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– ORIGINAL PAPERS –

Real-World Outcomes of Patients Diagnosed with Philadelphia-Positive Acute Lymphoblastic Leukemia: A Single-Center Experience Over Four Years

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Abstract

Acute lymphoblastic leukemia (ALL) is a subtype of hematological malignancy characterized by uncontrolled proliferation of immature lymphoid precursor cells. This study presents a retrospective analysis of a cohort of patients diagnosed with Philadelphia-positive acute lymphoblastic leukemia between 2020 and 2024 at the Fundeni Clinical Institute. This study was conducted retrospectively at a single center, utilizing data extracted from the electronic medical records maintained by the hospital. Among the 203 individuals diagnosed with ALL at our institution, 47 patients were identified as harboring the BCR::ABL fusion gene and were subsequently included in the analysis.

The median age of the study cohort was 49 years (range: 18–78 years), with a female predominance (female-to-male ratio: 1.28:1). Regarding therapeutic strategies, 57.4% of patients received induction therapy based on the GRAAPH 2005 (Group for Research on Adult Acute Lymphoblastic Leukemia Philadelphia-positive) protocol, which combines low-intensity chemotherapy with tyrosine kinase inhibitors. Post-induction, 76.6% of patients achieved complete morphological remission. Over a follow-up period of 54 months, 51% of patients experienced at least one relapse. Notably, mutations in the ABL1 kinase domain were detected in seven of the relapsed cases.

In accordance with current national protocols, the therapeutic approach for patients with relapsed or refractory (R/R) disease includes chemotherapy in combination with second- or third-generation tyrosine kinase inhibitors (TKIs), such as Dasatinib or Ponatinib. In recent years, Blinatumomab and Inotuzumab-Ozogamicin have been approved in our country as monotherapy options for the treatment of Philadelphia-positive ALL in patients who have progressed beyond second-line therapy.

The results of this real-world study align with existing literature regarding the efficacy of TKI-based therapies in combination with low-dose chemotherapy. Ph + R/R ALL remains a therapeutic challenge, since it is associated with resistant mutations in the BCR-ABL tyrosine kinase domain and a reduced survival rate.

Keywords: *Philadelphia Positive Acute Lymphoblastic Leukemia, Tyrosine Kinase Inhibitors, Real-World Experience*

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Introduction

Philadelphia positive Acute Lymphoblastic Leukemia is one of the most frequent type of acute lymphoblastic leukemia in adults. While ALL predominantly occurs in pediatric populations, it exhibits a more aggressive clinical course when diagnosed in adults. The incidence of adult ALL peaks notably around the fifth decade of life (1).

ALL can be classified based on immunophenotypic characteristics into B-lineage precursor and T-lineage precursor subtypes. From a cytogenetic and molecular standpoint, ALL is further categorized into Philadelphia chromosome-positive (Ph+ ALL) and Philadelphia chromosome-negative (Ph- ALL), with the latter frequently exhibiting other molecular aberrations. This article focuses specifically on acute lymphoblastic leukemia characterized by the presence of the BCR::ABL1 fusion gene, which defines the Philadelphia-positive subtype (2).

The introduction of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of Ph+ ALL, establishing them as the standard of care and significantly enhancing treatment response rates in affected patients (3). Moreover, evidence from the scientific literature highlights improved event-free survival rates in patients receiving TKI-based therapies. Current research efforts are focused on minimizing the role of chemotherapy in treatment regimens for this pathology. Ongoing studies are actively investigating the efficacy of combining monoclonal antibodies with TKIs, aiming to develop more targeted and less toxic therapeutic approaches (4); (5).

Material and methods

Our retrospective, unicentric study included 47 adult patients (over 18 years of age) diagnosed with Philadelphia positive ALL between 1st of January 2020 and 15th of July 2024. Patients included in the study constitute a heterogeneous group, which impacts the statistics. Comorbidities, age, and treatment-related risk factors have influenced therapeutic decisions. Baseline and clinical characteristics, including age, gender, salvage therapies and the procedure of allogeneic hematopoietic stem cell transplantation (allo-HSCT), were systematically collected. For some patients, an aggressive treatment approach was pursued, followed by hematopoietic stem cell transplantation, while for others, the primary objective was to extend survival and manage both the complications of the disease itself and those resulting from the treatment.

The diagnosis of Ph positive ALL was confirmed by the presence of t(9;22) in cytogenetic analysis or fluorescence in situ hybridization, and the positivity of BCR::ABL1 fusion gene in reverse-transcriptase polymerase chain reaction (RT-PCR). Measurable residual disease (MRD) was monitored using quantitative RT-PCR and flow cytometry. In patients with relapsed/refractory disease, ABL1 mutations were assessed through Sanger sequencing to identify potential resistance mechanisms.

