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ORIGINAL ARTICLE

Association between the BCR-ABL gene transcripts and the laboratory hematological profile

Associação entre os transcritos do gene BCR-ABL e o perfil hematológico laboratorial

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KEYWORDS

BCR ABL genes
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ABSTRACT

Objective: This study describes the hematological parameters associated with the *BCR-ABL* gene transcripts in patients with chronic myeloid leukemia (CML).
Methods: We reviewed the results of 100 detectable patients for one of the *BCR-ABL* gene transcripts. The eligibility criteria were based on the presence of one of the leukemic transcripts (b2a2, b3a2, and b2a2/b3a2) and complete epidemiological and hematological data. The data were obtained from the LabMaster computerized system. The Kruskal-Wallis test was used to compare the medians of the quantitative variables between the transcripts of the *BCR-ABL* gene and the chi-square test to compare the qualitative ones, adopting the p-value with a level of significance less than or equal to 0.05.
Results: Forty-five patients (45%) presented the b2a2 transcript, 24 (24%) the b3a2 transcript and 31 (31%) a b2a2/b3a2 coexpression. Individuals who expressed the b3a2 transcript had higher leukocyte counts and platelet levels, but we found no differences compared with individuals who expressed the other transcript.
Conclusion: In this study, the BCR-ABL gene transcripts did not influence the hematological parameters of patients with CML.

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PALAVRAS-CHAVE

Leucemia mieloide crônica
Gene *BCR ABL*
Hematologia

RESUMO

Objetivo: Neste estudo, descrevemos os parâmetros hematológicos associados com os transcritos do gene *BCR-ABL* em pacientes com leucemia mieloide crônica (LMC).
Métodos: Revisamos os resultados de 100 pacientes detectáveis para um dos transcritos do gene *BCR-ABL*. Os critérios de elegibilidade foram baseados na presença de um dos transcritos leucêmicos (b2a2, b3a2 e b2a2/b3a2), dados epidemiológicos e hematológicos completos. Os dados foram obtidos do sistema informatizado LABMASTER. O teste Kruskal-Wallis foi utilizado para comparar as medianas, das variáveis quantitativas, entre os transcritos do gene *BCR-ABL* e o teste qui-quadrado para comparar as variáveis qualitativas, adotando-se o p-valor com nível de significância menor ou igual a 0,05.
Resultados: Quarenta e cinco pacientes (45%) apresentaram o transcrito b2a2, 24 (24%) o transcrito b3a2 e 31 (31%) uma coexpressão de b2a2/b3a2. Os indivíduos que expressaram o transcrito b3a2 apresentaram maior contagem de leucócitos e níveis de plaquetas, porém não encontramos diferenças, quando comparados com indivíduos que expressaram o outro transcrito.
Conclusão: Concluímos que os transcritos do gene *BCR-ABL* não têm influência sobre os parâmetros hematológicos de pacientes com LMC nesse estudo.

INTRODUCTION

Chronic Myeloid Leukemia (CML) is one of the myeloproliferative neoplasms characterized by the proliferation of progenitor cells of the myeloid lineage, increasing circulating cells of the granulocytic lineage[1]. Worldwide, the annual incidence is 1–2 cases per 100,000 individuals, and it is more common in men than in women (1.3–1.7 to 1.0), diagnosed frequently among individuals with an average age of 53 years[1]. The National Cancer Institute (INCA) estimates that for each year of the triennium 2022/2022 5,920 new cases of leukemia will be diagnosed in Brazil in men, 4,890 in women and 15% of new leukemia cases are CML. There does not seem to be a hereditary propensity or geographic or ethnic issues that predispose the onset of the disease. Exposure to ionizing radiation is the risk factor previously characterized for the disease[2]. CML is divided into three phases: chronic, accelerated, and blast. The most accepted criterion for the diagnosis of CML is the 2017 WHO classification of myeloid neoplasms and acute leukemias. The majority (85%) of patients are diagnosed during the chronic phase of the disease, the initial diagnosis being an increase in leukocytes (> $100x10^9$/L) and the pool of myeloid progenitor cells in the peripheral blood[3,4].

