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Review Article

A summary of the molecular testing recommended in acute myeloid leukemia

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Abstract

Advances in Next-Generation Sequencing technologies (NGS) are revealing germline and somatic mutations that, together with karyotype, determine the diagnosis and subtype of Acute Myeloid Leukemia (AML). Molecular testing is also essential for the genetic risk stratification of patients with AML, in particular for those with normal karyotype AML (CN-AML), a large and highly heterogeneous group of patients. Patients determined to be at high risk could benefit from a more aggressive first-line therapy, or a more directed therapy, such as midostaurin (for *FLT3*-mutated AML) or ivosidenib (for *IDH1*-mutated AML). Here, we will summarize the molecular testing currently recommended in AML and introduce new mutations that may have prognostic value and clinical application in the near future.

Introduction

Acute Myeloid Leukemia (AML) is a complex hematological neoplasm, characterized by the World Health Organization (WHO) into multiple subtypes [1,2]. Cytogenetic analysis is essential for AML diagnosis since certain subtypes are characterized by numerical chromosome abnormalities or gross translocations, including loss of chromosome 5 or the common structural aberration t(8;21) (q22;q22), leading to production of the *AML-ETO* fusion gene, respectively. In fact, according to the National Comprehensive Cancer Network (NCCN), "karyotype represents the single most important prognostic factor for predicting remission rates, relapse risks and overall survival outcomes" [3].

In recent years, significant progress has been made in the biological understanding of AML [4]. In particular, as a result of advances in Next-Generation Sequencing technologies (NGS), genetic studies are revealing an ever-rising number of somatic mutations that help to determine both the phenotypic and prognostic heterogeneity of this pathology [5].

The increasingly widespread use of NGS technology with gene panels in clinics means that the simultaneous analysis of mutations in a high number of genes is both practical and economically feasible [5]. Moreover, the incorporation of molecular markers into current prognostic algorithms is permitting the more precise risk stratification of patients. Indeed, the European Leukemia Net (ELN) currently recommends the evaluation of mutations by NGS using a panel of genes commonly mutated in AML (or a generic myeloid neoplasm gene panel) at diagnosis and at relapse to inform the clinical management of patients with AML [6].

This review will summarize the mutations that currently serve as molecular markers of AML as well as introduce those that may have informative value in the diagnosis, risk stratification and follow-up of patients with AML in the near future.

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Genetic testing recommended in AML

To inform diagnosis

Advances in NGS technologies have driven the inclusion of several new AML subtypes according to their associated genetic alterations, highlighting the importance of molecular testing for a complete diagnosis. For instance, the WHO included the categories of "AML with mutated *NPM1*" and "AML with biallelic mutations of *CEBPA*" in 2008 [1], and "AML with mutated *RUNX1*" and "AML with *BCR-ABL1*" were provisionally recognized as new entities in the 2016 revision [2]. Although the latter entity is not frequent (less than 1% of all AML cases [7,8]), *de novo* AML patients identified as having this subtype may benefit from treatment with tyrosine kinase inhibitors [9,10].

Germline mutations

The presence of germline mutations in several genes have been shown to cause a predisposition to myeloid neoplasms, including AML. These observations led to the inclusion of a new category of myeloid neoplasms with germline predisposition (Table 1) in the 2016 revision of the WHO classification of hematological neoplasms [2].

Table 1: Classification of myeloid neoplasms with germline predisposition. Adapted from [2].

With pre-existing platelet disorders and With other organ dysfunction.
AML with *CEBPA* germline mutation
Myeloid neoplasms with germline mutation of *DDX41*
With pre-existing platelet disorders
Myeloid neoplasms with germline mutation of *RUNX1*
Myeloid neoplasms with germline mutation of *ANKRD26*
Myeloid neoplasms with germline mutation of *ETV6*
With other organ dysfunction
Myeloid neoplasms with germline mutation of *GATA2*
Myeloid neoplasms associated with bone marrow failure syndromes
Myeloid neoplasms associated with telomere biology disorders
Juvenile myelomonocytic leucemia associated with neurofibromatosis, Noonan syndrome or Noonan-syndrome like disorders
Myeloid neoplasms associated with Noonan syndrome
Myeloid neoplasms associated with Down syndrome

When there is a suspicion that a patient may harbor congenital AML-due to a family history of neoplasia, an exceptionally early age of AML presentation, or the presence of various tumors-the ELN recommends the genetic analysis of the genes *RUNX1*, *CEBPA*, *GATA2*, *DDX41*, *ANKRD26*, and *ETV6* [6]. Mutations in these genes are just some that bestow a predisposition to the development of AML; others include mutations in genes associated with a general susceptibility to cancer, such as the Fanconi anemia genes, or *TP53* and *BRCA1*/*BRCA2* [6,11-13], often mutated in therapy-related leukemias [12].

