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Adults philadelphia-positive B–acute lymphoblastic leukemia in a moderate Health Access and Quality Index country

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ABSTRACT

Aims: To describe clinical and demographic characteristics, as well as to evaluate response and survival outcomes in Philadelphia positive (Ph+) acute lymphoblastic leukemia (ALL) Ecuadorian adults.

Methods: A retrospective, multicenter cohort study in patients aged >15 years diagnosed with Ph+ B-cell ALL was carried out. Diagnosis of B-ALL was established based on 2016 WHO classification and Ph+ mutation was confirmed in all cases.

Results: Sixty one (12.4%) were identified with Ph+ chromosome. Fifty-six were included in the analysis, 33 (58.9%) were male, and median age was 40.5 years [interquartile range (IQR): 25-51; range: 16-85]. 46 (82.1%) subjects were treated with imatinib. CR was achieved in 30 (53.6%) patients. Minimal residual disease (MRD) was reported in 13/41 (31.7%). Only 5/29 eligible patients underwent hematopoietic stem cell transplantation (HSCT). 9 (16.1) died in induction phase, all deaths were attributed to bacterial infections. Relapse was recorded in 7 (12.5%). Median overall survival (OS) for total cohort was 11 months (95% CI 8.1-13.9), with a 5-year OS of 26.8%. Imatinib 800 mg (p=0.020) and achieving CR (p=0.002) were associated with better OS.

Conclusion: Response and survival outcomes in Ecuadorian population are poorer compared to high income countries caused by high rate of induction death, low availability of MRD monitoring, lack of standardization of treatment protocols, restricted access to HSCT, and delayed initiation to TKIs therapy.

Keywords: Philadelphia positive, acute lymphoblastic leukemia, overall survival, poor outcomes, Ecuador, middle-low income countries

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is characterized by malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, peripheral blood, and extramedullary sites.[1] ALL exhibits a bimodal age distribution, with the first peak occurring around 5 years of age and the second peak approximately at 50 years of age. Although primarily considered a pediatric leukemia—accounting for 80% of cases—ALL also occurs in adults, representing 20% of cases.[2] The Philadelphia chromosome (Ph), resulting from the t(9;22) translocation is observed in approximately 20-30% of adults with ALL and is associated with a poorer prognosis compared to Ph-negative ALL.[3] The incidence of Ph-positive (Ph+) ALL increases with age, and patients often present with a particularly aggressive form of leukemia that is resistant to standard therapies, resulting in high relapse rates.[4]

The advent of tyrosine kinase inhibitors (TKIs) has significantly improved treatment response and survival outcomes in ALL, particularly in adults. Imatinib, the first TKIs approved for Ph+ ALL, when combined with intensive chemotherapy, has significantly increased complete response (CR) rates in newly diagnosed Ph+ adults ALL from below 50% in the pre-TKIs era to over 90% in post-TKIs era.[5,6] Furthermore, 5-year overall survival (OS) and disease-free survival (DFS) rates have improved from 43% to 50% and 32%

to 52%, respectively.[7-9] Second-generation TKIs, combined with either intensive or low-intensity chemotherapy, have demonstrated even higher CR rates compared to imatinib-based regimens.[10-12] Ponatinib, a third-generation TKIs, is an emerging treatment option for non-response patients.[13,14]

In Latin America, the prevalence of Ph+ ALL appears to be slightly lower than those reported in Anglo-Saxon populations. While rates of 20-30% have been observed in U.S. and European cohorts reaching up to 50% in individuals ≥50 years,[3] studies in Latin America report a prevalence ranging from 12% to 30% in multicenter and single-center analyses.[15] This discrepancy may be partially explained by the presence of Philadelphia-like ALL (Ph-like ALL), which it is not routinely assessed in many Latin American specialized centers.[16] Notably, the prevalence of Ph-like ALL appears higher in Latin America compared to other regions.[17]

Despite remarkable advances achieved in the post- TKIs era, survival and response outcomes in Latin American populations remain suboptimal compared to high-income countries.[18] Limited studies have focused specifically on the outcomes of Ph+ ALL in adults from developing countries. Most available information is derived from studies evaluating general ALL cohorts, which have reported less favorable results with TKIs treatment, particularly with imatinib.[18-20] In Ecuador, the prevalence of Ph+ ALL in adults is unknown, as well as response and OS outcomes. In this study, we conducted a multicenter analysis to evaluate the demographic and clinical characteristics, as well as treatment response, and survival outcomes in adults Ph+ ALL in Ecuador.

