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ScienceDirect
Leukemia Research 32 (2008) 1518–1522
Leukemia Research
www.elsevier.com/locate/leukres

BCR-ABL, *ETV6-RUNX1* and *E2A-PBX1*: Prevalence of the most common acute lymphoblastic leukemia fusion genes in Mexican patients

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Received 28 November 2007; received in revised form 28 November 2007; accepted 15 March 2008
Available online 5 May 2008

Abstract

This study was conducted to determine the frequency of the most common fusion genes in Mexican pediatric patients with acute lymphoblastic leukemia (ALL). Molecular analysis using RT-PCR was carried out in 53-blood samples: 52 patients with *de novo* ALL and one with relapsed ALL. The *ETV6-RUNX1* fusion was found in 7 cases (13.5%), *BCR-ABL* fusion was detected in 2 cases (3.8%), and 6 patients (11.5%) expressed the chimeric gene *E2A-PBX1*. The prevalence of *E2A-PBX1* is one of the highest that has been described thus far in childhood ALL. Furthermore, we detected both the *BCR-ABL*, and *E2A-PBX1* fusion in the relapsed patient. With regards to the immunophenotype, *ETV6-RUNX1* was expressed in both pre-B and T-cell cases, while the presence of *E2A-PBX1* and *BCR-ABL* was associated with the pre-B ALL phenotype. The prevalence of *E2A-PBX1* in Mexican pediatric cases supports the existence of ethnic differences in the frequency of molecular markers of ALL.

Keywords: Acute lymphoblastic leukemia (ALL); *BCR-ABL*; *ETV6-RUNX1*; *E2A-PBX1* fusion genes; Mexican pediatric patients

1. Introduction

A recent epidemiological study in Mexico revealed a high incidence of childhood cancer (approximately 130 cases per 1,000,000 child each year, or 4000–4500 new cases annually). The most frequent of these malignancies in Mexican children younger than 14 years of age (80.2%) is acute lymphoblastic leukemia (ALL) [1]. Cytogenetics and molecular analysis of ALL patients have identified chromosomal translocations t(12;21)/*ETV6-RUNX1*, t(9;22)/*BCR-ABL*, and t(1;19)/*E2A-PBX1* as the most common abnormalities in ALL [2], and studies in some populations have shown that these play an important role in diagnosis and prognosis [3–8]. Furthermore, these are relevant parameters for the development of more specific anti-leukemic therapies [9–11].

The *ETV6-RUNX1* or *TEL-AML1* fusion is generally associated with a favourable prognosis and very low incidence of relapse following complete remission [12,13]. The positive treatment outcome for *ETV6-RUNX1* patients has been shown to be independent of other risk factors, such as age, initial

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doi:10.1016/j.leukres.2008.03.021

leukocyte count (WBC), and hyperdiploidy, making these patients good candidates for less intensive therapy designed to reduce both early and late adverse effects [14]. The incidence of this fusion gene shows a very high range (2–39%) in ALL pediatric cases [15,16], the differences results to date are explained by true racial differences.

The *BCR-ABL* and *E2A-PBX1* fusion genes are present in 3–5% of childhood ALL [2]. Both chimeric genes have shown to be associated with adverse prognosis in patients [17,18]. Children with the *BCR-ABL* fusion are recognized to have a dismal prognosis with 5-year survival rates of 65%, even if they undergo allogeneic stem cell transplant during the first remission [19]; while the poor outcome associated with *E2A-PBX1* may be improved with more intensive chemotherapy [20].

Accordingly, accurate molecular identification of these chromosomal changes is mandatory to correct prognostic assessment and to design optimal therapy allocation, particularly because the screening the ALL translocations suggests important racial differences in the genetic background of ALL patients [6,21,22].

In the present study, we analyzed the frequency of *BCR-ABL*, *ETV6-RUNX1* and *E2A-PBX1* translocations in ALL patients, and we identified one of the highest worldwide frequencies of *E2A-PBX1* fusion in these patients.

2. Materials and methods

2.1. Patients

Fifty-two ALL untreated patients and one treated patient, all younger than 16 years of age, were subject to molecular diagnosis. ALL diagnosis was performed in the Hema/Oncology Division of the National Institute of Pediatrics using standard morphologic, cytochemical, and immunological criteria (T cells: CD3, CD5, and CD7; B cells: CD10, CD19, CD20, CD22, and HLA-DR; myeloid cells: CD13 and CD33).

