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ORIGINAL ARTICLE

Frequency of the minor BCR-ABL (*e1;a2*) transcript oncogene in a Mexican population with adult acute lymphoblastic leukaemia

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KEYWORDS
Acute lymphoblastic leukaemia;
Philadelphia chromosome;
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Abstract
Background: The minor BCR-ABL (*e1;a2*) transcript oncogene is the most common genetic alteration in adults with acute lymphoblastic leukaemia (ALL). It is associated with a poor prognosis.
Aim: To determine the frequency of minor BCR-ABL (*e1;a2*) transcript oncogene expression in ALL patients in Mexico.
Material and methods: A cohort of 411 patients with *de novo* ALL were tested for the oncogene using reverse transcription polymerase chain reaction (RT-PCR).
Results: The oncogene was found in 14% ($n = 57$) of the study population. Mean age was 29 years, and 53% were male. Median leucocyte count was 53×10^3 μl.
Conclusion: Prevalence of BCR-ABL expression by RT-PCR has not previously been reported in Mexico. Our laboratory found a higher prevalence than that reported in Latin-American series, but lower than that reported for the European population.

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PALABRAS CLAVE
Leucemia aguda linfóblastica;
Cromosoma Philadelphia;
Oncogén BCR-ABL

Frecuencia del oncogén BCR-ABL (*e1;a2*) rompimiento menor en población mexicana con leucemia linfóblastica aguda del adulto

Resumen
Introducción: El oncogén BCR-ABL (*e1;a2*) rompimiento menor constituye la alteración de mayor frecuencia en la leucemia aguda linfóblastica (LAL) del adulto. Su presencia se asocia con pronóstico adverso.
Objetivo: Determinar la frecuencia de la expresión del oncogén BCR-ABL (*e1;a2*) en portadores de LAL en México.
Material y métodos: Se estudiaron 411 pacientes con diagnóstico de LAL *de novo* para la búsqueda del oncogén mediante Reacción de cadena de polimerasa por Punto final (RT-PCR).
Resultados: El 14% ($n = 57$) de la población estudiada presentó expresión positiva. La edad promedio fue 29 años, el 53% correspondió al sexo masculino, la mediana de leucocitos fue 53×10^3 μl.
Conclusión: En México no hay reportes de la frecuencia de expresión de BCR-ABL por RT-PCR, nuestro laboratorio encontró una frecuencia mayor que lo reportado en las series Latino-Americanas y menor a lo reportado para población europea.

Introduction

Acute lymphoblastic leukaemia (ALL) is one of the most common types of cancer found in Mexico, with an average incidence of 5 cases per 100,000 inhabitants.[1] On average, 70 new cases of ALL are admitted to the Haematology Department of the General Hospital of Mexico each year. Several cytogenetic abnormalities are involved in the development of this type of cancer. The t(9;22) (q34;q11) translocation, known as the Philadelphia chromosome or *Ph* gives rise to the BCR-ABL fusion transcript. This transcript, together with abnormalities such as t(4:11), is associated with an adverse prognosis.[2] Incidence of this gene varies; reports suggest it to be 5% in the paediatric population,[3–5] and 25–50% in adults.[6–9] The minor BCR-ABL transcript codes for a chimeric protein (190 kDa) with tyrosine kinase activity, which is implicated in both the activation of various cell signalling pathways (RAS-GTP) and cell apoptosis (PI3K).[10–13] The BCR-ABL transcript has been associated with an adverse prognosis in most international studies.[14] The introduction of therapies that act on specific molecular targets, such as BCR-ABL tyrosine kinase (TK) inhibitors (*Glivec*©, Novartis) has improved overall survival rates when compared to traditional chemotherapy. There are various methods for isolating the BCR-ABL transcript, the most common being conventional karyotyping, fluorescent *in situ* hybridization (FISH), and polymerase chain reaction.[15–17] In Mexico, the Philadelphia chromosome is found in around 3.8% of the paediatric population[18] and 16.7% of adults,[19] isolated by reverse transcription polymerase chain reaction (RT-PCR) and conventional cytogenetics, respectively. In our laboratory, we amplify the BCR-ABL fusion transcript by means of RT-PCR, and perform around 60 tests on ALL patients each year. In this study, we describe the frequency of minor BCR-ABL expression in ALL patients compared with the international literature.

Materials and methods

An experimental, prospective, longitudinal study conducted from February 2000 to January 2010 in the molecular biology laboratory of the Haematology Department. The study was approved by the institution's independent ethics committees. Male and female patients with *de novo* diagnosis of ALL that agreed to give peripheral blood samples after having signed the informed consent form were included in the study. ALL was diagnosed in accordance with the French–American–British (FAB) classification systems, with the help of immunophenotyping and cytochemistry assays. Clinical data were sourced from the patient's medical records (Table 1).

Methodology

Leukaemia cells

Bone marrow samples were collected from ALL patients that had signed the informed consent form. Samples were collected in heparinized tubes containing Lymphoprep (Nycomed Pharma AS, Oslo, Norway) and centrifuged to obtain mononuclear cells.

Reverse transcription polymerase chain reaction (RT-PCR)

Total-cell RNA was isolated with Trizol (Life Technologies, Paisley, UK), and 1 μg of RNA was used for cDNA synthesis by means of MMLV (Life Technologies, Paisley, UK). The CMLB primers 5′ATCTCCACTGGCCACAAAATCATACA3′.

ALLA 5 AGATCTGGCCCAACGATGGCGAGGGC3 were used for PCR amplification. Results were validated by sequencing two positive samples (ABI PRISM 3100, Applied Biosystem, San Francisco, USA). Each cDNA was tested by PCR using primers specific for the constituent β_2 *microglobulin* gene.