SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 13: 95-100, 2020

Core binding factor acute myeloid leukemia: Advances in the heterogeneity of *KIT*, *FLT3*, and *RAS* mutations (Review)

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Received June 14, 2019; Accepted February 5, 2020

DOI: 10.3892/mco.2020.2052

Abstract. Core binding factor (CBF) is a heterodimer protein complex involved in the transcriptional regulation of normal hematopoietic process. In addition, CBF molecular aberrations represent approximately 20% of all adult Acute Myeloid Leukemia (AML) patients. Treated with standard therapy, adult CBF AML has higher complete remission (CR) rate, longer CR duration, and better prognosis than that of AML patients with normal karyotype or other chromosomal aberrations. Although the prognosis of CBF AML is better than other subtypes of adult AML, it is still a group of heterogeneous diseases, and the prognosis is often different. Recurrence and relapse-related death are the main challenges to be faced following treatment. Mounting research shows the gene heterogeneity of CBF AML. Therefore, to achieve an improved clinical outcome, the differences in clinical and genotypic characteristics should be taken into account in the evaluation and management of such patients, so as to further improve the risk stratification of prognosis and develop targeted therapy. The present article is a comprehensive review of the differences in some common mutant genes between two subtypes of CBF AML.

Contents

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Key words: acute myeloid leukemia, core binding factor, heterogeneity, risk stratification, prognosis

1. Introduction

Core binding factor acute myeloid leukemia (CBF AML) codes for two types of recurrent abnormal cytogenesis referred to as t(8;21)(q22;q22) and inv (16)(p13q22) or t(16:16)(p13;q22), commonly as t(8;21) and inv (16). The European Leukemia Net (ELN) classifies acute myeloid leukemia (AML) into favorable, moderate, and poor risk groups, according to cellular genetic and molecular abnormalities. In this classification system, the favorable risk group includes AML with the following rearrangement: inv (16) or t(16;16), t(8;21), *NPM1* mutation, and biallelic mutated *CEBPA*. CBF AML associated with *CBF* gene aberration is a kind of acute myeloid leukemia with good prognosis (1,2). The prognosis of CBF AML patients is usually better than that of AML patients with normal karyotype or other chromosomal abnormalities (3). Approximately 55% of adults with *de novo* AML have non-random chromosomal abnormalities, which have long been considered an important independent predictor of clinical prognosis (4-6). Genetically based risk stratification of AML is also widely used for guiding therapy, It has been found that recurrent genetic changes may be involved in the leukemogenesis of CBF AML patients. More genetic studies are likely to contribute to leukemia pathogenesis as well as to potentially identify optimal therapeutics (7,8). Molecular aberrations of CBF are known to account for approximately 20% of all adult AML. The two subtypes of AML, t(8;21) and inv (16), are responsible for the production of corresponding abnormal fusion genes *RUNX1-RUNX1T1* and *CBFB-MYH11*, respectively, which are the most common recurrent gene mutations (9). The original RUNX1 and CBFB form a complex heterodimer transcription factor, CBF, which regulates normal hematopoiesis in individuals. CBF is necessary for the production of hematopoietic stem cells (HSCs) during embryonic development and is frequently mutated in human leukemia (9). The CBFs contain one β and one α subunit (3). The function of α subunit is to bind DNA. The α subunit is encoded by one of the mammalian genes *RUNX1*, *RUNX2*, and *RUNX3* (9-11). *RUNX2* and *RUNX3* are not significantly associated with leukemia (3,10). The β subunit is encoded by CBFB. The function of the β subunit is to stabilize the binding of the α subunit to DNA and protect *RUNX1* from ubiquitin-proteasome mediated degradation (10). However, t(8;21) and inv (16) form the fusion genes *RUNX1-RUNX1T1* and *CBFB-MYH11*. The two fusion genes disrupt the α and β subunits, respectively, of CBF, eventually affecting normal

hematopoiesis (5,12,13). CBF AML usually confers relatively favorable prognosis; however, recurrence remains the main problem after treatment (3,11,14-16). A 10 year follow-up study of CBF AML showed that the complete remission (CR) was 87-88% and relapse-free survival (RFS) was only 42% (14). Many studies have reported that CBF AML is a group of heterogeneous diseases (5,14,17,18). Improving prognostic risk stratification is necessary for hierarchcal management of t(8;21)and inv (16) (19). The review identifies the differences of common mutant genes between the two groups and the differences in morphological characteristics, clinical characteristics and therapeutic response.