METHODS

Ethics

The study protocol was reviewed and approved by the Human Investigation Committee of the Technical University of Manabi (Date: 27.04.2023, Decision No: CEISH-UTM-EXT_23-01-5_BESV) and the institutional review boards of all participating centers. The study was classified as minimal risk due to its retrospective design, and requirement for informed consent was waived by the Human Investigation Committee. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This is a retrospective, multicenter cohort study aimed to describes epidemiological characteristics and analysis response and survival outcomes in patients aged >15 years diagnosed with Ph+ B-cell ALL from January 2015 to December 2023 across five reference centers in Ecuador.

Diagnosis of B-lymphoblastic leukemia was established based on the 2016 World Health Organization (WHO) classification,[21] with the presence of the Philadelphia chromosome confirmed in all cases via fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR) for BCR-ABL. Imatinib, a first-generation tyrosine kinase inhibitor (TKI), is the only agent approved for first-line therapy of Ph+ ALL in the public healthcare system in Ecuador. In private healthcare settings, dasatinib is available; however, only one patient was switched from imatinib to dasatinib due to loss of response.

The lineage of ALL was determined using immunohistochemistry and/or flow cytometry (FC). The data registry included karyotype analysis by conventional cytogenetic techniques, and central nervous system (CNS) infiltration assessed at diagnosis through FC of cerebrospinal fluid (CSF) by the presence of more than 5 leukocytes/µL or greater, or the presence of lymphoblasts in CSF was considered positive.

Risk stratification was performed according medical research council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial criteria.[22] Patients were categorized as follows: (1) high risk—defined by the presence of one or more of the following: age ≥35 years, leukocyte count ≥30.000/mm^3, or CNS infiltration at baseline; and (2) standard risk—defined by the absence of all high-risk factors.

Age Groups Definition

Subjects were classified based on the AYA classification. Groups were defined as 15-39 years (AYA) and ≥40 years old.[23]

Treatment and Response to Treatment

Treatment protocols were recorded, 5 different protocols were prescribed during study time: BFM, HyperCVAD/MTX-ARAC, PETHEMA, CALGB 8811 and GATLA (Argentine Group for the Treatment of Acute Leukemia). One palliative management were recorded in our cohort. In addition, hematopoietic stem cell transplantation (HSCT) was registered.

Several imatinib formulations, including both generic and branded versions were documented in the study. The registered brands included CLINID® (Bago Laboratory), generic imatinib from Glucosamine Laboratory, and generic imatinib from Gutierrez Laboratories. To evaluate treatment response within the imatinib cohort, data were collected about dosage, interruptions in imatinib therapy, reasons for treatment discontinuation, delays in treatment initiation, and the overall duration of imatinib administration.

Response and survival outcomes were assessed using the following criteria: (1) post-induction CR, (2) post-induction minimal residual disease (MRD), (3) induction mortality rate (IMR), (4) relapse, (5) relapse-free survival (RFS), (6) 5-year OS, (7) median OS, and (8) event-free survival (EFS). (9) disease-free survival (DFS).

CR was evaluated based on the Cheson criteria, defined as the absence of extramedullary disease, no detectable peripheral blasts, bone marrow blasts <5%, neutrophil count ≥1.5×10^9/L, and platelet count ≥100×10^9/L; any deviation from these criteria was classified as non-response (NR).[24] MRD was assessed by FC and defined as <0.01%, corresponding to fewer than 1 leukemic cell per 10.000 mononuclear cells in a bone marrow sample.[25]

IMR was defined as the proportion of patients undergoing induction chemotherapy who died during the induction phase due to treatment-related complications or toxicities, excluding deaths caused by disease progression or unrelated factors. Relapse was defined in CR patients as ≥5% blasts in the bone marrow, the presence of blasts in the peripheral blood, or evidence of extramedullary disease, according to the consensus of the European Working Group for Adult ALL (EWALL).[26]

RFS was defined as the time from achieving CR to relapse, death, or last follow-up, whichever occurred first. OS was evaluated as the time from diagnosis to death or last follow-up, with 5-year OS and median OS specifically reported. EFS was defined as the time from diagnosis to treatment failure, relapse, death, or last follow-up, whichever occurred first. DFS was defined as the time from diagnosis to recurrence of disease, development of a second primary cancer, death from any cause, or last follow-up, whichever occurred first.

