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Case Report

Detection of T315I Mutation in Ph+ Leukemias: Clinical Insights from One Case Report

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Abstract

The reciprocal translocation between chromosomes 9 and 22, known as the Philadelphia chromosome, results in the formation of the BCR/ABL fusion gene. This genetic aberration leads to dysregulation of intracellular kinase activity. The detection of the Philadelphia chromosome is a critical component of the diagnostic evaluation of myeloproliferative neoplasms and acute lymphoid leukemia. In treatments involving tyrosine kinase inhibitors, at least 70 genetic variants have been documented as factors that induce resistance to drugs. This includes the T315I mutation, which has been identified as the most prevalent in multiple countries and is of significant clinical significance. This mutation is detected in patients who have experienced therapeutic failure, thereby significantly restricting the available treatment options. In Colombia, the prevalence of this mutation and the dynamics of its appearance are not yet fully understood. Furthermore, there is a paucity of information regarding the management and prognosis of patients who express the mutation. In this study, the genomic DNA of 26 patients with Philadelphia chromosome was analyzed using the real-time molecular technique PCR. The objective was to identify the T315I genetic variant, which was positive in two of the patients diagnosed with CML. We present a case of a 39-year-old female patient diagnosed with Ph+ CML who exhibited resistance to treatment and detection of this mutation.

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1. INTRODUCTION

Leukemias are a heterogeneous group of hematological neoplasms whose behavior and clinical manifestations depend on the affected cell line. These entities are the result of the clonal proliferation of cells of myeloid or lymphoid lineage, generally associated with genetic alterations that give rise to acute or chronic leukemic processes, each with different clinical manifestations. This clonal proliferation process involves complex evolutionary dynamics at the cellular level, as has recently been evidenced by single-cell genomic studies, which allow a better understanding of clonal evolution in different hematological neoplasms, as has been demonstrated in mantle lymphoma (1-3).

Myeloproliferative neoplasms include chronic myeloid leukemia (CML). One of its main characteristics is the predominance of mature and intermediate forms, with a small number of blasts in circulation (generally less than 2% in the chronic phase), usually with leukocytosis, thrombocytosis, anemia and basophilia. However, hematologic findings depend on the stage of the disease (1,4,5). Chronic myeloid leukemia (CML) has a biphasic progression according to the fifth edition of the WHO classification (2022), distinguishing into chronic phase (CF) and blast crisis (BC) (6).

During the progression of the disease, neoplastic cells experience a progressive loss of their ability to differentiate, resulting in an increase in blasts in the peripheral blood and bone marrow, as well as a decrease in the proliferation of other cell lineages. This process results in the onset of thrombocytopenia and anemia, which in turn generates a number of systemic clinical manifestations including, among other nonspecific signs and symptoms, unexplained fever, splenomegaly, and weight loss (7,8). This functional deterioration of malignant hematopoietic cells not only reflects an advance in the aggressiveness of the disease, but also poses significant clinical challenges in its management, especially in contexts associated with high-risk mutations such as T315I (9).

Clonal expansion in this neoplasm is due to the presence of the cytogenetic abnormality known as the Philadelphia chromosome (Ph), which is the result of a reciprocal translocation, t(9; 22)(Q34; q11.2), between the oncogene ABL1 (Abelson murine leukemia viral oncogene homolog 1) located on the long arm of chromosome 9 and the BCR (Breakpoint Cluster Region) gene located on the long arm of chromosome 22. The molecular consequence of this event is the presence of the fusion gene that codes for the chimeric protein of 210 Kd BCR-ABL1 (10-13). which has a constitutively activated tyrosine kinase activity, with the ability to inhibit apoptosis and favor the proliferation of neoplastic cells. In the development of any of the three clinical phases mentioned above, the detection of the Philadelphia chromosome is performed, this being the most important criterion for the diagnosis of CML, since it is found in more than 95% of patients with this disease (5).

