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Impact of molecular prognostic factors in cytogenetically normal acute myeloid leukemia at diagnosis and relapse

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While morphological evaluation of bone marrow and blood remains a cornerstone for the diagnosis of acute myeloid leukemia (AML), it is clear that the presence or absence of specific cytogenetic and molecular abnormalities is not only useful for determining overall prognosis, but is also used to guide treatment. However, while cytogenetic abnormalities present at diagnosis enable prediction of outcome and, in turn, stratification to risk-adapted treatments, clonal chromosomal aberrations are not detected in 40 to 50% of patients.[1] It is within this cytogenetically normal (CN) group that the presence of acquired mutations, in addition to the expression of deregulated genes and non-coding RNA (i.e. microRNA), allows for molecular-risk classification of what has hitherto been a clinically heterogeneous subset of patients.[2-5] Indeed, the relevance of recurrent molecular abnormalities in CN-AML has been recently acknowledged by the inclusion of these markers within both the World Health Organization (WHO) and the European LeukemiaNet (ELN) classifications as a complement to cytogenetics.[6,7]

Molecular analysis of markers that have been incorporated in both the WHO and ELN classifications (i.e., *NPM1*, *FLT3* and *CEBPA*) is now routine. However, other mutated genes (e.g. *WT1*, *IDH1/IDH2*, *TET2*, *RUNX1*, *MLL*) or aberrantly expressed ones (e.g. *BAALC*, *ERG*, *EVI1*, *miR-181a*) will likely become useful in refining molecular risk in CN-AML.[8-21] Furthermore, as these molecular markers are not mutually exclusive, the prognostic impact of the different combinations of mutated and/or aberrantly expressed genes present within the same patient should be carefully evaluated to construct a molecular-risk score for practicing hematologists.

The *NPM1* gene encodes a protein that functions as a nucleus-cytoplasm chaperone and is involved in intracellular processes including transport of pre-ribosomal particles, response to stress stimuli and DNA repair, and regulation of the activity and stability of tumor suppressors such as p53.[22] Acquired mutations in the *NPM1* gene are found in 45-60% of patients with CN-AML, and result in aberrant cytoplasmic expression of the protein.[23] The presence of an *NPM1*

Table 1. Prognostic markers in acute myeloid leukemia.

Genetic aberration	Chromosome	Prognostic Impact	References
NPM1	5q35	Favorable in younger patients with mutated *NPM1* without *FLT3*-ITD Favorable in older patients regardless of *FLT3*-ITD	5,23-25
FLT3-ITD *FLT3*-TKD	13q12	Unfavorable Controversial	27,28
CEBPA	19q13.1	Favorable, especially if both alleles mutated	29
IDH1 *IDH2*	2q33 15q26	Unfavorable in younger *NPM1* wild-type CN-AML Unfavorable in older patients	8,14,19,30
WT1	11p13	Unfavorable	18
RUNX1	8q22	Unfavorable, but evaluation of prognostic significance ongoing	10,21
MLL-PTD	11q23	Unfavorable if not treated with high-dose chemotherapy and hematopoietic stem cell transplantation	31
NRAS	1p13	No prognostic significance, but increases sensitivity to cytarabine	17
TET2	4q24	Unfavorable in the favorable risk category of ELN classification	9,16
ASXL1	20q11	Evaluation of prognostic significance ongoing	3
BAALC	8q22.3	Increased expression is unfavorable	12,15
ERG	21q22	Increased expression is unfavorable	13,15
EVI1	3q26.2	Increased expression is unfavorable	3
MN1	22q12.3	Increased expression is unfavorable	11,15
miR-181a	1q32.1 9q33.3	Increased expression is favorable	20

mutation is associated with achievement of complete remission and an overall favorable outcome, especially in the absence of a *FLT3*-ITD mutation.[5,24] The favorable outcome associated with *NPM1* mutations also extends to older patients, particularly those 70 years old or over, in whom it is associated with higher complete remission rates and longer disease-free and overall survival.[25] Indeed, CN-AML with mutated *NPM1* without *FLT3*-ITD is now included within the favorable risk category along with the core-binding factor (CBF) leukemia by the ELN classification,[6] and similar chemotherapy approaches have been recommended for both molecular groups, reserving allogeneic hematopoietic stem cell transplantation until the time of relapse.[6]