Statistical Analysis

Study variables were summarized as means or medians, depending on their distribution, while categorical variables were presented as frequencies or percentages. Pairwise comparisons between subject groups were conducted using the Chi-square test, Fisher's exact test, or Mann-Whitney U test, depending on the data distribution and sample size.

Optimal cutoff values for age, delay in treatment initiation, and duration of imatinib therapy were determined using receiver operating characteristic (ROC) curve analysis and the corrected Akaike Information Criterion (cAIC) to evaluate response and survival outcomes.[27,28]

Survival analysis was performed using the Kaplan–Meier method to estimate 5-year OS and median OS, with comparisons between groups assessed using the log-rank test. Factors associated with treatment outcomes, including CR and IMR were evaluated using logistic regression. Associations between prognostic factors were analyzed through logistic regression for response outcomes. Relapse was assessed using the cumulative incidence function with death as a competing event, and the Fine-Gray model was employed to identify risk factors significantly associated with relapse risk.

MRD was included solely in the descriptive results due to the limited number of patients evaluated. For the analysis of treatment outcomes, only the BFM and HyperCVAD protocols were included in the assessment of treatment response and survival outcomes. Other protocols containing asparaginase (pediatric protocols) were aggregated with BFM as pediatric protocols for the purpose of survival analysis. A comparison of treatment outcomes between Imatinib doses of 400 mg and 800 mg was included in the analysis; 600 mg dose was not analyzed due to a lack of representative sample. Subgroup analyses within groups were not conducted because of inadequate sample sizes.

Statistical analyses were performed using SPSS Statistics for Windows, version 25.0 (IBM, 2015), and R software, version 4.4.2 (R Foundation for Statistical Computing, www.r-project.org). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 653 adult patients were diagnosed with B-ALL during the study period, of whom 61 (12.4%) were identified with Ph+ chromosome. Five Ph+ subjects were excluded due to missing data on imatinib use, 56 Phi+ adult ALL subjects were included in the analysis. Of the 56 subjects, 33 (58.9%) were male, and median age was 40.5 years [interquartile range (IQR): 25–51; range: 16–85], and 25 (44.6%) belonged to the adolescent and young adult (AYA) group. Fifty-five individuals received chemotherapy, most frequent treatment protocols were HyperCVAD and BFM with 25 (44.5%) and 22 (40%), respectively. 47 (83.9%) patients were classified in high risk group. Normal karyotype was observed in 25 (44.6%) of those evaluated. CNS infiltration was assessed in 50 (89.3%) individuals, with blast cells confirmed in 9 (18%).

A detailed summary of the cohort's clinical and demographic characteristics is presented in **Table 1**.

Imatinib Therapy

46 (82.1%) subjects were treated with Imatinib plus conventional chemotherapy, 25 (54.3%), 6 (13%), and 15 (32.6%) were on dosage of 400 mg, 600 mg and 800 mg, respectively. 16 suspended Imatinib treatment during follow-up period, these were the recorded causes of suspension: septic shock (n=5), loss of response (n=5), lack of adherence (n=3), neutropenia (n=1), renal failure (n=1), non-availability and/or financial constraints (n=1). The median weeks of treatment with Imatinib was 29 [(IQR 7.5-42.5), range 0-105], and the median days of delay to initiate imatinib was 19 [(IQR 9-36), range 0 -363]. Only 9 subject initiated Imatinib therapy within 7 days after diagnose. The median weeks of treatment before loss of response was 13 weeks.

The median follow-up for the cohort was 31.0 months (95% CI: 21.0–60.0), with a minimum of 6 months and a maximum of 90 months.

Response to Treatment

CR was achieved in 30 (53.6%) patients. MRD negativity was achieved in 13 of 41 (31.7%) patients. Male gender in imatinib group was associated to better CR [OR 4 (95% CI 1.6-12.3) p=0.004].

Mortality

Nine (16.1%) died during the induction phase, all deaths were caused by bacterial infections (septic shock). Among protocols, induction deaths were 7 (31.8%), 1 (4%) for BFM, HyperCVAD, respectively.

