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Revista Brasileira de Hematologia e Hemoterapia
Brazilian Journal of Hematology and Hemotherapy
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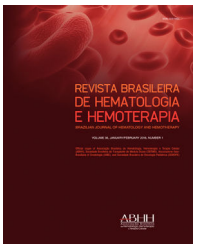

Letter to the Editor

FMS-related tyrosine kinase 3 internal tandem duplication (FLT3-ITD): a villain among others

Acute myeloid leukemia (AML) is the most frequent acute leukemia of adult patients with an estimated 10,070 new cases in Brazil in 2016. Most of the cases are *de novo*, without a defined etiology, and around two thirds of the patients will die of the disease, according to the Instituto Nacional de Câncer (INCA).[1] Genetic aberrations may help to differentiate patients who have a good from those with a dismal prognosis.

In fact, chromosomal abnormalities detected by G-banding karyotype and gene rearrangements revealed by molecular tests are important tools to stratify patients into favorable, intermediate or unfavorable prognoses. The World Health Organization (WHO) classification of hematopoietic tumors lists recurrent genetic abnormalities.[2]

FMS-related tyrosine kinase 3 (FLT3), a tyrosine kinase receptor usually expressed in hematopoietic progenitors, is the most common genetic lesion in AML with mutations detected in from 25% to 40% of the cases.[3] These mutations may occur in any subtype of AML (including acute promyelocytic leukemia – APL), and are frequent with the normal karyotype or t(6;9).

There are two main types of mutations: internal tandem duplication (ITD), which is the most common (~25% of cases), and a point mutation (D835) (~5%).[4]

Except for APL, AML patients with FLT3-ITD present increased chance of relapse, short disease-free survival and reduced overall survival, despite an unchanged complete remission rate.[5] The detection of FLT3-ITD is important for prognosis particularly in those with a normal karyotype.

However, there remains some controversy about the impact of the size of FLT3-ITD fragment on the prognosis. One study showed that 48–60 base-pair duplications are associated with a worse outcome[6] and other authors reported that it is not possible to confirm this relationship by the length of FLT3-ITD alone. There is a large variation in the clinical characteristics of patients, making it difficult to correlate data and set standards.[7,8]

Aiming to evaluate the length of duplication in Brazilian patients, we evaluated AML cases diagnosed from January 2013 until July 2015 at the Fleury Medicina Diagnóstica laboratory according to the WHO classification using bone marrow morphology and flow cytometry immunophenotyping. We identified 26 (29%) out of 89 AML cases with FLT3–ITD. The mean age of the patients was 54 years old (range: 13–79 years) and the male to female ratio was 1:0.7. The size of the duplication varied from 21 to 87 base pairs (mean: 57 base pairs) and only two cases had two peaks, showing a very heterogeneous pattern. From these cases, ten (38%) had follow-ups with no differences being found (unpaired *t*-test: p-value = 0.44) in respect to the size of the duplication and survival, probably due to the low number of cases studied. Indeed, many factors contribute to the lack of success and deaths during induction remains a significant problem in AML independently of the mutation. In fact, age, white blood cell count and primary or secondary leukemia add to the prognostic difficulties.[7]

Moreover, the impact of FLT3-ITD on prognosis may depend on the presence of biallelic mutations. Studies have shown a significantly worse prognosis in patients with higher mutant to wild-type allelic ratios (>0.4).[8]

As FLT3-ITD is a common mutation, tyrosine kinase inhibitors have been recognized as potential therapeutic agents, and many drugs are in clinical development including sorafenib, sunitinib, midostaurin, quizartinib, lestaurtinib, crenolanib and gilteritinib, in the hope of reducing this therapeutic failure.[9] Nevertheless, taking into account the multiple hits that are thought necessary in leukemogenesis, FLT3 plays a small role. It activates proliferation pathways (class I mutations, such as of the K/N *RAS*, *TP53* and *c-KIT* genes), while other mutations impair differentiation (class II: *NPM1* and *CEBPa* genes), epigenetic regulation (class III: *DNMT3A*, *TET2* and *IDH1/2* genes), the p53 pathway, with even more also playing a role.[10] In this scenario, the *FLT3* mutation is not the only villain.

In conclusion, further studies are needed to confirm whether the size of the *FLT3*-ITD mutation is correlated to a worse prognosis.[7,8,11]

Conflicts of interest

The authors declare no conflicts of interest.

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Received 23 November 2016
Accepted 7 March 2017
Available online 3 April 2017
1516-8484/
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http://dx.doi.org/10.1016/j.bjhh.2017.03.001