In the 1960s, the researchers Nowell and Hungerford discovered the Philadelphia (Ph) chromosome, which led to a better understanding of the disease pathogenesis[5]. The Philadelphia (Ph) chromosome consists of a reciprocal translocation between the long arms of chromosomes 9 and 22, resulting in the formation of a hybrid gene *BCR-ABL*, which encodes proteins with tyrosine kinase activity, responsible for activating metabolic pathways of bone marrow progenitor cells, generating an increase in the production of granulocytic cells (leukocytes, eosinophils, and basophils), abnormal interaction with the extracellular matrix of the bone marrow and resistance to cell death[6,7]. The breakpoint cluster of the ABL gene (located on chromosome 9), formed by 11 exons, occurs between exons 1a, 1b, and a2. Alternatively, the breakpoints of the BCR gene (located on chromosome 22), consisting of 23 exons, generally occur in a region between exons b1-b5, within the major region (M-BCR)[8]. In CML, the most frequent fusion transcripts of the *BCR-ABL* genes are two variants: b2a2 and b3a2. The b2a2 transcript is formed by the fusion of exon 13 of the BCR gene with exon 2 of the ABL gene, whereas the transcript b3a2 is derived from the fusion between exon 14 of the BCR gene with exon 2 of the ABL gene. Transcripts are formed as a result of alternative splicing[9].

Over the years, some studies have been conducted to understand the influence of the transcripts on hematological parameters in patients detectable with a particular type of transcript (b2a2 and/or b3a2)[10-12]. Detection of the type of transcript can be a differential in the patient's treatment. A study showed that patients who expressed the b2a2 transcript were more sensitive to the use of imatinib than those who expressed the b3a2, concluding that patients detectable for b2a2 may have a better prognosis of the disease[12]. Two studies revealed that patients who expressed the b3a2 transcript have increased platelet count[11,12].

The study described the laboratory hematological profile associated with the presence of the *BCR-ABL* gene transcripts in patients referred with CML to the Hemopa Foundation.

METHODS

Study design

This descriptive and retrospective study was conducted by collecting and analyzing epidemiological, hematological, and molecular data of 100 patients with CML from detectable samples with leukemic transcripts at the Hemopa Foundation from 2015 to 2019.

The diagnosis of CML was established based on the peripheral blood parameters and the presence of the fusion BCR-ABL gene. The clinical features concerning the white blood count, platelet, and hemoglobin levels are taken at diagnosis. The eligibility criteria were based on the availability of epidemiological, hematological, and molecular data present in the LabMaster system. Patients expressing the b2a2, b3a2, or co-expressing b2a2/b3a2 transcripts were included in the analysis. The reverse transcription polymerase chain reaction (RT-

PCR) was applied for transcript detection using cDNA, and the sample sequencing was not performed. Patients with an undetectable result for a transcript and incomplete hematological data were excluded.

Ethical considerations

This study was conducted after the approval of the Research Ethics Committee of the Ophir Loyola Hospital (CAAE 20528519.8.0000.5550, decision nr. 3.751.436) and followed the Resolution 466/2012 from the Brazilian National Council of Health and the Hong Kong principles for research integrity.

Statistics

The information in the LabMaster System was digitized to form a database in the Statistical Package for Social Sciences (SPSS), version 20 (SPSS Inc, Chicago, USA). Descriptive statistics were used to determine the absolute and relative frequencies of the qualitative variables. For quantitative variables, the mean, median, standard deviation, and minimum and maximum values were calculated according to the characteristics of the variables under study. The chi-square test was applied to compare the frequencies of the transcripts by sex. The Kruskal-Wallis test was used to compare the medians of quantitative variables (number of median leukocyte values, platelet count, basophils and eosinophils, hemoglobin levels, and age) between transcripts b2a2, b3a2, and b2a2/b3a2, adopting the p-value with a significance level less than or equal to 0.05.

RESULTS

Forty-five (45%) patients expressed the b2a2 transcript, twenty-four (24%) the b3a2 transcript, and thirty-one (31%) a coexpression of the b2a2/b3a2 transcripts. Of the 100 patients, 59% were male and 41% female (M:F ratio of 1.44: 1), with a mean age of 47.4 ± 17.2 years (18–83 years), and the median was 44 years. Table 1 summarizes the demographic and hematological characteristics of the patients studied.

The b2a2 transcript was detected in 56% (25/45) of male patients and 44% (20/45) among females, b3a2 in 63% (15/24) of males and 38% (9/24) of females, and coexpression of b2a2/b3a2 transcripts in 61% (19/31) of male and 39% (12/31) of female patients. The chi-square test showed no significant difference between sex and type of transcript (Table 2).

The hematological characteristics of the detectable patients for the *BCR-ABL* gene transcripts are shown in Table 3.