Relapse

Relapse was recorded in 7 (12.5%). Median and 5-year RFS was 22 months (95% CI 10-no reached) and 37%, respectively. Cumulative incidence for relapse (CIR), considering death as a competing event, was 22.1% (95% CI 3.5–40.8), while the non-relapse mortality (NRM) throughout the follow-up was 40.8 % (95% CI 16.2–65.5), **Figure 1**.

Hematopoietic Stem Cell Transplantation (HSCT)

Only 5 of 29 eligible patients underwent HSCT, transplanted patients reached a median OS 29 months and a 5-years OS of 30%. Relapse was recorded in 1 (20%) of transplanted subject.

Table 1. Baseline characteristics of Phi+ B-ALL patients at diagnosis.*

Factors	Use of imatinib (n=56)			
	No imatinib (n=10)	Imatinib therapy (n=46)		
	n (%)	400 mg (n=25)	600 mg (n=6)	800 mg (n=15)
Median age [IQR (range)]	41 [27-64.75 (16-85)]	41.50 [24.25-51 (18-76)]		
AYA classification				
<40-year old	5 (50)	11 (44)	2 (33.3)	7 (46.6)
>=40-year old	5 (50)	14 (56)	4 (66.6)	8 (53.3)
Sex				
Male	8 (80)	12 (48)	3 (50)	10 (66.6)
Female	2 (20)	13 (52)	3 (50)	5 (33.3)
Leukocytes count				
<30.000mm^3	6 (60)	9 (36)	2 (33.3)	10 (66.6)
30.000mm^3-100.000mm^3	4 (40)	14 (56)	0	2 (13.3)
>=100.000mm^3	0	2 (8)	4 (66.6)	3 (20)
Risk group				
Standard	3 (30)	1 (4)	1 (16.6)	3 (20)
High	6 (60)	24 (96)	5 (83.3)	12 (80)
Karyotype				
Normal	5 (50)	18 (72)	1 (16.6)	1 (6.6)
Others CGT abnormalities	0	5 (20)	2 (33.3)	5 (33.3)
Too few metaphases	2 (20)	0	0	2 (13.3)
Hyperdiploid	1 (10)	0	2 (33.3)	1 (6.6)
Low hypodiploid	0	1 (4)	1 (16.6)	0
Complex	1 (10)	0	0	1 (6.6)
CNS infiltration				
No	7 (80)	19 (76)	3 (50)	12 (80)
Yes	1 (10)	3 (12)	2 (33.3)	3 (20)
Treatment protocols				
BFM	6 (60)	16 (64)	0	0
HyperCVAD	4 (40)	2 (8)	4 (66.6)	15 (100)
PETHEMA	0	3 (12)	2 (33.3)	0
CALGB 881	0	2 (8)	0	0
GATLA	0	1 (4)	0	0
HSCT				
No	1 (10)	11 (44)	2 (33.3)	10 (66.6)
Yes	1 (10)	1 (4)	2 (33.3)	1 (6.6)

IQR: Interquartile range, AYA: Adolescent and young adult, CNS: Central nervous system, GATLA: Grupo Argentino de Tratamiento de la Leucemia Aguda, HSCT: Hematopoietic stem cell transplantation.
*Percentages of every factor are within non imatinib group and imatinib's subgroup.

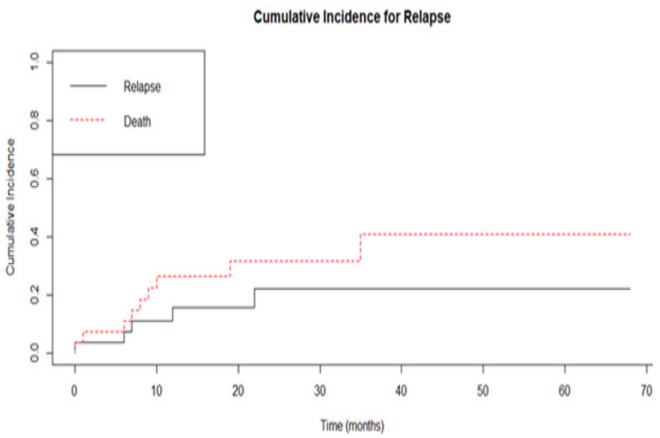

Figure 1. Cumulative incidence function. Cumulative incidence curves for relapse and non-relapse mortality (NRM)