2. Clinical and diagnostic features of CBF AML

Previous findings have shown that there is obvious heterogeneity in morphology, clinical features and cytogenetics between t(8;21) and inv (16) AML (3). At diagnosis, 80-90% patients of t(8,21) are classified as type M2 of French-American-British (FAB) and 10% as type M1 of FAB. When compared to inv (16), t(8;21) often shows a mild leukocyte increase and lower level of bone marrow primitive cell, and is often related to thrombocytopenia and anemia (3,5). The incidence of secondary cytogenetic mutation of patients with t(8,21) is significantly higher than that for inv (16) (20,21), and most have at least one extra chromosomal abnormality, such as sex chromosome loss (male-y, female-x) and del(9q). By contrast, the sub-classification of most patients with inv (16) is usually designated as FAB M4Eos, which have a higher proportion of bone marrow primitive cells and peripheral primitive cells (3,5,19). Inv (16) is more likely to affect skin, lung or central nervous system, and is more prone to hepatosplenomegaly, lymphadenopathy, and gingival hyperplasia when compared to t(8;21) (3). Chromosomal abnormalities are uncommon, which can be +22, +8, +21, 7q-. Patients with inv (16) often present at an older age (median 41 vs. 36 years) and it is more common in individuals of African descent (3,18,22). With regard to treatment response and clinical outcome, patients with inv (16) more often respond to a single cycle of induction chemotherapy, while t(8;21) require two cycles of induction therapy. Compared with inv (16) AML, t(8;21) AML patients have shorter overall survival (OS) and a higher risk of death. As previously shown, the median OS time of the two groups was 4.4 and 7.1 years, respectively, and the risk of death of the latter was 1.5-fold as high as that of the former (5). Inv (16) AML had longer survival after relapse from CR, approximately 1.2 years, compared to t(8;21) AML (0.7 years), suggesting that inv (16) was easier to reinduce, and t(8;21) AML has an inferior response to salvage therapy (5,14).

3. Heterogeneity of common mutant genes between two subtypes of CBF AML

The clinical prognosis of AML patients is largely dependent on the cytogenetic subgroup, as well as focus on the gene level, to analyze the differences of the common mutant genes between the two subtypes of CBF AML. As t(8;21) and inv (16) can interfere with CBF of AML, and both have relatively good prognosis, they often receive similar treatment. In CBF AML, the disruption of the *CBF* α/β gene interferes with normal hematopoietic differentiation. In recent years, however, some progress has been made in understanding the molecular events that led to the leukogenesis of AML. It is believed that the pathogenesis of CBF AML requires the joint participation of fusion genes and additional mutant genes. Studies have shown that the role of two CBF AML fusion genes in leukogenesis was necessary, but not sufficient to cause leukemia, which means that the pathogenesis of CBF leukemia requires additional mutations (23,24). The study also proposed that CBF AML was the result of a combination of at least two classes of mutations: Mutations that confer a reproductive and/or survival advantage, known as class I events, and mutations that impair differentiation, known as class II events (24). In CBF AML, *RUNX1-RUNX1T1* and *CBFB-MYH11* gene fusions generated by t(8;21) or inv (16) rearrangements represent these class II mutations. The two-hit model (25) proposed by Kelly and Gilliland suggests that the occurrence of AML may be associated with a combination of class II events that modify normal hematopoietic differentiation and class I events that lead to reduced apoptosis and/or enhanced proliferation predominance in leukemia cells (26). In the two subtypes of CBF AML, class II events, the fusion genes, are responsible for hematopoietic differentiation block, and studies have shown that they alone are not sufficient to induce AML in animal (13,27). By contrast, mutations in related class I events such as *KIT*, *RAS*, and *FLT3* have proven to be necessary to confer a proliferation and survival advantage on transformed cells (18). However, recent findings regarding microarray gene expression profile showed that t(8;21) and inv (16) AML patients were divided into two or more different groups (5), showing different gene profiling for the two groups and underscoring potential biologic differences.