The FMS-like tyrosine kinase 3 gene (*FLT3*) encodes for a receptor tyrosine kinase involved in the regulation of proliferation, differentiation and apoptosis of hematopoietic cells.[26] Mutations that occur within the receptor confer a proliferative and survival advantage. The most common form of the *FLT3* mutation is an internal tandem duplication (ITD) in exons 14 and 15 that maps to the juxtamembrane domain and occurs in 25-35% of CN-AML.[26] The presence of this mutation confers an increased risk of relapse and death. However, in cases in which the allelic ratio (ratio of mutant to wild-type *FLT3*) is low, patients appear to have an outcome similar to that of patients without a *FLT3*-ITD mutation, while an increased allelic ratio predicts for worse survival.[27,28] The second type of *FLT3* mutation is due to missense point mutations within the tyrosine kinase domain (TKD) and occurs in 5-10% of all cases of AML.[26] While the prognostic relevance of *FLT3*-ITD mutations is clear, that of *FLT3*-TKD mutations remains controversial.[3] Clinical trials investigating the combination of tyrosine kinase inhibitors with standard chemotherapy in patients with newly diagnosed AML and either mutation are ongoing. Given the prognostic risk associated with the *FLT3*-ITD mutation, allogeneic hematopoietic stem cell transplantation has been recommended in these patients if not entered in clinical trials.[5]

Mutations in the transcription factor CCAAT/enhancer binding protein α gene (*CEBPA*) are found in 10-15% of CN-AML and have been associated with a relatively favorable outcome, such that patients with this abnormality are now included in the favorable risk category of the ELN classifcation.[6] There are two types of *CEBPA* mutations that affect normal function of the encoded protein. Nonsense mutations occur in the N-terminal region of *CEBPA* and lead to the expression of a truncated isoform that lacks the transactivating N-terminus, while the other type of mutation occurs within the C-terminal leucine zipper domain.[29] Most cases of *CEBPA* mutant AML exhibit two mutations (double mutants) and are either homozygous (same type of mutation present on each allele) or compound heterozygous (different types of mutations present on each allele).[29] In either case, no wild-type *CEBPA* is expressed. Importantly, *CEBPA* mutants with only one affected allele do not have a gene expression profile similar to that of *CEBPA* double mutants and, clinically, cannot be distinguished from wild-type cases with regard to outcome. In contrast, patients with double *CEBPA* mutations have a more favorable outcome.[29]

As molecular diagnostics in CN-AML evolves, the list of new prognostic markers continues to expand. Most of these markers have yet to enter routine practice; nonetheless, they provide insight into the complex mechanisms of leukemogenesis. Isocitrate dehydrogenase (IDH), a member of the β-decarboxylating dehydrogenase family of enzymes, catalyzes the oxidative decarboxylation of 2,3-isocitrate to yield 2-oxoglutarate and carbon dioxide in the Krebs' cycle.[8] Mutations within *IDH1* and *IDH2*, which encode the IDH isoforms, create a loss of function that impair this reaction, while simultaneously creating a gain of function in the reverse reaction that reduces α-ketoglutarate to 2-hydroxyglutarate, an oncogenic molecule.[8] *IDH1* and *IDH2* mutations occur in 25-30% of patients with CN-AML, and in general predict for worse outcome in certain molecular (*NPM1* wild-type) and clinical (older age) subsets of patients, and for the first time implicate metabolic enzymes in leukemogenesis.[19,30]

WT1, *RUNX1* and *MLL* mutations, found in approximately 5 to 10% of CN-AML, have been associated with an inferior outcome.[10,18,21,31] *TET2*, *AXSL1*, and *NRAS* mutations are also recurrent abnormalities that are undergoing further evaluation to identify their prognostic significance.[3,9,16,17] Recently, a mutation within a gene encoding for a DNA methyltransferase, *DNMT3A*, has been reported and is associated with a significantly shorter overall survival in AML patients with intermediate cytogenetic risk, including the CN-AML subset.[32] Aberrant expression of certain wild-

type genes is also known to affect prognosis. Higher expression of the *BAALC* gene is associated with inferior outcome, as is over-expression of *MN1*, *ERG* and *EVI1* genes.[3,11-13,15] Finally, aberrant microRNA expression profiling has been reported in AML, in which up-regulated *miR-181a* predicted a favorable outcome in CN-AML, while increased expression of *miR-20a*, *miR-25*, *miR-191*, *miR-199a*, and *miR-199b* adversely affected overall survival.[20,33]