This retrospective, single-center study used data from the Fundeni Clinical Institute's electronic medical records. Absolute numbers and percentages were used for categorical variables. We considered indicators of central tendency (mean, median), dispersion indicators (range), associations of some variables and the Kaplan Meyer survival function, which were illustrated in plots and through tables. Statistical analysis was performed using IBM SPSS software.

Results

The data of 203 patients was considered, however only 47 were eligible for the analysis, being tested positive for Philadelphia chromosome. The demographic profile of the study group is characterized by a median age of 49 years (range 18-78) (Fig. 1). The eligible patients consisted of 20 males and 27 females, resulting in a female to male gender ratio of 1.28:1 (Fig. 2).

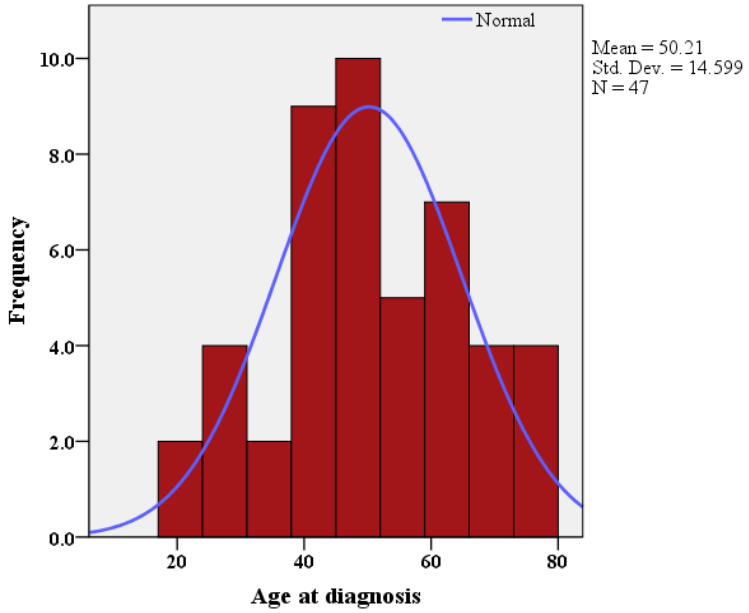

Figure 1 *Distribution of patients' ages at disease onset*

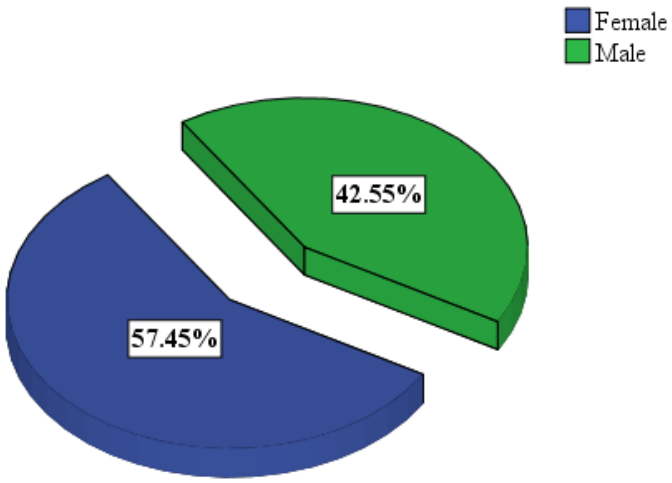

Figure 2 *Gender of the patients by percentage*

The complete blood count revealed a white blood cell count exceeding 90,000/mm³ in the majority of patients (Fig. 3). All 203 patients underwent nested polymerase chain reaction (PCR) testing for the detection of BCR::ABL1 fusion transcripts, specifically p190 and p210 isoforms. Among these, the BCR::ABL1 fusion was identified in 47 patients. Of those with a detectable fusion, more than half exhibited the p190 isoform (n=57, 45%), while some had the p210 isoform (n=27, 67%), and a subset presented with both isoforms (n=14, 54%) (Fig. 4).

As illustrated in Figure 5, fluorescence in situ hybridization (FISH) and conventional cytogenetic analysis were employed to identify the presence of the t(9;22) translocation. Among the cohort, a subset of patients demonstrated a complex karyotype (n=10), while others exhibited additional structural chromosomal abnormalities (n=7).