With the development of molecular research, an increasing number of gene mutations are related to CBF AML. Findings have shown that, mutations in addition to CBF AML were identified in *RAS (K/NRAS)* and in tyrosine kinase signaling pathways (*RAS/RTK; CBL*, *FLT3, JAK2, KIT, PTPN11*), chromatin modifiers/epigenetic regulators of transcription (*ASXL1/2, BCOR/L1, TET2*) and an additional 50 genes (28); however, not all of these mutations are associated with outcome (20,21). Of note, t(8;21) and inv (16) demonstrated remarkably different spectra of cooperating mutations. For example, *ASXL2, ZBTB7A* and cohesin mutations were found exclusively in t(8;21) AML, although none had an impact on overall or event-free survival (20,21,28,29). In addition, although both types share tyrosine kinase (TK) mutations, there are significant differences in the incidence and prognosis of mutations in patients with both subtypes (30). Recently, data on CBF AML in Asian countries have been reported. The heterogeneity of these two subtypes in mutated genes and prognosis was discussed (19,31). Research also shows that, the gene heterogeneity of CBF AML, and gene rearrangement in patients with CBF AML causes the activation of *FLT3, cKIT, JAK2,* and *RAS* (24). *KIT, FLT3*, and *RAS* are the most common mutations. They are three genes that encode TK receptors or molecules, which are frequently mutated in both CBF AML subtypes (16,32,33). It is well established that CBF AMLs

frequently harbor TK pathway mutations including *KIT*, *FLT3*, and *NRAS*/*KRAS* mutations.

CBF AML and KIT mutations. The *KIT* gene, located on chromosome 4q, encodes a glycoprotein that belongs to the type III receptor tyrosine kinase family (3). *KIT* gene mutations activate signaling pathways related to proliferation, differentiation and survival (34), and *KIT* mutations generally occur late in the process of AML leukemogenesis (35). Most of the *KIT* mutation sites of CBF AML were located on exons 17 and 8 (3). Numerous studies have shown different incidence and prognostic value of *KIT* in both types. Park *et al* studied *c-KIT* mutation in patients with CBF AML (36). A total of 116 patients diagnosed as CBF AML were analyzed, and the differences in *KIT* gene expression in that study were as follows: The incidence of *c-KIT* exon 8 mutation in inv (16) patients was significantly higher than that in t(8;21) patients, and the difference reached statistical significance (P=0.045). By contrast, the incidence of *c-KIT* exon 17 mutation in patients with t(8;21) was higher than that in patients with inv (16), but the difference was not statistically significant (P=0.105). A similar conclusion was reached in an original study by Boissel *et al* (26). A number of studies have shown the difference in the prognostic effects of *KIT* mutations in patients with two types of CBF AML: *c-KIT* mutation was related to lower CR, shorter overall survival (OS) and event-free survival (EFS) in t(8;21) AML patients, but it had no effect on inv (16) AML. A genetic mutation study that included 103 patients with newly diagnosed CBF AML showed that in all t(8;21) patients, the CR rate, 6 year OS, and 6 year EFS were 98, 46, and 36%, respectively, while t(8;21) patients with *c-KIT* mutation were 83, 0 and 0%, respectively (26,37). Park *et al* (36) demonstrated that in patients with t(8;21), the presence of *c-KIT* exon 17 mutation was associated with poor prognosis in both OS and EFS, which was statistically significant, and the difference was limited to adults. The prognostic significance of *KIT* mutations in CBF AML in children is controversial (38). However, in patients with inv (16), *c-KIT* exon 17 mutation had no independent adverse prognostic effect on OS or EFS, The study also recommended *KIT17* as a predictor of adult CBF AML patients (36). Jones *et al* also concluded that *KIT* point mutation was only related to the adverse outcome of t(8;21) AML, while completely irrelevant to the outcome of inv (16) AML (39). Therefore, as mentioned above, due to the difference of the mutant gene *KIT* between the two subtypes, t(8;21) AML and inv (16) AML were layered and reported separately, and thus the prognostic value of *KIT* mutations in newly diagnosed adult AML should be further investigated. Additionally, some genetic aberrations including *KIT* mutations have been reported to confer poor prognosis in a few but not all studies (28,40). It has been suggested that this poor prognosis is restricted to patients with a high allele burden of these mutant genes (28,40). Thus, quantification of allele levels through new techniques such as second-generation sequencing would be necessary to modify therapy. Given all the results reported thus far, it is difficult to recommend the detection of *KIT* mutations to specifically guide the treatment of patients with CBF AML. However, if the corresponding mutations are associated with higher recurrence rates and poorer survival, intensive chemotherapy may be an option for patients with CBF AML who have not yet clearly assessed the prognostic risk. In addition, targeted TK inhibitor therapy with novel targeted *KIT* such as imatinib or dasatinib is also an option, and preliminary treatment experience of imatinib has been reported (41-43), Research by Cammenga on CBF AML regarding sensitivity to imatinib suggested CBF AML patients with *KIT* mutation showed significant response to imatinib (43). However, *KIT* mutations are often absent in relapse, suggesting that the therapeutic value of *KIT* inhibitors is likely to be limited (40). Homoharringtonine (HHT) features activity against tumor cells harboring *c-KIT* mutations (44). In clinical practice, HHT has an anti-myeloid leukemia effect and enhances the efficacy of anthracycline/cytosine arabinoside induction regimens in the treatment of AML, especially in the t(8;21) subtype (45).