The analysis of germline mutations is critical to inform the selection of a suitable donor if the patient is a candidate for Hematopoietic Stem Cell Transplantation (HSCT). Germline mutations can also confer a higher risk of relapse in AML or a predisposition to the development of a secondary leukemia, including therapy-related leukemias [12]. For example, between 5% and 7% of patients with *CEBPA*-mutated AML harbor germline mutations [13] and although the majority reach complete remission following chemotherapy, recurrent disease is frequent [13].

If a positive result is detected, it is recommended that genetic counseling be offered to the patient's family members for the prevention and/or early detection of germline myeloid neoplasms [11].

The importance of studying *TP53*

In the case of *TP53*, the study of mutations in this gene is of particular importance given that their presence predicts a particularly poor outcome for the patient [4,14,15]. Mutations in the *TP53* gene locus may be point mutations or deletions of 17p13 of a range of sizes, and either somatic or germline [16].

TP53 mutations usually coincide with a complex karyotype [14,15]. However, their presence in conjunction with a monosomal karyotype or aneuplodies such as-5/5q and -7/7q-themselves associated with high risk-is independent and additive in terms of risk stratification, giving rise to an extremely adverse prognosis [4,15].

Recently, the presence of *ASXL1* and *RUNX1* mutations were also included in the high-risk category of AML due to their association with a worse prognosis and poor survival, respectively [2]. Germline mutations of the latter are associated with familial platelet disorder with associated myeloid malignancy, a disorder of abnormal hematopoiesis that confers affected individuals with a higher risk of AML [17]. Moreover, germline mutations in *ASXL1* [18], have been reported as causing a predisposition to myelodysplastic syndrome and/or AML. However, further studies are required to confirm the impact of germline mutations in *ASXL1*, as well as other germline mutations such as *SRP72* [19], and *CBFA2* [20] before their possible inclusion in congenital AML genetic testing recommendations in the future.

Risk stratification

The genetic risk stratification of patients with AML is especially useful to determine the response to therapy of patients with normal karyotype AML (CN-AML), a particularly heterogeneous group of patients representing 40%-50% of all new cases.

Analysis of *FLT3* mutations

The analysis of mutations in the Fms-Like Tyrosine kinase 3 gene (*FLT3*), including Internal Tandem Duplications (ITD) and mutations in the Tyrosine Kinase Domain (TKD), is recommended by the WHO, NCCN and ELN for patients with CN-AML due to its prognostic value [2,3,6]. Specifically, numerous studies have reported higher relapse rates and worse

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overall survival after chemotherapy for patients with *FLT3*-ITD [21,22]. On the other hand, the prognostic impact of *FLT3*-TKD mutations is not as well defined.

Mutations in *FLT3* are identified in approximately a third of *de novo* AML cases and are common in many AML subtypes. Such mutations frequently co-exist with mutations in exon 12 of *NPM1*, detected in approximately 30% of adults aged up to 65 years with AML, and reaching up to 50% in patients with CN-AML [23], with *FLT3*-ITD mutations present in 40% of cases. For example, *FLT3* mutations often coexist with chromatin-spliceosome-mutated AML, accounting for 13% of AML cases (*FLT3*-ITD mutations present in 15%); *PML-RARA* AML (t(15;17)(q22;q21), accounting for 13%·of AML cases (*FLT3*-ITD mutations present in 35% and *FLT3*-TKD mutations present in 15%); *CBFB-MYH11* AML (inv(16)(p13.1q22)), accounting for 7% of AML cases (*FLT3*-TKD mutations present in 20%), and *DEK-NUP214* AML (t6;9)(p23;q34.1), accounting for 1% of AML cases (*FLT3*-ITD mutations present in 70%) [6].