On the other hand, this cytogenetic alteration can also occur in approximately 20-30% of adult patients diagnosed with acute lymphoid leukemia (ALL), while in children the frequency of the translocation decreases to 5% of cases. The World Health Organization (WHO) establishes the detection of the t(9; 22) as a criterion of poor prognosis for this entity (1,14,15). Its presence may be associated with therapeutic resistance, especially in cases with mutations such as T315I, whose characterization has allowed the development of more sensitive diagnostic tools and specific therapeutic strategies (16).

ALL is characterized by an uncontrolled proliferation of lymphoid progenitor cells. Malignant transformation can occur at various stages of maturation, as a result, neoplastic cells express a specific phenotypic variety. This phenotypic diversity is closely linked to the developmental dynamics of lymphoid progenitors, whose alterations at various stages can trigger distinctive leukemogenesis mechanisms, as has recently been examined from a cell development perspective (15,17).

The use of chemotherapeutic agents as an option for the treatment of hematological malignancies has been established as the therapy of choice to achieve complete remission. The progress in the pharmaceutical industry to reduce the negative impact on treated patients has allowed in a novel way to venture into tyrosine kinase inhibitor drugs (TKIs) as the therapeutic option of choice. Imatinib mesylate (IM) is a first-line TKI approved in 2001 by the Food and Drugs Administration (FDA) and is currently used as the first choice in the treatment of patients with BCR-ABL1-positive leukemias. In 2006 and 2007, two second-generation KTIs, Nilotinib and Dasatinib, were approved as second-line therapy (18-26).

The advent of Imatinib and more effective ITKs has led to a notable increase in remission rates in affected patients. However, an increase in the manifestation of resistance associated with various factors has been observed, such as the amplification of the BCR-ABL1 gene, clonal evolution in patients with leukemia and the presence of mutations in the BCR-ABL1 fusion gene, which is the most prevalent and significant mechanism associated with resistance. These mutations have the potential to compromise inhibitor binding to protein kinase, resulting in a significant reduction in the therapeutic efficacy of conventional

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treatments and consequently necessitating the development of personalized clinical management strategies (27,28).

At least 70-point mutations have been described that encode more than 50 different amino acids involved in resistance to treatment. Among them, the T315I mutation that is generated by an exchange of a Threonine for an Isoleucine at position 315 belonging to the ABL1 fragment of the protein. This genetic alteration becomes clinically important when detected in patients with therapeutic failure with first and second generation TKIs, leaving Ponatinib as the only treatment option with this type of medication, providing difficult management at the clinical level and greater impact on the patient's health status, due to the high risk of thrombotic effects (18,29-31).

In the scientific field, several studies carried out in Europe and the United States have revealed that the T315I mutation is one of the most prevalent genetic variants and with significant clinical implications in individuals affected by its presence. However, in Colombia there is no knowledge about the incidence of this mutation in patients with Philadelphia chromosome-positive leukemia treated with TKIs. The dynamics of the appearance of the mutation lacks conclusive data that can provide valuable information for management and prognosis (18,32).

The increase in resistance to tyrosine kinase inhibitors and the scarcity of information on the prevalence of the T315I mutation in Colombian patients with Philadelphia chromosome-positive leukemias require its systematic characterization. This need is reinforced by the fact that leukemias represent a significant proportion of cancer cases in Colombia and that certain variants with the Philadelphia chromosome, especially in the pediatric population, are notifiable diseases. Although studies have been reported on mutations in the tyrosine kinase domain of BCR-ABL1 in imatinib-resistant patients, their frequency in diverse clinical settings is still unknown. Therefore, the present study aims to evaluate the frequency of the T315I mutation in patients with Philadelphia chromosome-positive leukemia treated at the Sura Diagnostic Aids laboratory (33).

This study is original because it detects the T315I mutation early in patients with Ph+ chronic myeloid leukemia. This genetic event is associated with resistance to first- and second-generation tyrosine kinase inhibitors. Timely identification of this mutation enables therapeutic intervention based on third-generation inhibitors, such as ponatinib, or more extensive procedures, such as allogeneic bone marrow transplantation. This optimizes the clinical prognosis. Advanced molecular sequencing technologies were used to achieve high diagnostic sensitivity in detecting resistant variants, contributing to a personalized medicine approach. The analysis focuses on a population that is underrepresented in the literature, thereby enriching knowledge about the genomic distribution of CML in specific contexts. Integrating molecular findings with clinical decisions emphasizes the importance of dynamic mutational monitoring as a predictive tool for therapeutic failure and in supporting more effective, personalized clinical decisions.