CBF AML and FLT3 mutations. The *FLT3* gene encodes a kind of receptor tyrosine kinase (RTK), which is member of the type III receptor tyrosine kinase family. *FLT3* is expressed in early hematopoietic stem cells and dendritic cell progenitor cell subsets. *FLT3* signal transduction can activate intracellular pathways [such as (PI3K)-AKT], by which it may promote proliferation and inhibit apoptosis (46-48). *FLT3-ITD* mutations can be found in 20-30% of AML patients, and are more common in normal karyotype (NK)-AML, but less common in CBF-associated AML, while 5-10% of patients with CBF AML have *FLT3-ITD* mutations (49-52). Regarding the *FLT3* mutation in patients with CBF AML, studies have suggested that *FLT3* mutation may play an important role in the leukogenesis in CBF AML, because *FLT3* and t(8;21) AML fusion gene (*CBFB-MYH11*) interaction can induce mouse leukemia phenotype (53,54). It has been found that *FLT3-TKD* in CBF AML may make the cells resistant to chemotherapy, and even if the low-frequency clone after treatment is retained, it will appear as the main clone in subsequent recurrence (30). There have been a number of retrospective studies reporting that *FLT3* mutation in patients with inv (16) is more common than that in patients with t(8;21) (46,55). In terms of prognosis, Boissel *et al* reported that *FLT3* mutation resulted in reduced EFS and OS in patients with CBF AML, especially due to the occurrence of many early events (26). In both subtypes, *FLT3* mutation is predictive of short progression-free survival (PFS) in patients with inv (16), whereas not in t(8;21) AML (39). Although the prognostic association of *FLT3* mutations in CBF AML remains controversial, the activated *FLT3* kinase can be used as a further therapeutic target for TK inhibitors. Recent findings have shown single-agent *FLT3*-targeted therapies as a means to an end for relapsed patients may be of value (56).

CBF AML and RAS mutations. The *RAS* gene family consists of the G-proteins, *NRAS, KRAS* and *HRAS*. *RAS* plays an important role in signaling the proliferation and survival of cell membrane receptors (including *KIT* and *FLT3*) to intracellular signal pathways. Certain mutations in *RAS* lead to permanent activation of *RAS*. *NRAS* or *KRAS* mutations have been found in many malignancies, including leukemia, such as AML (57). *RAS* mutation seems to be particularly frequent in inv (16) AML, with a reported incidence of up to 36% (26,58). Solh *et al* (3) and Boissel *et al* (26) have reported that *NRAS* or *KRAS* mutation was more common in patients

with inv (16) than in patients with t(8;21). Further studies by Boissel *et al* (26) showed that *RAS* mutation had no effect on CR rate, EFS or survival rates of t(8;21) AML and inv (16) AML.

