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Invited review

Role of genotype-based approach in the clinical management of adult acute myeloid leukemia with normal cytogenetics

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ABSTRACT

Acute myeloid leukemia (AML) is the most common form of acute leukemia affecting adults. Although it is a complex disease driven by numerous genetic and epigenetic abnormalities, nearly 50% of patients exhibit a normal karyotype (CN-AML) with an intermediate cytogenetic risk. However, a widespread genomic analysis has recently shown the recurrence of genomic aberrations in this category (mutations of *FLT3*, *CEBPA*, *NPM1*, *RUNX1*, *TET2*, *IDH1/2*, *DNMT3A*, *ASXL1*, *MLL* and *WT1*) thus revealing its marked genomic heterogeneity. In this perspective, a global gene expression analysis of AML patients provides an independent prognostic marker to categorize each patient into clinic-pathologic subgroups based on its molecular genetic defects. Consistently such classification, taking into account the uniqueness of each AML patient, furnishes an individualized treatment approach leading a step closer to personalized medicine. Overall the genome-wide analysis of AML patients, by providing novel insights into biology of this tumor, furnishes accurate prognostic markers as well as useful tools for selecting the most appropriate treatment option. Moreover it provides novel therapeutic targets useful to enhance efficacy of the current anti-AML therapeutics. Here we describe the prognostic relevance of such new genetic data and discuss how this approach can be used to improve survival and treatment of AML patients.

Contents

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ASX, additional sex combs; BM, bone marrow; bZIP, leucine zipper; C/EBPα, CCAAT/enhancer binding protein α; CN-AML, normal karyotype-AML; CR, complete remissions; DFS, disease-free survival; DNMT, DNA methyltransferase; DNMT3a, DNA methyltransferase 3A; 2HG, 2-hydroxyglutarate; HSCT, allogeneic hematopoietic stem cell transplantation; ITDs, internal tandem duplications; JM, juxtamembrane; α-KG, α-ketoglutarate; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; ncRNAs, non-coding RNAs; NFkB, nuclear factor kappa B; NGS, next generation sequencing; NPM, nucleophosmin; OS, overall survival; PCR, polymerase chain reaction; PTD, partial tandem duplication; TET2, ten–eleven translocation 2; TKD, tyrosine kinase domain; WT1, Wilms tumor.

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1. Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults, with an estimated annual incidence of 3–4 cases per 100,000 people [1,2]. Clinically, it is characterized by a failure in differentiation and proliferation of stem cell compartment resulting in accumulation of myeloblasts [3]. Although extraordinary progresses in diagnosis and therapy, the outcome of AML patients, mainly elderly remains poor. Less than 50% of adult AML patients have a 5-year overall survival (OS) whilst about 20% of elderly survives more than 2 years [4]. Notably, an exception to this is acute promyelocytic leukemia (APL, not reviewed here), which is the only AML subtype completely cured in more than 75% of patients. (4) Unfortunately this variant represents only 10% of all adult AML and the treatment of residual forms remains still a challenge.

In the last few years, progresses of genomics technologies have led to identify AML as highly heterogeneous disease improving enormously the previous cytogenetic-based risk groups. The advent of innovative laboratory skills has revealed the intricate network characterizing AML which involves gene mutations/deregulation (*FLT3*, *NPM1*, *CEBPA*, *TET2*, *DNMT3A* and *IDH1/2*), non-coding RNAs (ncRNAs) and distinctive epigenetic changes. Overall this knowledge has provided useful elements to stratify AML patients into different subgroups, resulting in better prognosis and therapy (Fig. 1).

In such a scenario patients with normal cytogenetic (CN-AML) might be further classified in different subgroups, resulting in a more prominent impact on their clinical management. Interestingly, a recent study from TCGA (The Cancer Genome Atlas), by analyzing the genomes of 200 adult AML patients, has demonstrated that leukemia is unique by having fewer mutations compared with other tumors [5]. As result, mutations can affect one of the nine categories of genes which are relevant for pathogenesis, including transcription-factor fusions (18% of cases), the gene encoding nucleophosmin (27%), tumor-suppressor genes (16%), DNA-methylation-related genes (44%), signaling genes (59%), chromatin-modifying genes (30%), myeloid transcription-factor genes (22%), cohesin-complex genes (13%), and spliceosome-complex genes (14%). Importantly, multiple mutations can also coexist in a single patient thus suggesting the existence of strong link between different genes and categories. Such heterogeneity also affects therapeutic decisions considering that the current therapeutic options are not equally effective in all subgroups. Therefore, the identification of genetic features to predict response to treatment is crucial not only to guide but also to optimize the current therapeutic strategies available for CN-AML patients [2,6].

Here we will review the importance of a genomic-based approach in the clinical management of CN-AML patients through a discussion of its prognostic relevance. Moreover we will outline the clinical benefit of this approach, by analyzing not only its impact on choosing the best therapeutic strategy, but also its role in providing novel targets for the treatment of AML.

2. Prognostic factors

Conventional cytogenetic analysis and FISH have long been used to stratify AML patients into three major risk-based categories (favorable, intermediate and unfavorable) with prognostic and therapeutic relevance [7–10]. Accordingly, patients with favorable cytogenetic alterations (e.g. inv(16) which generates CBFB-MYH11 fusion protein, t(15;17) encoding for PML-RARA fusion protein and t(8;21) encoding AML-ETO fusion protein), exhibit an OS of 55% after treatment with conventional therapies, while patients in poor risk groups gain more benefit with more intensive approaches such as allogeneic hematopoietic stem cell transplantation (HSCT). Nearly 50% of AML patients have an intermediate cytogenetic risk and many of these genomes lack structural abnormalities as confirmed by microarray-based analysis [5,7,11,12]. AML patients assigned to the intermediate-risk group have a 5-years OS rate ranging between 24 and 42% (depending on the study), but no accordance about the best therapeutic strategy to use has been identified [13,14]. The recent progresses in genomics and molecular technologies as next-generation sequencing (NGS), global gene expression analysis, single nucleotide polymorphism (SNP) array analysis have identified recurrent mutations in several genes associated to AML (i.e. *FLT3*, *NPM1*, *CEBPA*, *RUNX1*, *ASXL1*, and *MLL*) suggesting their prognostic relevance in CN-AML patients [15–24]. Importantly these technologies, by identifying new AML- associated mutations (Table 1), have provided a more useful classification system to stratify AML patients into prognostically relevant categories, mainly for patients with an intermediate-risk profile. Also they have furnished methods promoting a genome-tailored therapeutic approach in AML.

Nevertheless it is worth remembering that current clinical management of these patients is based on a quite small number of genetic abnormalities due to some limits:

1. The prognostic impact of some genetic aberrations has been evaluated in retrospective studies that although considering large cohorts of AML patients, due to low prevalence of specific mutations or combination of multiple aberrations, resulted in misleading clinical conclusions.
2. Most studies have been conducted by analyzing specific genetic lesions rather than consider the entire set of known mutations in parallel, aiming to reveal mutations able to independently predict the outcome in AML patients. Unfortunately this approach does not consider the genome complexity of leukemia cells in which multiple mutations have different impact on outcome than a single mutation.
3. The multi-gene analysis performed by NGS techniques has revealed that tumor cell harbors hundreds of mutated genes. Most of them are *passengers mutations* (do not provide a selective advantage) and a limited number are *driver mutations* (i.e. causing the tumor) with the recurrence as the most important criteria for distinguishing each other. Up to now driver genes mutations identified in AML patients are 1–30% but further NGS