2. MATERIALS AND METHODS

A total of 25 patients with a confirmed diagnosis of Chronic Myeloid Leukemia (CML) and Acute Lymphoblastic Leukemia (ALL) were included in the present study. Informed consent was applied to each of the participants in accordance with the established ethical principles, after which the corresponding sample was taken. Once the samples were collected, the process of extraction and amplification of nucleic acids began, with the aim of detecting mutations associated with therapeutic resistance in the BCR-ABL1 fusion gene, specifically the T315I mutation.

For genomic DNA extraction, the commercial mSample Preparation System DNA Abbott-Promega® kit was used, following the manufacturer's instructions. Once extracted, the DNA was quantified by spectrophotometry, using Thermo Scientific's NanoDrop™ 2000 equipment, which made it possible to determine the concentration and purity of the genetic material obtained. This stage was essential to ensure the quality of the DNA before proceeding with the amplification, thus guaranteeing the reliability of the results.

The detection of the T315I mutation was carried out using the specific amplification technique using the AmoyDx® BCR-ABL T315I Mutation Detection Kit. A mixture of 35 µL of the reagent provided by the kit was prepared for the reaction, to which 5 µL of the patient's genomic DNA was added. Simultaneously, negative and positive controls were prepared, in accordance with the recommendations of the protocol, which allowed each run to be validated and ensure accuracy in the detection of the mutation sought.

Finally, the results were interpreted according to the detection threshold values of the trial. A negative result was considered when the Ct (cycle threshold) value of the FAM channel was equal to or greater than 29. In contrast, a result was interpreted as positively strong if the Ct value was less than 26, this being the critical cut-off point defined by the manufacturer. This classification made it possible to clearly establish the presence or absence of the T315I mutation in each sample analyzed.

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3. RESULTS

The study population was composed of 25 patients diagnosed with CML and ALL, with a mean age of 49 years. Females accounted for 44% and males for 56% **(Table 1)**.
In relation to the hematological entities present in the population, 24 patients had a diagnosis of CML and only one of them had ALL; At the time of study participation, 23 patients were on treatment. Among the ITKs used, the one that predominated was Dasatinib with 41.7%, followed by Nilotinib with 20.8%, imatinib and bosutinib with 3% and ultimately the combination Imatinib/Dasatinib. 18 patients presented treatment failure and one of them intolerance. Regarding response to treatment, refractoriness to imatinib was observed in 6 patients **(Table 2)**.

Table 1. Patient characteristics (n=25).

Variable	Total
Age; Average (SD)	49 (±14.7)
Sex; n(%)	
Woman	11 (44)
Man	14 (56)

SD: Standard Deviation

The T315I mutation was positive in 2 of the patients who had been diagnosed with CML and who had also presented treatment failure, which corresponds to 8%. In the rest of the patients, it was not detectable **(Table 3)**.
The following is a list of patients with the T315I genetic variant diagnosed with CML: a 47-year-old female patient, a housewife, who consulted for asthenia, dynamia and intermittent dizziness, nasal congestion; In systems review, she presented blood pressure of 125/70 mm Hg, pulse 74 bpm, normal head and neck, soft abdomen without pain or megaly, extremities without edema, pale nasal mucosa, no turbinate hypertrophy, no rhinorrhea, no wheezing on auscultation.
Laboratory tests show thrombocytosis, leukocytosis with mild basophilia, and normal lactic dehydrogenase values. The bone marrow study is compatible with chronic myeloproliferative neoplasia without the presence of immature cells or significant increase in basophils. The bone marrow biopsy report was consistent with CML.
Flow cytometry reported granulocytes with accelerated gain of the CD11b marker. An abnormal chromosomal constitution was found in the karyotype with the presence of the Philadelphia chromosome **(Figure 1)**. The PCR result for BCR-ABL p210 transcript was 23%.