The co-existence of *FLT3* mutations has a significant impact on the prognosis of patients with normal karyotype, differentiating the *NPM1*-mutated subgroup into patients with wild-type *FLT3*, of favorable prognosis, from patients with *FLT3*-ITD, of intermediate prognosis (Table 2). Likewise, patients with *FLT3*-ITD without an *NPM1* mutation have a higher estimated risk of relapse following chemotherapy and are normally considered as candidates for HSCT [6,21-25].

Table 2: Genetic risk stratification according to the NCCN and ELN guidelines. Adapted from [3,6].

Risk	Cytogenetics	Molecular abnormalities
Favorable	CBF: inv(16) or t(16;16); *CBFB-MYH11* t(8;21) or t(15;17); *RUNX1-RUNX1T1*	Normal cytogenetics: Mutated *NPM1* without *FLT3*-ITD or *FLT3*-ITD^{low†} or biallelic *CEBPA* mutation
Intermediate	Normal cytogenetics: t(9;11); *MLLT3-KMT2A* t(8;21), inv(16), t(16;16) No other defined abnormality	CBF with *c-KIT* mutation *NPM1* mutated with *FLT3*-ITD^{high†} *NPM1* wild-type without *FLT3*-ITD or with *FLT3*-ITD^{low†} (without adverse genetic lesions)
Adverse	Complex* or monosomal karyotype -5, -5q, -7, -7q t(v;11q23.3); reordered *KMT2A* inv(3) or t(3;3); *GATA2, MECOM(EVI1)* t(6;9); *DEK-NUP214* t(9;22); *BCR-ABL1*	Normal cytogenetics: *NPM1* wild-type with *FLT3*-ITD^{high†} *TP53* mutated *RUNX1* mutated *ASXL1* mutated

CBF: Core Binding Factor; ITD: Internal Tandem Duplications; †: high allelic ratio ≥0.5, low allelic ratio <0.5;*: ≥3 chromosomal abnormalities

Finally, the identification of the molecular alterations that underlie AML is leading to the development of novel directed therapies. This is the case for midostaurin, a multikinase inhibitor, approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) in combination with chemotherapy for the first-line treatment of adults with *FLT3*-mutated AML [26]. Another second-generation Tyrosine Kinase Inhibitor (TKI) gilteritinib has also been approved by the FDA for the treatment of relapsed or refractory *FLT3*-mutated AML [27].

Despite this, a 2017 survey carried out among AML experts in Europe and the United States reported that only 51.4% of specialists evaluate *FLT3*-ITD in all patients [28]; while at the national level, a recent survey among AML experts in Spanish clinics revealed that 7.5% "never" or "sometimes" carried out the analysis of *FLT3* mutations [29]. These data demonstrate that there is still a lack of understanding of the prognostic and therapeutic indications of the presence of *FLT3* mutations.

Molecular analysis for risk stratification

Since 2017, both the NCCN and the ELN recommend the routine detection of mutations in the genes *CEBPA*, *NPM1* and *RUNX1* at diagnosis to define the category of AML, as well as mutations in the genes *KIT*, *FLT3* (ITD and TKD), *NPM1*, *CEBPA*, *RUNX1*, *ASXL1* and *TP53* (together with cytogenetic alterations) in order to refine to prognosis of patients with AML [3,6,30].

In the case of core binding factor AML (CBF-AML), the presence of mutations in the *KIT* gene reduces the prognosis from favorable to intermediate risk [31]. Meanwhile, in the case of CN-AML, the presence of mutations in *NPM1* and *CEBPA* (in the absence of *FLT3*-ITD mutations) improves the prognosis from intermediate risk to favorable, although the presence of *FLT3*-ITD mutations modifies the risk to adverse (Table 2) [6,21-25]. Specifically, *FLT3*-ITD with a high allelic ratio (≥0.5) is associated with a poor prognosis (higher relapse rate and worse overall survival) [21-25]. However, AML patients mutated in *NPM1* with a low *FLT3*-ITD allelic ratio (<0.5) have a similar prognosis to patients mutated in *NPM1* without *FLT3*-ITD; in other words, a favorable prognosis. [6,21-25].

It is important that mutational analysis is carried out promptly so that patients identified as high risk can benefit from a more aggressive first-line therapy, or a more directed therapy in some cases. For example, patients with a positive result for *FLT3*-ITD (with a ratio > 0.5) may be candidates for the addition of the TKI midostaurin to their chemotherapy regime or for HSCT.