2.2. Reverse transcriptase-polymerase chain reaction assay

Total RNA was extracted from mononuclear cells by the guanidium isothiocyanate technique. cDNA was synthesized from 5 mg of total RNA according to the manufacturer's instructions (Gibco). For each cDNA sample, co-amplification of β2 *microglobulin* was performed as an internal cDNA quality control.

PCR amplification of the *BCR-ABL* [23], *ETV6-RUNX1* [24] and *E2A-PBX1* [25] fusion genes were carried out using 1/10 μl of cDNA, 100 ng of each primer, 20 nM of each dNTPs, and 1 U of Taq Gold Polymerase in a final volume of 50 μl. Amplification was performed with an initial denaturing step of 95 °C for 10 min, followed by 33 cycles of 30 s denaturation at 94 °C, 1 min annealing at 60 or 58 °C (*ETV6-RUNX1* or *BCR-ABL* and *E2A-PBX1*, respectively) and 72 °C for 1 min extension; an additional extension step of 7 min for 72 °C completed the reaction.

To validate the results, three positive samples from each fusion gene were sequenced (ABI PRISM 3100 system, Applied Biosystem). Each sequence was compared to GenBank entries (http://www.ncbi.nlm.nih.gov/blast/Blast.cgi).

3. Results

Fifty-three ALL pediatric patients (one relapsed patient) were included in this study. Patients' ages ranged from 9 months to 15 years with a median of 7 years; 24 were female (45%) and 29 were male (55%). The median leukocyte count at diagnosis was 44×10^9/L. Regarding immunophenotypes, 41 patients (77.5%) were B-ALL, 5 (9.5%) T-ALL and 5 (9.5%) expressed myeloid and lymphoid markers. In two cases, immunophenotype data were not available (3.5%). Pre-B CD10+ (67%) was the most common phenotype.

Sixteen of the 53 patients (30.1%) were positive for the fusion genes. Seven (13.5%) of the 52 *de novo* cases were *ETV6-RUNX1* positive, 2 (3.8%) showed *BCR-ABL*, and 6 (11.5%) had *E2A-PBX*. In the patient with ALL relapsed (1.8%), both the *BCR-ABL* and *E2A-PBX1* transcripts were detected (Table 1).

Regarding *ETV6-RUNX1*, the clinical characteristics of the molecular subgroups are listed in Table 1. Five (5/7) cases exhibited B-cell precursor ALL CD10+, one had T-cell ALL and the last one showed both B-cell and T-cell antigen expression. The median age at diagnosis was 9.5 years. The WBC was extremely variable, ranging from 1.6×109 to 360×10^9/L leukocytes (median 79.9×10^9/L).

The *BCR-ABL* fusion gene was found in two female patients, both of which had pre-B-ALL; the WBC were 20×10^9/L and 87.7×10^9/L. *E2A-PBX1* positive patients were mostly B-precursor ALL. These patients also tended to show lower WBC at diagnosis (median 22.8×10^9/L) and only one had counts greater than 50×10^9/L.

Table 1
Clinical characteristics of the molecular subgroups

	Number (%)	M/F	Age (years)		Immunophenotype (%)			WBC ($\times 10^9$/L)	
			Range	Median	Pre-B *n* (%)	T-cell *n* (%)	Multilinage *n* (%)	Range	Median
ETV6-RUNX1	7 (13.5)	2/5	1–15	9.5	5 (9.6)	1 (1.9)	1 (1.9)	1.6–360	79.4
BCR-ABL	2 (3.8)	0/2	9–12	10.7	2 (3.8)	0	0	20–87.7	53.8
E2A-PBX1	6 (11.5)	5/1	3–13	7.5	4* (7.7)	0	0	1.4–53.2	22.8
BCR-ABL/E2A-PBX1	1 (1.8)	0/1	9	–	1	0	0	35	–
Other/none	37 (69.8)	22/15	0–15	6.7	29 (55.8)	4 (7.7)	4 (7.7)	1.6–400	35.9

M: male, F: female, WBC: white blood cell count.
* Immunophenotype from two patients were not available.