Table 2. Characteristics associated with the pathology

Variable	Total
Diagnosis; n(%)	
Acute lymphoid leukemia	1 (4)
Chronic myeloid leukemia	24 (96)
Treatment; n (%)	
No	2 (8)
Yes	23 (92)
Type of treatment; n (%)	
Dasatinib	10 (41,7)
Imatinib	3 (12,5)
Imatinib/dasatinib	1 (4,2)
Nilotinib	5 (20,8)
Bosotinib	3 (12,5)
Not applicable	2 (8,3)
Treatment failure	
No	6 (24)
Yes	18 (72)
Intolerance	1 (4)
Refractory medication; n (%)	
Bosutinib	1 (4,2)
Dasatinib	2 (8,3)
Dasatinib /Bosutinib	1 (4,2)
Imatinib	6 (25)
Imatinib/nilotinib	1 (4,2)
Imatinib/Nilotinib/Dasatinib	3 (12,5)
Imatinib/Nilotinib/Dasatinib/Bosutinib	1 (4,2)
Nilotinib	1 (4,2)

Years later, DNA amplification was requested to search for BCR ABL1-T315I mutations, which presented a positive result with a CT of 25.64.

4. DISCUSSION

This discussion section is structured in five sections that allow for a critical interpretation of the findings of the study. First, a detailed analysis of the results obtained is presented, contextualizing them according to the clinical and molecular behavior of Philadelphia positive leukemias. Next, a comparison is made with other studies, which allows us to assess the coherence of the findings with the existing literature and to recognize possible variations according to the methodological approach or the clinical context. Subsequently, the practical and medical implications derived from the results are discussed, considering their relevance for the diagnosis, treatment and follow-up of

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Table 3. Frequency of detection of the T315I genetic variant in patients with oncohematological disease.

Clinical Dx	Treatment failure	T315I	
		DETECTABLE	NOT DETECTABLE
LLA	NO	0	1
	YES	0	0
	YES (INTOLERANCE)	0	0
CML	NO	0	5
	YES	2	16
	YES (INTOLERANCE)	0	1

patients. The limitations of the study, both methodological and contextual, that condition the scope of the conclusions are also addressed. Finally, a future research agenda is proposed aimed at overcoming these limitations and delving into critical aspects that have not yet been resolved.

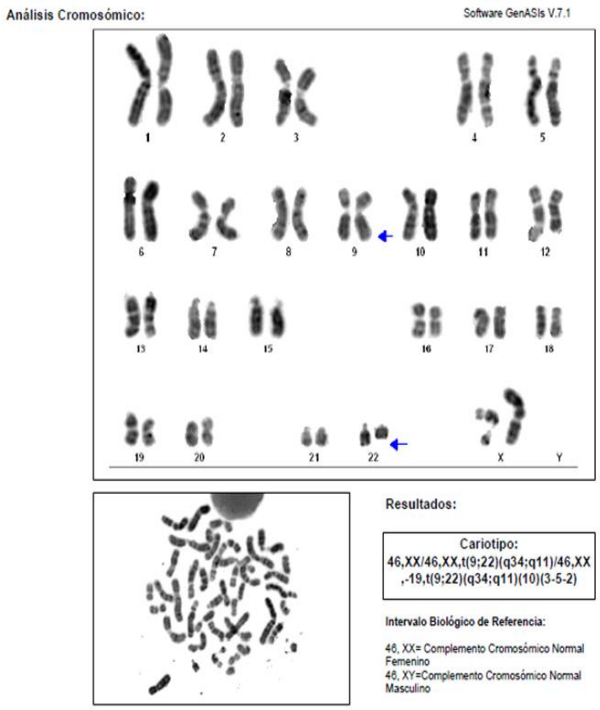

Figure 1. Karyotype Analysis.