4. Discussion and conclusion

There is increasing evidence of genetic heterogeneity of CBF AML, which may be mainly driven by synergistic genetic or epigenetic events, these events are certainly present because the *CBF AML* fusion gene is necessary, but not sufficient, for leukogenesis (30). In addition to the known secondary chromosomal aberrations, *RAS-KIT* and *FLT3* gene mutations have been found to be the most common molecular alteration in CBF AML (16,59). Second-generation sequencing can identify subsets of patients with the highest risk of recurrence, and more molecular alterations are likely to be found, providing more clues for the occurrence of CBF AML. For example, *ASXL2, ZBTB7A* and cohesin mutations are usually found in t(8;21) AML, but hardly in inv (16) AML (20,21). Recent studies identified no mutations had an impact on overall or event-free survival, albeit this findings requires further investigation (20,21). Other mutations including *JAK2, CBL*, and *CCND1/2*, have been reported in recent studies (21,60). Large amounts of clinical data and gene sequencing studies are needed to describe the genetic differences between the two types, and new prognostic prediction models are also necessary. Genetic markers may be useful in predicting the prognosis of CBF AML and become new therapeutic targets, especially for those patients who cannot be cured by chemotherapy alone. In fact, targeting the highly expressed and frequently mutated *KIT* or *FLT3* kinases, the addition of the second-generation tyrosine kinase inhibitor dasatinib to chemotherapy is currently being evaluated in clinical trials (35,38,61). The standard DA regimen combined with mutagen-specific targeted therapy, allogeneic hematopoietic stem cell transplantation and immunotherapy may reduce the recurrence of CBF AML and improve the cure rate (9). In a word, based on gene heterogeneity, stratified management at diagnosis, targeted therapy at treatment, and quantitative monitoring of minimal residual disease (MRD) during remission may help improve the prognosis and management of CBF AML.

Of note, ethnicity and other factors should be considered when applying new drugs that target genetic mutations. In recent years, several data describing the differences between CBF AML cytogenetic abnormalities between Western and Asian populations have been reported. For example, Wang *et al* (62) reported that in the mutant subtypes of *c-KIT*, the *N822K* mutation was more common in Chinese patients with CBF AML than in Caucasian patients, which is consistent with findings of Shimada *et al*. Those findings suggest that *N822K* may be another typical mutant subtype of Asian CBF AML (63). It has also been reported that *NPM1* and *FLT3-ITD* mutations were less common in AML patients in China than in Europe (64). Differences of the frequency of del(9q) and del(7q) cytogenetic abnormalities in CBF AML between Asia and Europe have also been reported (19). Thus, CBF AML cytogenetic abnormalities are different between Western and Asian populations. However, further studies are needed to assess the comprehensive differences.

There are some limitations in our review. The above prognostic data have not taken into account clonal interference. Itzykson *et al* (65) reported that clonal interference in RAS/RTK pathways, and the relevant mutations largely arise in independent sub-clones, thus resulting in clonal interference. Authors of that study reported that the presence of clonal interference is associated with shorter event-free survival (28,65). In addition, when referencing data of mutation frequency, there is a lack of analysis on sequencing technology and sensitivity threshold, as well as the number of genes and exon sequencing.

In summary, CBF AML is a group of heterogeneous disease with good prognosis, with recurrence remaining the main issue after treatment. CBF AML has a large difference both in terms of the macro level such as morphological characteristics, clinical characteristics and treatment response, or the micro level, class I mutation-related gene mutation. Further research on the prognostic value of class I mutation-related gene mutations in newly diagnosed adult AML, and stratification of the risk based on genetics is imperative. In order to reduce the recurrence of CBF AML and improve the cure rate, so as to achieve good prognosis, management should be carried out on the basis of improving the risk stratification of prognosis in these patients.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

XQ collated the references and wrote this review. JCD reviewed and edited the manuscript. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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