Table 2
Frequency of *E2A-PBX1* gene in childhood ALL in different studies

Region	*N*	ALL type	Frequency (%)	References
USA	68	ALL	11.8	Pui et al. [6]
Mexico	53	ALL	11.5	Current study
Austria	221	Pre-B	9.5	Izraeli et al. [17]
Spain	12	ALL	8.3	Anguita et al. [41]
Switzerland	12	ALL	8.3	Meyer-Monard et al. [7]
Italy	70	ALL	7.1	Elia et al. [42]
Taiwan	165	ALL	7	Liang et al. [43]
Spain	42	ALL	4.8	Marín et al. [44]
Arabia	92	ALL	4.3	Siraj et al. [45]
USA	642	Pre-B	3.3	Gaynon et al. [46]
China/Malay	236	ALL	3.1	Ariffin et al. [22]
USA	338	ALL	3.0	Pui et al. [6]
Brazil	145	ALL	2.7	Emerenciano et al. [39]
UK	43*	ALL	2.3	Devaraj et al. [27]
Russia	156	ALL	1.6	Nasedkina et al. [47]
India	43	ALL	0	Hill et al. [48]

* With failed or normal cytogenetics.

The pre-B immunophenotype and a high WBC were found in the patient with both *BCR-ABL* and *E2A-PBX1* fusions. This patient relapsed and died 2 years after diagnosis.

4. Discussion

We performed a screening of *BCR-ABL*, *E2A-PBX1* and *ETV6-RUNX1* translocations in a group of 53 ALL pediatric Mexican patients using RT-PCR analysis. Biological and clinical characteristics of each translocation group were according with those reported elsewhere [3–6,15–18].

We identified three *BCR-ABL* carriers, the frequency of this translocation was similar to that described in other reports, including studies in Mexico [26]. Interestingly, one of the *BCR-ABL* positive cases expressed *E2A-PBX1* gene fusion too. Cases with both translations have been rarely reported either in adults [27] or children [28]. Similar to our patient, all published cases have been described with severe clinical evolution. The existence of both fusions is possibly due to two independent events. *E2A-PBX1* translocation occurs likely as a second abnormality in the ALL, since this fusion appears later than other pediatric leukemia translocations [29]. However, we cannot confirm this hypothesis, as the occurrence of *BCR-ABL* fusion gene can also be late as a therapy-related secondary event; in fact, the t(9;22) translocation has been reported significantly associated with previous therapy with topoisomerase II inhibitors [30,31]. It is important to determine the time that these translocations occurred, in order to improve the patient management and our understanding on the biology of leukemia.

Otherwise, although the *ETV6-RUNX1* fusion gene usually occurs in patients aged between 1 and 10 years old [32], in our sample 57% (4/7) was 11 years old or older. It could be possible that the mild clinical evolution of ALL patients with that chromosomal alteration is reflected in a delay diagnosis of ALL in our population or perhaps this age discrepancy could due to ethnical differences.

In a previous study, Pérez-Vera et al. [33] studied 71 cases using fluorescence *in situ* hybridization (FISH) technique and detected only 6 carriers (8.5%) of the *ETV6-RUNX1* chimeric gene, in contrast with the 13.5% detected in this study with RT-PCR technique. Although this difference was not statistically significant, this discrepancy could be explained by technical management, because it is known that there is a good correlation between both the techniques [23,34,35].

Our results showed that the frequency of the *ETV6-RUNX1* fusion (13.5%) in Mexican ALL patients is similar to those reported in Asian (Korea: 14.1%, Japan: 13%) [36,37], Afro-American (13.2%) [6], and American-Hispanic (12.6%) [21] patients, but is lower than those found in Caucasian (25%) [2] and South American (19–23%) ALL cases [38,39]. Hispanic term describes a common language and cultural heritage rather than a race or uniform ethnicity [40], therefore, the differences among Hispanic populations could be due to they are genetically complex, comprising different proportions of native American, African and European genetic origins.

Otherwise, interestingly, a high frequency (11.5%) of the *E2A-PBX1* fusion was observed in our ALL patients, which was similar to that found in Afro-American patients (11.8%) [6]. This is one of the highest frequencies worldwide described (Table 2) [6,7,17,22,27,39,41–48].

These findings support that there are racial and geographic differences in the frequency of molecular markers of childhood ALL, including among Hispanic populations. This study illustrates the necessity to make a focused national effort to develop specific and sensible tests that could be used by clinicians as diagnostic, prognostic and treatment tools.

Conflicts of interest

None.

Acknowledgements

Silvia Jimenez gratefuls Consejo Nacional de Ciencia y Tecnologia, Mexico (CONACyT) for the scholarship (153007).

Contributions: S. Jimenez-Morales and L. Orozco are responsible for the project idea and the manuscript preparation; S. Jimenez-Morales, E. Miranda-Peralta, Y. Saldaña-Alvarez, R. Velázquez-Cruz, and J. Ramírez-Bello: realized the molecular analysis; P. Pérez-Vera, R. Paredes-Aguilera and R. Rivera-Luna: contributed with patients to this series and A. Carnevale: provided critical revision.

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