Patient follow-up

Relapsed and refractory AML

In addition to its role in the accurate diagnosis of patients with AML, mutational analysis is also very informative in cases of relapsed or refractory AML. The repetition of mutational analysis (because a patient's profile of mutations may change over time or as the result of chemotherapy or other therapies) may identify possible targets against which there may be an approved directed treatment or an agent undergoing clinical trial. For example, gilteritinib, an inhibitor of *FLT3* is approved to treat refractory AML or relapsed patients with mutated *FLT3* [27].

Currently, there is a difference between the NCCN and ELN recommendations on molecular testing in AML. Specifically, in

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the 2017 update the ELN did not include a recommendation for the analysis of mutations in *IDH1* and *IDH2* in the evaluation of AML at diagnosis due to lack of evidence [6]. However, shortly after its publication, the FDA approved two directed therapies, ivosidenib (AG-120, Tibsovo®) against *IDH1*-mutated AML andenasidenib (AG-221, IDHIFA®) against *IDH2*-mutated AML [32, 33]. Thus, in 2018 the NCCN included the recommendation for the analysis of mutations in the *IDH1* and *IDH2* genes because of the availability of FDA-approved directed therapies [30].

Minimal residual disease MRD

Minimal Residual Disease (MRD) has been shown to be a very important prognostic factor. High levels after chemotherapy are associated with relapse and so patients with a positive MRD are considered to be at risk [34]. The analysis of mutations, such as insertions and deletions in *NPM1*, permit their monitoring as a molecular marker of MRD [35]. The ELN's current recommendations describe the applicability of MRD testing for the follow-up of AML patients because it allows different therapeutic options to be optimized and personalized for patients with high MRD, such as an indication for HSCT or not [6].

Future perspectives

Updating of risk stratification algorithms

The list of mutations in genes with prognostic value is continually increasing. For example, studies have demonstrated that certain *MCM7* polymorphisms are associated with relapse and overall survival in AML patients [36], while the partial tandem duplication of *MLL* (*MLL*-PTD) confers worse prognosis to patients with CN-AML [37]. In the future it's probable that these or other genes could be incorporated into risk algorithms to help stratify patient subgroups, but only when sufficient evidence exists to support their prognostic value [4,6,37].

Prognostic relevance of mutations according to age

Finally, another possible future modification to the NCCN and ELN's recommendations could be the inclusion of risk stratification algorithms not only optimized to the mutational profile of the patient but also to the patient's age.

In general, older patients with AML tend to have poorer results with standard chemotherapy regimens [38,39]. This could be caused by adverse karyotypes that are more common and/or the higher number of mutations in older patients with AML than younger patients with AML [4], although the association between the number of mutations and prognosis continues to be a matter of debate.

A phenomenon called clonal hematopoiesis of indeterminate potential (CHIP), which is intrinsic to aging, is characterized by the accumulation of mutations in the *DNMT3A*, *TET2* and *ASXL1* genes (collectively known as DTA mutations). A positive correlation exists between age and the presence of DTA mutations, even in healthy individuals [40,41], although studies have found an association between the accumulation of DTA mutations and a higher risk for developing myeloid neoplasms, including AML, as well as cardiovascular pathologies [40-42]. Nevertheless, the detection of DTA mutations in AML patients in remission is not associated with relapse [43].

It still remains to be determined whether the presence of different mutations in patients aged over 65 years of age has the same prognostic value as in patients aged under 65 years, although several groups are actively investigating this matter. For instance, preliminary data from the Alliance group indicates that mutations in the splicing factor *SF1* may refine the prognosis of *NPM1*-mutated AML patients aged over 60 years [44].

Conclusion

Molecular testing at diagnosis, remission and relapse can provide large amounts of data to guide the individualized clinical management of patients with AML. In addition, the analysis of mutations is particularly useful for informing the treatment choice.

The ELN recommends the evaluation of mutations in patients with AML at diagnosis and at relapse using NGS technology with gene panels, with which it's possible to analyze a high number of genes simultaneously and at an ever-decreasing cost.

These panels generate more data than is currently recommended for the diagnosis and prognosis of patients with AML. However, with the continual advancements in our understanding of the impact of somatic mutations and the complex interactions between them, it may be possible to utilize this data in the future to optimize and personalize therapy for patients and in this way maximize their possibilities of reaching complete remission. As such, it is very important to store the samples of patients with AML in biobanks because, although the presence of a certain mutation is not prognostic in the current day, a new targeted therapy may be developed in the future.

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