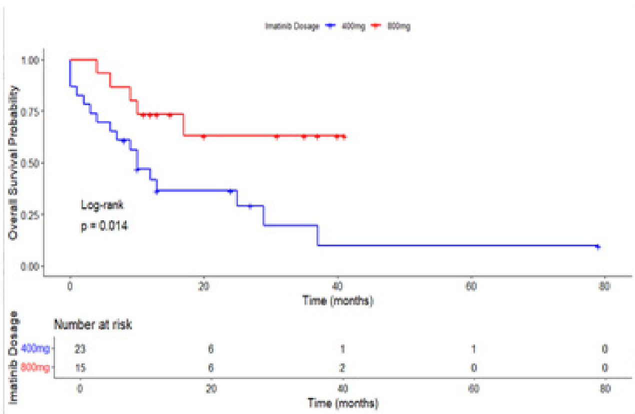

Figure 2. Kaplan–Meier curve. Overall survival (OS) in 800 mg vs 400 mg imatinib dosage

Survival Analysis

Median OS for total cohort was 11 months (95% CI 8.1-13.9), with a 5-year OS of 26.8%. OS univariate analysis showed statistically significant differences for: Imatinib dosage, 400mg dosage 5-years OS was 9.7% vs 62.9% on 800 mg (**Figure 2**). Median and 5-year DFS for total cohort was 19 months (95% CI 10-no reached) and 36.9%, respectively. Median and 5-year EFS for total cohort was 25 months (95% CI 10-no reached) and 34.5%, respectively. See **Table 2** for factors influencing DFS and EFS.

In a univariate analysis significant differences in OS were observed for the following factors: imatinib 800 mg vs imatinib 400 mg; p=0.020 and for subject who achieved CR, p=0.002. Details of the univariate survival analysis are expressed in **Table 3**.

DISCUSSION

TKI drugs has drastically shifted the management of Ph+ ALL subjects. Doubtlessly, incorporation of TKIs evolved the landscape of leukemia. Improvement in response and survival parameters were first observed in chronic myeloid leukemia,[29] and these benefits were subsequently trialed

Table 2. DFS and EFS univariate analysis of patients in Phi+ according to group

Factor	Median DFS	5-year OS	OS p value	Median EFS	5-year EFS	EFS p value
AYA group						
<40-years old	NA	63.5%	p=0.581	NA	62.3%	p=0.361
>=40-year old	20 (95% CI:5.5-39.5)	31.6%		13 (95% CI:5.5-44.4)	28.1%	
Imatinib						
Yes	23 (95% CI:2.9-43.1)	39.1%	p=0.058	25 (95% CI:0.3-49.6)	36.9%	p=0.207
No	6 (95% CI: NA)	0%		9 (95%CI: NA)	0%	
Sex						
Male	20 (95% CI:5.2-34.7)	39.9%	p= 0.932	25 (95% CI:6.5-43.3)	39.7%	p=0.703
Female	35 (95% CI: NA)	0%		10 (95% CI:0-25.5)	0%	
Risk group						
High	23 (95% CI:1.9-44)	35.5%	p=0.934	25 (95% CI:2.4-47.6)	33.3%	p=0.847
Standard	10 (95% CI: NA)	50%		11 (95% CI: NA)	50%	
Complete response						
No	NA	NA%	p=NA	0 (95% CI: NA)	0%	p<0.001
Yes	23 (95% CI:0.-46.2)	37.7%		25 (95% CI:0.6-49.3)	38.1%	
CNS infiltration at diagnosis						
No	23 (95% CI:9.8-14.1)	30.8%	p=0.432	25 (95% CI:0.6-49.3)	29%	p=0.383
Yes	NA	60%		NA	60%	
# of leukocytes/mm3 at debut						
<30.000	23 (95% CI: NA)	50%	p=0.805	25 (95% CI:0-50.8)	44.1%	p=0.932
30.000-<100.000	35 (95% CI:9.7-60.2)	25.7%		25 (95% CI:1.3-48.6)	25%	
>=100.000	12 (95% CI: 2.4-21.6)	33.3%		13 (95% CI:3.39-22.6)	33.3%	
Pediatric protocols						
No	NA	57.9%	p=0.101	NA	57.9%	p=0.038
Yes	10 (95% CI:94.5-15.5)	15%		10 (95% CI:6.7-13.2)	14%	