Table 1 — Description of the hematological parameters of the 100 patients.

Hematological parameters	Median (max-min)
Leukocyte count (median) [x10^3/L]	146.1 (5.42 - 639)
Basophil count (median) [%]	4.5 (0 - 18)
Eosinophil count (median) [%]	3.5 (0 - 13)
Platelet count (median) [x10^3/L]	393.5 (55.8 - 2164)
Hemoglobin measurement (median) [g/dL]	11.0 (2.09 - 16.8)

Table 2 — Distribution of BCR-ABL transcripts according to sex.

BCR-ABL Transcript	Sex		p-value*
	M	F	
b2a2 n= 45 (45%)	25	20	0.46
b3a2 n= 24 (24%)	15	9	0.22
b2a2/b3a2 n=31 (31%)	19	12	0.21

M: male, F: female. *chi-square

Table 3 — Demographic and hematological characteristics of patients according to the type of BCR-ABL transcripts.

Variables	N (b2a2/b3a2/ b2a2;b3a2)	Median (Lowest - Highest)			*p-value
		b2a2	b3a2	b2a2/b3a2	
Leukocytes (10^3/L)	100 (45/24/31)	147.0 (6.79 - 546)	187.1 (5,42 - 639)	140.4 (6.42 - 524)	0.54
Platelets (10^3/L)		322.2 (55.8 - 1324)	480 (79.6 - 1794)	397 (79.2 - 2164)	0.36
Basophils (%)		4 (0 - 18)	5 (0 - 14)	5 (1 - 13)	0.54
Eosinophils (%)		3 (0 -11)	4 (0 - 13)	3 (0 - 11)	0.95
Hemoglobin (g/dL)		11.10 (2.09 - 16.8)	10.90 (4.95 - 15.3)	11 (3,67 - 14,6)	0.94
Age (years)		47 (18 - 79)	39.5 (20 - 78)	49 (21 - 83)	0.32

N: Study population; * Kruskal-Wallis

DISCUSSION

The incidence of *BCR-ABL* gene transcripts in patients with CML varies in different studies conducted worldwide (Table 4). In European countries (England, Italy, Bulgaria), it was observed that the incidence of b3a2 transcripts was higher than that of b2a2 transcripts[13-15] and agrees with what was found in North American countries (USA and Canada)[16,17].

However, the study of the incidence of *BCR-ABL* gene transcripts in South American countries (Argentina, Ecuador, and Colombia) recorded different frequencies with a higher percentage of b2a2 transcripts compared to the b3a2 ones[18-20]. In this study, the frequency of b2a2

Table 4 — Frequency of leukemic transcripts described by studies in several countries.

Authors	N	b2a2	b3a2	b2a2/b3a2	Country
[11]	50	36%	48%	16%	Brazil
[5]	44	36%	64%	-	Tunisia
[10]	45	47%	51%	-	Syria
[13]	319	41%	46%	12%	England
[14]	493	41%	59%	-	Italy
[15]	98	45%	55%	-	Bulgaria
[12]	85	29.41%	62.3%	-	Iran
[17]	166	37%	50%	13%	Canada
[16]	372	30.2%	67.9%	-	USA
[18]	24	41.7%	37.5%	8.3%	Argentina
[19]	37	94.6%	5.4%	-	Ecuador
[20]	31	52%	32%	10%	Colombia
Present study	**100**	**45%**	**24%**	**31%**	**Brazil**

N: study population; -: not found

Table 5 — Main published studies on the association between BCR-ABL gene transcripts and laboratory data (leukocytes and platelets) from CML patients.

Studies	B2A2		B3A2		p-value leu	p-value plat
	Leu (x10³/L)	Plat (x10³/L)	Leu (x10³/L)	Plat (x10³/L)		
[10]	143.1	293	115	257	0.64	0.44
[28]	195	413	217	481	-	-
[11]	152.5	320.6	153.7	396	0.74	0.88
[12]	135.1	343.1	133.6	401.7	-	-
[15]	132.4	440.4	119.5	791.3	NS	0.007
[14]	61.6	293	52.2	401	0.17	0.25
[9]	45	297	37.7	206	-	-
[30]	87.7	65.3	296	430	<0.001	<0.001
[26]	31.0	288	28	405	0.94	0.001
[27]	162	373	120	250	-	-
[29]	110	343,3	112	431	0.70	0.09
[24]	200	413	215	481	-	-
Present study	**147**	**322.2**	**187.1**	**480**	**0.54**	**0.36**

NS: insignificant; -: not found; leu: leukocytes, Plat: platelets

and b3a2 was 45% and 24%, respectively, which conforms to studies conducted in some countries in South America[18-20], but it differs from what was observed in European countries[13-15].