4.1. Analysis of results

The early detection of mutations in BCR-ABL1 is becoming increasingly important in our setting due to the implications they have on the effectiveness of existing treatments for Philadelphia Chromosome-positive leukemias. Although the prevalence of these leukemias is low worldwide – 2% for CML, 25% of all cases of ALL in adults and 3% in children – in our country approximately 400 to 800 new cases of CML are diagnosed per year, while ALL ranked ninth in frequency among the eleven types of cancer prioritized by the Colombian health system. representing 1.06% of the new cases reported in both sexes and all ages (1,2,34).

The impact of mutations in the BCR-ABL1 fusion gene on treatment response makes the mutational analysis of this gene increasingly relevant. Mutational analysis of the kinase domain has shown the existence of numerous mutations that are currently considered the most common mechanism of resistance to tyrosine kinase inhibitors (TKIs) in Ph+ leukemias. In this study, the frequency found was 4 to 8% (1 to 2 positive cases out of 25 analyzed), which coincides with values reported in the literature (35,36).

The clinical case included in this study illustrates how the emergence of mutations in BCR-ABL1 can be dynamic. The patient was initially evaluated for the T315I mutation upon therapeutic failure with Imatinib, Nilotinib and Dasatinib, but this mutation was not detected in the first evaluation. However, about a year later, the mutation was identified. This variable behavior has been previously reported and may be due to treatment-induced onset. In a study by Kim WS et al., 55 patients with CML and therapeutic failure were analyzed, finding the T315I mutation in 23 patients, 11 of whom developed it after the start of treatment with ITKs. Similarly, Lee-Yung Shin et al. analyzed 202 samples from patients with CML—45 with suboptimal response and 157 with therapeutic failure—detecting mutations exclusively in the latter group, including T315I in 9 patients, all within the first 12 months after treatment (37,38).

Although a direct relationship has been sought between the administration of ITKs and the appearance of resistant mutations, the mechanism remains a source of scientific controversy. The most accepted theory posits a possible interaction of the drug with DNA as the origin of these mutations. However, a common difficulty is the lack of information on the initial mutational status of the BCR-

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ABL1 gene, which complicates the monitoring of resistance evolution. This was the case of the reported patient, in whom no mutation was documented prior to the initiation of Imatinib in 2014, four years prior to the detection of T315I (39).

Additionally, the possibility of underdiagnosed mutations should be considered, since the sample was evaluated only for T315I and a complete mutational analysis was not performed. More than 100 mutations related to resistance to ITKs have been described in the literature. Among them, the E459K mutation confers high resistance to Imatinib and intermediate resistance to Dasatinib, while others such as E255K and V299L are associated with intermediate resistance to the same drug (1,22,24).

Khorashad JS et al. describe the existence of compound mutations (two or more mutations in the same BCR-ABL1 molecule) and polyclonal mutations (different mutations in different molecules), pointing to T315I as one of the most frequent mutations in cases of compound mutations. This phenomenon could explain the initial negative result and the subsequent positive result in the patient evaluated, as different clones were evaluated at different times during the course of the disease (40).

In patients with resistant CML, in whom hematological, cytogenetic, or molecular remission is not achieved, the use of highly sensitive and specific techniques is recommended to detect malignant clones that may prevent complete remission. Direct Sanger sequencing is considered the gold standard for the detection of mutations in BCR-ABL1, although other methodologies are also accepted for their ease of implementation and diagnostic reliability. Among these are Quantitative Polymerase Chain Reaction (Q-PCR) and Digital Polymerase Chain Reaction (D-PCR), both of which have high sensitivity and specificity (1,2,41,42).

4.2. Comparison with other studies

The findings of this study are consistent with reports of mutational frequency in BCR-ABL1 in patients with Philadelphia positive leukemias. The observed prevalence of 4–8% (1–2 positive cases in 25 samples) is comparable to that reported by Breccia et al., who found 7 positive cases in a cohort of 29 patients. Similarly, Liu et al. documented a frequency of 8% in one study with a larger sample size (175 samples, 14 positive) (31,43).