AYA: Adolescent and young adult, OR: Overall survival, DFS: Disease free survival, EFS: Event-free survival, MRD: Minimal residual disease, CNS: Central nervous system, NA: No reached values caused by disproportionate sample representation within groups

Table 3. Univariate analysis of Phi+ adults ALL patients treated with imatinib

Factor	n (%)	Median OS in months	5 year OS	p value
AYA group				
15-39 years	20 (43.5)	17 (95% CI:9-NA)	48.6%	p=0.225
≥40 years	26 (56.5)	10 (95% CI:7.6-12.4)	20.6%	
Sex				
Female	21 (45.7)	10 (95% CI:5.7-14.2)	12.8%	p= 0.055
Male	25 (54.3)	25 (95% CI:5.8-44.2)	39.2%	
Imatinib dosage				
400 mg	25 (62.5)	10 (95% CI:7.8-14.2)	9.7%	p=0.020
800 mg	15 (37.5)	NA	62.9%	
Risk group				
High	41 (89.1%)	12 (95% CI:6.6-17.4)	25.4%	p=0.336
Standard	5 (10.9%)	NA	60%	
Pediatric protocols				
Yes	24 (53.3%)	11 (95% CI:8.9-13)	15.7%	p=0.078
No	21 (46.7%)	25 (95% CI:7.6-42.4)	44.9%	
CR				
No	12 (30.8)	6 (95% CI:3-NA)	39%	p=0.002
Yes	27 (69.2)	29 (95% CI:11-NA)	15%	
CNS infiltration at diagnosis				
No	34 (80.9)	14 (95% CI:0-30.1)	29.6%	p=0.761
Yes	8 (19.1)	17 (95% CI:2.7-31.3)	33.3%	
# of leukocytes/mm^3 at debut				
<30.000	21 (45.6)	12 (95% CI:0-40.7)	41.6%	p=0.068
30.000-100.000	16 (34.7)	25 (95% CI:2.5-47.4)	28.9%	
>100.000	9 (19.7)	8 (95% CI:2.2-13.8)	11.1%	

AYA: Adolescent and young adult, CR: Complete response, CNS: Central nervous system, NA: No reached

in others leukemia diseases.[4] Although the advent of these new therapies brought a dramatic enhancement in adults-ALL,[8] however, the underscored subgroup of individuals with this particular mutation (BCR-ABL) exhibit substantial geographical variations in terms of in response and survival outcomes when results are assessed in populations outside US and Western European countries, especially outside prospective clinical trials.[19,30] This geographical variation notoriously applies to Latin American, a region in which the scarce epidemiological studies reported poorer response and survival outcomes.

Although, the entire Ph+ adults ALL landscape changed with the entrance on scene of TKIs, this genetic mutation once considered a poor prognostic marker, undergone a radical switch since the arrival of imatinib. Unfortunately, these benefits are not observed when assessing cohorts from low- and middle-income countries. Our results are consistent with this concerning situation, reflecting poorer outcomes, but also different epidemiological and cytogenetic characteristics. Demographical aspects of our cohort revealed a younger onset at diagnosis (median 40.5 years) compared to >50 years in most of international cohorts.[3,31,32] Although, studies from lower-middle-income economies also reported a younger onset at diagnose.[18,33] A male predominance was seen in our cohort but, gender variations are observed across studies, any defined gender prevalence has not been established.[18,33,34]

Importantly, prevalence of Philadelphia chromosome in our cohort was 12.4%, a result lower than those reported in most studies, between 20-30%.[3,18,22,34] Differences in prevalence for t(9;22)/BCR-ABL1translocation is not rare, and variations across different regions has been reported. Values above 30% are more commons in Anglo-Saxons heritage regions.[31,35] Otherwise, some studies from Hispanic ascending countries have reported a Ph+ prevalence inferior than 20%.[15,36] Prevalence of this relevant mutation differs by age, race and ethnicity.[37] Some key aspects of this variability may be marked by the presence of mutations more prevalent in Latin America, highlighting the case of Philadelphia-like chromosome mutation, which has been observed to be more prevalent in black and Hispanic populations.[17,38] In the long term, assessment of the presence of this mutation and others through new and more advanced techniques such as next sequence generation (NSG) could eventually impact the management of ALL in Hispanic populations.