These differences can be attributed to some reasons, such as the ethnicity of the study population, the sample size, and the differences in sensitivity in the methodologies used[10,21].

The present study found a frequency of 31% in the coexpression of b2a2/b3a3. This coexpression can be explained as a result of an alternative splicing mechanism instead of the presence of two different genes[10]. Relevant studies have shown that the frequency of b2a2/b3a2 was 16%, 12%, 13%, respectively[11,13,17].

Regarding the median age, studies have shown values that range from 35.3 to 60 years. In this study, the median found was 44 years. National series show that the median age is at least ten years lower (national median = 43 years) than the one found in the international literature (55 years)[22], which corroborates what was found in this study. The results can be explained by the ethnic differences[5].

Concerning sex, this study revealed a higher frequency of transcripts b2a2, b3a2, and b2a2/b3a2 in men than in women, respectively; however, there is no significant difference between the type of transcript expressed and sex. In a study developed in Iran, the b3a2 and b2a2 transcripts were found with male to female ratios of 64:36% and 40:60%[24]. In Iraq, the researchers found transcripts b3a2 and b2a2 with male to female ratios of 68:32% and 46:54%[21]. These findings showed that the b2a2 transcript is more present in females, differing from what was found in this study.

The question of how sex can influence the type of fusion of the *BCR-ABL* gene has been studied and may be related to sex hormones (testosterone and estradiol)

that affect alternative splicing in the way how *BCR-ABL* gene transcripts are formed[9,25].

The association between *BCR-ABL* gene transcripts and hematological findings has been addressed by many researchers around the world[9-12,14-15,24,26-30]. Many studies have found a significant increase in leukocytes in patients who expressed the b2a2 transcript[9-10,12,14-15,26-27,30] and a high platelet count in those with the b3a2 transcript[11-12,14-15,24,26,28-29]. Table 5 shows some publications of works that dealt with hematological data (number of leukocytes and platelet count) associated with the *BCR-ABL* gene transcripts.

The hematopoiesis process becomes unregulated when the cell signaling pathways, in addition to tyrosine kinase, are compromised, generating the condition of leukocytosis and thrombocytosis[21]. The variability in the correlation between the type of expressed transcript and hematological findings was explained by many authors[9-12,14-15,24,26-30]. The b3a2 and b2a2 transcripts differ by only 25 amino acids in the BCR region. Although BCR does not have a tyrosine kinase activity, the extra 25 residues can somehow alter the conformation of the fusion protein of the *BCR-ABL* gene, thus reducing kinase activity[17]. It was reported that patients who expressed the b2a2 transcript had a high white cell count[10,14,26-27]. However, this explanation does not confirm what was found in the present study, as b3a2 presented an increased number of leukocytes, although not significant.

A matter worth debating is the relationship between the breaking point within the major region of the *BCR-ABL* gene and the platelet count. Most studies in which the platelet count was stratified according to the type of expressed transcript revealed that, although not significant, the platelet count is higher in patients detectable for the transcript b3a2[11,14,28-29], which confirms the findings found in this study. Thus, we hypothesized that a diagnosis of thrombocytosis can be made regardless of the type of transcript for this sample. However, few studies have found an increased and statistically significant number of platelets in patients expressing the b3a2 transcript, indicating a distinct phenotype of the disease[26,30]. Regarding hemoglobin measurement, studies have shown no significant difference between the type of expressed transcript and hemoglobin dosage[11,29-30], which was also observed in this study. However, these values were below normal for individuals who expressed both transcripts. Thus, it is assumed that anemia can be present regardless of the type of transcript expressed.

CONCLUSION

Our results indicate that the b2a2 transcript was the most frequent in patients diagnosed with CML. Male patients were more prevalent in all types of transcripts. The median age indicated that patients detectable for b3a2 were younger than the other transcript groups. Patients with the b3a2 transcript showed an increase in the number of leukocytes and the platelet count, but there was no statistically significant difference. There was no correlation between the types of BCR-ABL gene transcripts and the hematological findings of patients with CML studied. More data will be needed to understand whether a type of transcript can influence laboratory hematological parameters.

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