of extremely poor prognosis, with the projected 4-year survival <4% (SWOG data).

The International European LeukemiaNet expert panel has recently proposed a standardized reporting system integrating data from cytogenetic and mutation screening for the *NPM1*, *CEBPA* and *FLT3* genes, which categorizes AML into four risk groups (favorable, intermediate I, intermediate II and adverse), with the aim to better compare data among studies.²

Mutations

It is well known that about 40% of patients with AML have a 'normal' karyotype and are frequently categorized into the intermediate-risk group. However, an expanding range of genetic abnormalities having prognostic impact, assessable in the majority of patients, lead to better refine risk groups, particularly in patients with cytogenetically normal AML (Table 1).³

PROGNOSTIC FACTORS IN CBFL

Among AMLs with recurrent genetic abnormalities, patients with t(8;21)(q22;q22), inv(16)(p13;q22) or t(16;16)(p13;q22) are referred to as having CBFL. Although CBFL patients share a common molecular pathogenetic event, nominally the creation of a fusion protein involving a CBF gene unit, these two types of AML differ with regard to morphologic presentation, immunophenotypic marker expression, prognostic factors and response to treatments, and should be considered as distinct clinical entities.⁴ Clinically, patients with CBFL are categorized into a favourable-risk group as compared with other AML subtypes. High complete remission (CR) rate and prolonged disease-free survival (DFS) may be achieved when patients are treated with standard induction therapy followed by repetitive courses of high-dose cytarabine.

In patients with inv(16), female gender, older age, higher WBC counts and low platelet count have been reported as predictors for inferior CR achievements and/or shorter DFS in patients enrolled in prospective trials. Conversely, nonrandom additional cytogenetic abnormalities such as trisomy +22 and male sex predicted better outcome.^{4–6}

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Table 1. Prognostic factors in acute myeloid leukemia

Mutation	Prognostic impact	Impact on therapy
FLT3-ITD	Unfavorable	HSCT in younger patients; Trials with FLT3-TKIs (www.clinicaltrials.gov identifier NCT00989261)
NPM1	Favorable (CN-AML)	Induction '3+7', consolidation with repetitive HD-ARAC courses; HSCT in individual patients with high-risk factors (for example, high tumor burden), low risk of transplantation-related mortality; clinical trial
CEBPA ^{dm}	Favorable (CN-AML)	
IDH1, IDH2-WT1 RUNX1-TET2- DNMT3A	Unclear, controversial	None known

KIT mutations represent novel prognostic markers in CBFL.⁷ In this view, it is of interest that expression levels of both *KIT* mRNA and proteins are much higher in CBFL, with either wild-type or mutant *KIT*, than in leukemia cells negative for CBF rearrangements. Moreover, we have recently reported that CBF genetic abnormalities can target microRNA genes (Mir222/221) involved in the regulation of the *KIT* receptor, leading to *KIT* overexpression in CBFL.⁸ Furthermore, it has been postulated that mutations of the *KIT* gene may drive the WBC proliferation in CBFL, and the clinical observations that affected patients with t(8;21) appear to have a higher WBC count and WBC index at presentation and a higher frequency of EML might support this hypothesis.^{9,10}

KIT mutation testing has been recently incorporated into National Cancer Guidelines to better stratify such patients into different prognostic subgroups.¹¹ Furthermore, the *KIT* inhibitor Dasatinib, in combination with intensive induction and consolidation therapies, is being tested in phase II clinical trials. However, although several studies showed that activating *KIT* mutations confer a significantly lower survival in AML with t(8;21)(q22;q22), the negative prognostic impact of *KIT* mutations in AML with inv(16) is still a matter of debate.⁷

We have recently studied the prognostic significance of clinical and genetic features such as age, gender, WBC count, the presence of EML, additional cytogenetic abnormalities and *KIT* mutations on long-term outcome of a large group of uniformly treated adult patients with inv(16)/t(16;16). Our results indicated that increasing age was the only predictor for survival at univariate and multivariate analysis, with an optimal cutoff point at 43 years. WBC count at diagnosis emerged as an independent risk factor for

relapse incidence at multivariate analysis, with a 1.1% increase of hazard of relapse for each $1.0 \times 10^9/l$ WBC increment. Interestingly, *KIT* mutations lacked prognostic value both in terms of survival and relapse incidence (unpublished results). This result contrasts with that observed in AML with t(8;21)(q22;q22) and confirms differences in biology between the two types of CBFLs.

CONFLICT OF INTEREST

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