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Short communication

BCR-ABL rearrangement frequencies in chronic myeloid leukemia and acute lymphoblastic leukemia in Ecuador, South America

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Abstract Different *BCR-ABL* transcript variants occur more or less frequently, according to the leukemia type. We report the frequencies of *BCR-ABL* transcript variants studied in chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) patients in the Ecuadorian population. The frequencies found for CML patients in this study were 94.6% for the b2/a2 rearrangement and 5.4% for the b3/a2 rearrangement; whereas in ALL, all cases (100%) that presented the *BCR-ABL* rearrangement had the e1/a2 junction. Since our results differ from the frequencies previously reported, we suggest that this may be due to a different genetic background in the population involved in this study when compared to the populations analyzed in prior studies. Furthermore, we recommend a survey of the *BCR-ABL* transcript variants and their frequencies in different ethnic groups.

1. Introduction

The (9;22)(q34;q11) chromosomal translocation resulting in the *BCR-ABL* fusion gene in hematomopoietic cells establishes the diagnosis of chronic myeloid leukemia (CML) in patients with clinical features of a chronic myeloproliferative disorder; likewise, the presence of *BCR-ABL* in the blast cell population of patients with acute leukemia is generally accepted as the molecular basis of Philadelphia (Ph) positive acute lymphoblastic leukemia (ALL) or, more rarely, of acute myeloblastic leukemia (AML) [1]. The t(9;22) occurs in greater than 90% of CML and 25–30% of adult ALL [2]. In CML, the breakpoint in the *BCR* gene nearly always (95%) falls within the major breakpoint cluster region (M-*bcr*), and the resultant *BCR-ABL* mRNA molecules with a b2a2 (40%) or b3a2 (55%) junction encode a 210 kDa fusion protein ($p210^{BCR-ABL}$) [1]. In approximately 60% Ph^+ ALL cases the *BCR* breakpoint falls in the minor breakpoint cluster region (m-*bcr*) and the resulting hybrid transcript contains an e1a2 junction, which is translated into a 190 kDa fusion protein ($p190^{BCR-ABL}$), whereas in 40% of the cases the breakpoint occurs in the M-*bcr* region [1,3]. In ALL, the breakpoints in the *ABL* gene are virtually all located in the large intron region; as a consequence, the most common junction related to ALL (m-*bcr*) is the e1a2 junction (~100%) [4].

These frequencies of *BCR-ABL* mRNA transcripts in CML and ALL patients have been reported in several studies, nevertheless, there are not any studies carried on the Ecuadorian population. Due to this, the aim of this work was to study the occurrence of the most frequent *BCR-ABL* transcript variants (b3/a2, b2/a2, and e1/a2) in CML and ALL diagnosed in patients in the Ecuadorian population for a additional comparison to frequencies reported in other populations.

2. Materials and methods

The type of *BCR-ABL* rearrangement was studied in 40 CML and 49 ALL patients from 1996 to 2000. Cytogenetic analysis was performed at diagnosis in bone marrow cells immediately after collection. One hundred metaphases were analyzed for each patient after using the G-banding technique and at least five metaphases were photographed and karyotyped.

For the molecular study, total and messenger RNA was extracted from bone marrow samples, using methods previ-

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ously described [5]. Analysis by reverse transcriptase-polymerase chain reaction of the RNA of the same cells was carried using nested primers defining the junction site of the chimeric *BCR/ABL* and amplifying of the b2a2, b2a3, or e1a2 transcript variants using primers previously described [6]. Polymerase chain reaction (PCR) products were separated and visualized on a 2% ethidium bromide stained agarose gel. The chi square method was applied to compare the frequencies obtained to frequencies previously reported.

3. Results

3.1. Cytogenetics

In the 40 CML diagnosed patients 35 (87.5%) were Philadelphia positive (Ph+), whereas in 49 ALL diagnosed patients, only 6 (12.2%) were Ph+.

3.2. Molecular analysis

Among the 40 CML patients studied, 37 (92.5%) presented *BCR-ABL* rearrangements; from these, 2 (5.4%) presented the b3/a2 rearrangement, 35 (94.6%) presented the b2/a2 rearrangement, and none of them presented the e1/a2 rearrangement in the m-*bcr* region. In 49 patients diagnosed with ALL, only 21(42.8%) presented any kind of *BCR-ABL* rearrangement, from these, all of them presented the e1/a2 rearrangement in the m-*bcr* region (Table 1).

The fragment size for the PCR products were 400 bp for the b3/a2 rearrangement, 267 bp for the b2/a2 rearrangement, and 100 bp for the e1/a2 rearrangement. The average age for the CML study group was of 34 years (range 15–74 years old; 23 males and 17 females). For the ALL study group the average age was of 22.4 (range 1–24 years old; 29 males and 20 females). No differences were observed between females and males.

4. Discussion

The frequencies of *BCR-ABL* rearrangements obtained by the results reported in this study demonstrate significant statistical differences when compared to frequencies reported in related studies worldwide (Table 1). We suggest that the frequencies reported in this work and the difference observed when compared to related studies worldwide, are a consequence of different target populations. The population analyzed in prior studies involved mostly Caucasian individuals, whereas the individuals studied for this report mostly belong to the Mestizo ethnic group (a mixture of Spaniard and Amerindian) [7]. In addition, our results suggest that the different *BCR-ABL* transcript variants in Ecuador have a different behavior from that of Caucasian populations, probably due to a different genetic component in the Ecuadorian population, when compared to Caucasian populations. A geographical component concerning *BCR-ABL* rearrangements has not been reported, nevertheless, evidence for geographical variation in the Ecuadorian population as a consequence of a different genetic background when compared to Caucasian populations has been observed in studies involving other genes related to disease, such as the ΔF508 in cystic fibrosis [8].

The study of the frequencies of the different *BCR-ABL* transcript variants involved in leukemia in ethnic groups other than Caucasian may be useful to approach for a better understanding of the causes that lead to different *BCR-ABL* transcript variants in leukemia. Thus, a complete survey of the frequencies of *BCR-ABL* rearrangements in other populations and/or ethnic groups is fundamental to acknowledge this approach. The high altitude of Ecuador and Quito in particular may have a played a role in the observations reported in this article. Though it is known that hypoxia may affect chromosomal behavior (e.g., non-disjunction [9], its exact role in the changes observed by us remains to be determined.

Table 1
Genotype frequencies found in Ecuadorian population vs. frequencies previously reported

	Transcript variant	Frequencies previously reported[a]	Frequencies in Ecuadorian population
CML	b2/a2	40%	94.6%*
(*n*=37)	b3/a2	55%	5.4%*
	Others	5%	—
ALL	e1/a2	95%	100%[b]
(n=21)	Others	5%	—

Abbreviations: AML, acute myeloblastic leukemia; CML, chronic myeloid leukemia.

[a]See Melo [1] and Hermans et al. [4].

[b]Not significant.

*P=0.01.

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