Also Bahram et al. reported a prevalence of 7% when detecting mutations in 4 of the 60 patients evaluated. In contrast, Hala et al. reported the highest prevalence found in the reviewed literature (43.4%), after analyzing 99 patients, mainly new cases of CML. However, the results of this study present important methodological ambiguities, since it is not specified whether the positive cases correspond to mutations in the kinase domain of the BCR-ABL1 gene or specifically to the T315I mutation, which limits the interpretation of their findings (37,44).

Regarding the dynamics of mutation appearance, studies by Kim et al. and Lee-Yung Shin et al. reinforce the pattern observed in this research. In the first, the T315I mutation was found in patients both before and after the start of treatment with TKIs. In the second, mutations were found only in those who presented therapeutic failure, with a clear predominance in the first 12 months of treatment (38,45).

These studies, together with the clinical case described, show that mutational detection should not be limited to a single moment of treatment, but should be considered as a dynamic process, subject to clonal variability and therapeutic pressures. In addition, the literature supports the existence of compound and polyclonal mutations, such as those described by Khorashad et al., which could explain phenomena of initial negativity in the tests and subsequent positivity, as occurred in the patient in this study (40).

Finally, the literature suggests that techniques such as Q-PCR and D-PCR, although they do not replace the Sanger sequencing standard, are valid and useful diagnostic tools, particularly in contexts where diagnostic sensitivity and specificity are critical for therapeutic decision-making (41,42).

4.3. Implications

The practical implications of the findings of this study highlight the need to systematically incorporate mutational analysis of the BCR-ABL1 gene as part of the clinical follow-up of patients with Philadelphia positive leukemias, especially those who have a suboptimal response or failure to treatment with tyrosine kinase inhibitors (TKIs). Early identification of mutations associated with therapeutic resistance, such as T315I, can guide more timely and personalized clinical decisions, avoiding prolonged exposure to ineffective therapies and thus reducing the risk of disease progression.

From a medical point of view, the results support the need to use highly sensitive techniques, such as Digital Polymerase Chain Reaction (D-PCR) or deep genetic sequencing, which allow the detection of minority clones or emerging mutations before they manifest themselves clinically. This diagnostic approach improves the accuracy of treatment, and also favors the stratification of patients according to their mutational profile, which can have a direct impact on the choice of the most appropriate TKI or on the indication of alternative therapies such as allogeneic bone marrow transplantation.

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Likewise, the findings of the study show the need to develop standardized protocols for mutational monitoring in the national context, considering that in many cases the mutational status prior to the initiation of treatment is not documented. The implementation of such protocols would facilitate the detection of primary or acquired resistance and would allow a more precise characterization of therapeutic response patterns in local populations, contributing to the strengthening of public health policies aimed at rare hematological diseases.

In the educational field, these results suggest that training programs in hematology and internal medicine should include updated content on molecular biology applied to oncohematological diagnosis, as well as on the genetic bases of therapeutic resistance. Understanding the role mutations play in the evolution of Philadelphia-positive leukemias allows healthcare professionals to make more informed decisions and fosters evidence-based clinical practice.

The need to train clinical and molecular laboratory personnel in the use and interpretation of techniques such as Q-PCR, D-PCR and sequencing is also evident, with emphasis on their clinical application and the integration of the results with the therapeutic history of the patients. This training component is key in the Latin American context, where the availability of technology is not always accompanied by specialized training, limiting the diagnostic and prognostic potential of these tools.

Finally, this study can be used as reference material in continuing medical education programs, clinical update workshops or academic seminars on oncohematological diseases. Its didactic application strengthens the knowledge of professionals in training, while promoting a more critical, informed medical culture oriented to the personalization of treatment, thus improving the quality of care provided to patients with Ph+ leukemias.

5. LIMITATIONS

One of the main limitations of the present study lies in the restricted focus of the mutational analysis, since only the presence of the T315I mutation in the BCR-ABL1 gene was evaluated, without considering other potentially relevant mutations that are also associated with resistance to tyrosine kinase inhibitor treatment. This methodological decision, while responding to practical considerations and the availability of the commercial AmoyDx® kit, reduces the possibility of identifying additional mutations that could be present and that, together or in composite form, would better explain therapeutic failure in some patients.