Response outcomes in our cohort were 53.6% and 31.7% for CR and MRD negativity, respectively. These results are well below (90% in CR and 70% in MRD) than those reported in imatinib clinical trials from high-income countries.[5,39-41] Survival outcomes were also inferior, 5-years OS and DFS were 26.8% and 36.9%, respectively. A real-world multicenter cohort from Brazil reported similar results, 4-year OS and RFS were 25.5% (95% CI 18.4-35.4) and 24.2% (95% CI 17.3-34), respectively. Nevertheless, significant differences are observed when comparing to high-income cohorts, with values of OS and DFS between 30-50%.[3] These results evidence worse outcomes in Latin American populations compared with those from the United States and Western Europe, highlighting the influence of socioeconomic factors on survival outcomes.

A significant difference in induction deaths and OS was observed in patients treated with Hyper-CVAD, this effect was attribute to high doses of imatinib used in Hyper-CVAD compared to other regimens. Use of high dosage of imatinib combined with reduced-intensity chemotherapy versus standard Imatinib/HyperCVAD has been associated to fewer induction deaths and higher rate of CR favored to former group.[42] These data warranted that treatment protocols including high dose of imatinib (800 mg daily) may be considered a feasible treatment option in Ph+ ALL patients from middle-lower income countries like Ecuador, in which high induction death rates and lower OS are observed. Additionally, Imatinib high doses plus steroids has been associated to higher complete remission rate and prolonged survival in elderly population without additional chemotherapy,[43] a notable treatment approach for a age population highly sensitive to chemotherapy-related toxicity.

Importantly, the incorporation of TKIs into treatment regimens has allowed for a significant reduction in the intensity of chemotherapy, thereby lowering treatment-related toxicity and decreasing induction mortality. This strategy is particularly effective in older patients, who are especially vulnerable to the adverse effects of intensive chemotherapy.[44-46] As a result, treatment paradigms in high-income countries are increasingly shifting toward reduced-intensity or even chemotherapy-free approaches, facilitated by the use of newer agents such as blinatumomab and more potent second- and third-generation TKIs, including ponatinib. These advances help to explain the substantial survival differences observed between our population and those reported in the U.S. and Europe.

Limitations

This study is not exempt to limitations, starting by inherent obstacles owns to retrospective research works, which prevent data collection related to treatment protocols being standardized recorded. Furthermore, heterogeneity of chemotherapy protocols added to the diverse formulations of imatinib used in this cohort, some of these brands without studies of equivalence or observation trials that attest to their effectiveness, limit to accurately interpret these results and elucidate the total effect attributable to imatinib. Another important aspect is lack of HSCT availability; a reduced number of patients did benefit from HSCT in this study, negatively impacting survival outcomes.

In spite of that MRD assessment was not available to evaluate all subject of this cohort, MRD has become the most precisely monitoring stratification tool in ALL, and also allow to promptly evaluate early response, helping to timely consideration of novel agents and need to switch TKIs during the follow-up period, as well as assisting to detect hematologic relapses earlier. Routinely MRD assessment is essential to achieve improvements in the management of ALL.

However, beyond these limitations, a significant improvement in response and survival outcomes in our cohort has been observed in Imatinib group, highlighting the fact that even in precarious conditions, as presented in this cohort, use of TKIs in adults Phi+ ALL represent the standard care of treatment to improve outcomes in Phi+ ALL in middle-lower income countries like Ecuador. This research is added to those few studies coming from developing countries, helping to elucidate the reality and factors associated to poor outcomes in these geographically, economically, and ethnically diverse populations.

CONCLUSION

Although, advent of TKIs totally changed landscape management of Phi+ adult ALL patients, yielding to better response and survival outcomes. However, populations from middle-lower incomes countries like Ecuador still face poor outcomes, most in part due to high rate of induction death, low availability of MRD monitoring, lack of standardization of treatment protocols, restricted access to HSCT, and delayed initiation to TKIs therapy. Breaking these barriers through public health policies as well as expand access to new groundbreaking therapies represent a major goal to achieve and improve outcomes in Ecuador, likewise other middle-lower incomes countries dealing with same adversities.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was reviewed and approved by the Human Investigation Committee of the Technical University of Manabi (Date: 27.04.2023, Decision No: CEISH-UTM-EXT_23-01-5_BESV).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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