It is important to underscore that, to date, the prognostic impact of these markers has mostly been considered in previously untreated patients. In a study published in this issue of the Journal, Wagner *et al.* sought to determine whether molecular factors present at diagnosis maintain their prognostic impact at the time of relapse.[34] This is important as not only is little known about the prognostic value of these markers at this time point, but also, the information could guide therapeutic decisions for patients with relapsed disease based on a more accurate assessment of the likelihood of achieving remission. The authors retrospectively analyzed patients with CN-AML who achieved a first complete remission following double induction and consolidation chemotherapy, which also included allogeneic or autologous hematopoietic stem cell transplantation according to the original study, but then subsequently relapsed. Of the 149 relapsed patients, 94 patients fulfilled the inclusion criteria for further study. Among the patients who went on to receive a cytarabine-based salvage regimen, only 22% of those with a *FLT3*-ITD achieved a second complete remission. Duration of first complete remission and age are known predictive factors at the time of relapse, and it is not surprising that in the multivariate analysis, a first complete remission lasting less than 6 months and age above the median were associated with an increasing risk of failing to benefit from salvage treatment. However, it is remarkable that among the molecular markers considered, *FLT3*-ITD was the only one that independently predicted failure to achieve second complete remission. Furthermore, the presence of *FLT3*-ITD was the only factor along with age that had an independent negative impact on the duration of survival after salvage treatment in patients who received chemotherapy alone and were not transplanted.

This study is noteworthy as it demonstrates that the prognostic risk associated with *FLT3*-ITD at diagnosis carries through at the time of relapse. Patients with *FLT3*-ITD were less likely to achieve second complete remission, and in those patients who were also older (≥ 47 years), the 6-year survival rate following relapse was a dismal 6%. It is becoming increasingly clear that standard induction and consolidation alone is unlikely to offer long-term survival in patients with previously untreated AML with *FLT3*-ITD. Therefore, screening at diagnosis for *FLT3*-ITD and redirecting patients to clinical trials with novel targeted therapies such as tyrosine kinase inhibitors in combination with chemotherapy and/or allogeneic hematopoietic stem cell transplantation following achievement of first complete remission has been clinically important. The results of the study by Wagner *et al.* now suggest that molecular screening for *FLT3*-ITD may also be necessary for deciding salvage treatment for relapsed patients, who may benefit from molecular targeting treatment if not already received upfront. To date, tyrosine kinase inhibitors such as sorafenib or lestaurtinib given in combination with chemotherapy have not produced a significant improvement in the outcome of AML patients, as shown in relatively large clinical trials.[35,36] However, development of tyrosine kinase inhibitors that are more specific for FLT3 inhibition and better selection of patients may improve on these initial clinical results.

While the prognostic relevance of these various markers is broadly accepted, we cannot forget that this information must be integrated with the biological and clinical significance of other leukemogenic mechanisms including those involved in loss of function due to epigenetic gene silencing. It will only be with an improvement in our comprehensive understanding of the complex networks at play, and then aiming at these mechanisms with combinations of diversified molecularly targeted compounds, that we will effectively treat AML and improve on the currently poor clinical results.

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Life beyond the disease: relationships, parenting, and quality of life among survivors of childhood cancer

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Advances in cancer therapies and supportive care have contributed to significant increases in survival rates for children diagnosed with a malignancy. As overall survival rates approach 80%, research has focused on the long-term effects and adverse health outcomes these individuals experience later in life. Nearly two-thirds of survivors report at least one chronic medical condition related to their prior therapy, with 25% being classified as severe or life-threatening.[1] These adverse outcomes stress the importance of ongoing monitoring and surveillance. Just as important as the medical implications are the social implications of childhood cancer and its long-term effects