In addition, the lack of a baseline mutational analysis prior to initiation of treatment in most of the included cases makes it impossible to clearly distinguish between primary and acquired mutations, which limits the interpretation of the dynamics of mutation emergence in relation to the therapy received. In addition, the relatively small sample size (25 patients) restricts the generalizability of the findings, especially with regard to the estimation of the frequency of mutations in the national population. Finally, although a validated methodology and adequate controls were used for the detection of T315I, more sensitive techniques such as next-generation sequencing (NGS) were not incorporated, which could have allowed a deeper characterization of the molecular variants present in the analyzed samples.

6. FUTURE RESEARCH

For future research, it is recommended to broaden the spectrum of mutations evaluated in the BCR-ABL1 fusion gene by implementing more sensitive and comprehensive sequencing techniques, such as next-generation sequencing (NGS). This approach would allow individual mutations to be detected more accurately, and to identify compound and polyclonal mutations, phenomena that have been reported in patients with resistance to tyrosine kinase inhibitors and that cannot be detected by assays targeting a single mutation such as T315I. Early identification of these variants could provide valuable information for clinical decision-making and the selection of more effective therapies from the early stages of treatment.

In addition, it is essential to include baseline mutational analyses prior to the initiation of therapy, which would allow for a clearer establishment of whether the mutations present are of a primary nature (pre-existing) or if they emerge as a result of the selective pressure of treatment. This longitudinal approach would facilitate the study of the kinetics of mutations, contributing to a better understanding of the phenomenon of resistance and the identification of specific clinical patterns associated with certain mutations. Including this type of analysis in larger cohorts would strengthen existing evidence and increase the representativeness of the findings.

Another key recommendation is to establish multicenter study designs at the national or regional level that allow data from different institutions and clinical contexts to be integrated. This strategy would favor the construction of a robust database on the prevalence and distribution of mutations in patients with Ph+ leukemias, which would serve as an input for future public health policies, molecular screening programs, and guidelines for standardized therapeutic management. Coordination with research centers and clinical laboratories could facilitate the implementation of homogeneous protocols for sample

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collection and analysis, as well as improve access to advanced diagnostic technologies.

Finally, it is suggested to incorporate an educational component aimed at both health professionals and students of biomedical sciences, focused on the importance of continuous molecular monitoring and the clinical impact of mutations in BCR-ABL1. Strengthening local capacities in clinical molecular biology is essential to ensure more precise and personalized care, as well as fostering a research culture that prioritizes genomic surveillance as a key tool in the management of leukemias. This component could be developed through continuing education programs, seminars, and clinical practices in institutions with expertise in molecular diagnostics.

7. CONCLUSION

The present study and most of the studies analyzed corroborate the low prevalence of the T315I mutation worldwide, however, each of them emphasizes the importance of detecting this and other mutations in the BCR-ABL fusion gene, especially in the kinase domain of the protein, both at the time of diagnosis of the disease and during therapy with ITKs in order to guarantee effective treatment with a lower probability of long-term failure. However, and according to the Colombian Leukemia and Lymphoma Foundation, this type of analysis is considered difficult to access in our country due to the high costs involved in the application of molecular biology techniques in the diagnosis and monitoring of low-prevalence diseases. Another variable analyzed in this study that draws attention, and that opens the doors to future research projects, is the analysis between the time of onset of symptoms, diagnosis and start of treatment, which reports that 69% of the patients with CML analyzed accessed the diagnosis two months after the onset of symptoms. The gap between the onset of symptoms and the initiation of treatment can be considered as a factor that possibly has an influence on therapeutic failure in patients with CML, in these cases, the mutational analysis of the BCR-ABL1 gene is of great relevance and represents a holistic analysis of Ph+ leukemias and helps to comply with the opportunity and choice of the appropriate treatment for each patient.

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Conflict of interest

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Ethical statement

Ethics approval and consent to participate: Informed consent was obtained from patient.

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