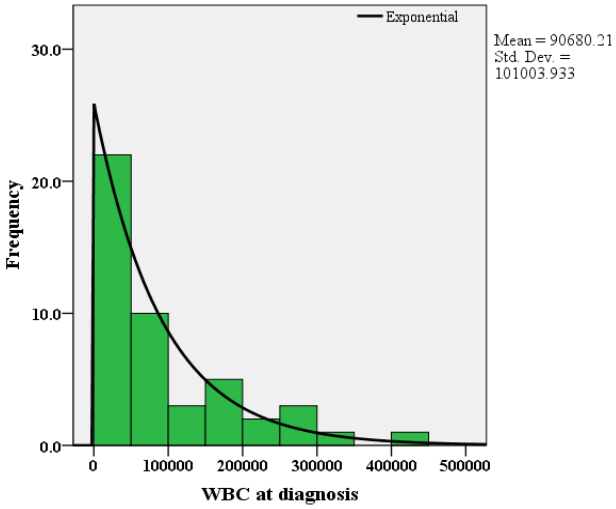

Figure 3 *Distribution of the number of the patient's white blood cells at the onset of the disease*

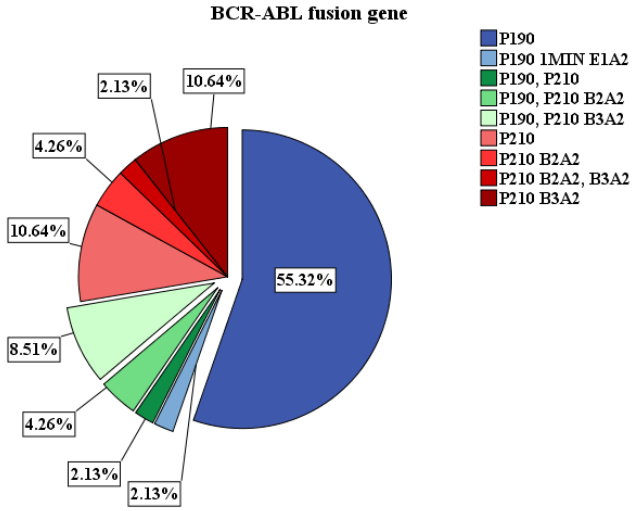

Figure 4 *Percentage of detected BCR-ABL fusion gene; Method: nested PCR (sensitivity of 10-6)*

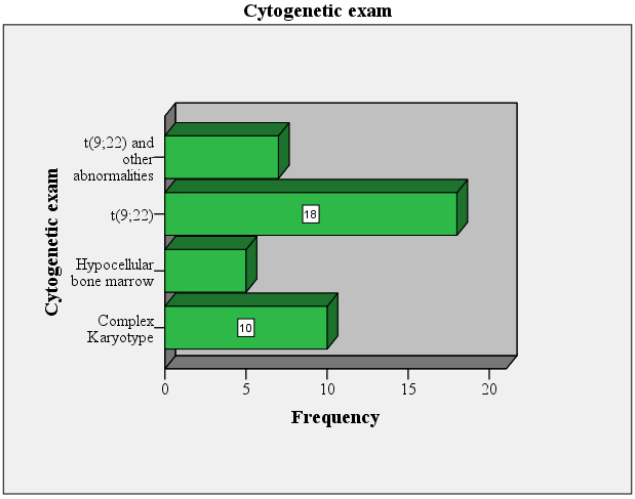

Figure 5 *Karyotype of the patients*

The main therapeutic regimen, utilized for 57.4% of patients, was GRAAPH 2005, while alternative protocols included EWALL, Hyper-CVAD, PETHEMA, among others. Protocol selection was guided by factors such as patient age, comorbidities, and associated risk factors. Consolidation therapy consisted of Hyper-CVAD combined with a tyrosine kinase inhibitor in 23.4% of cases, whereas the GRAAPH protocol was used in 38.30% of patients.

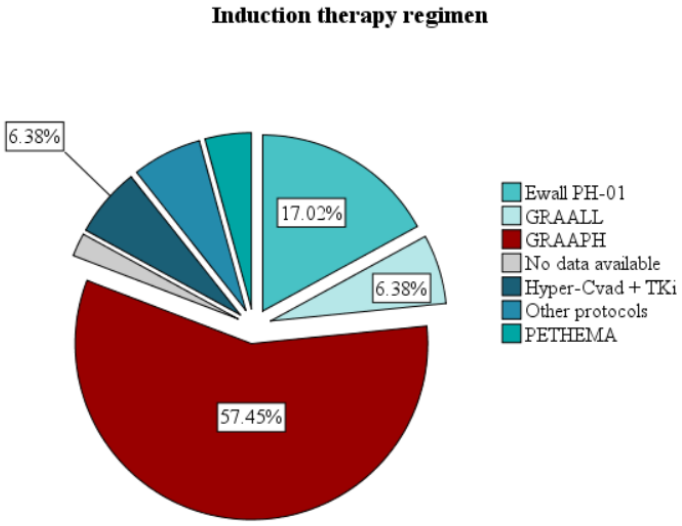

Figure 6 *Induction therapy regimen*

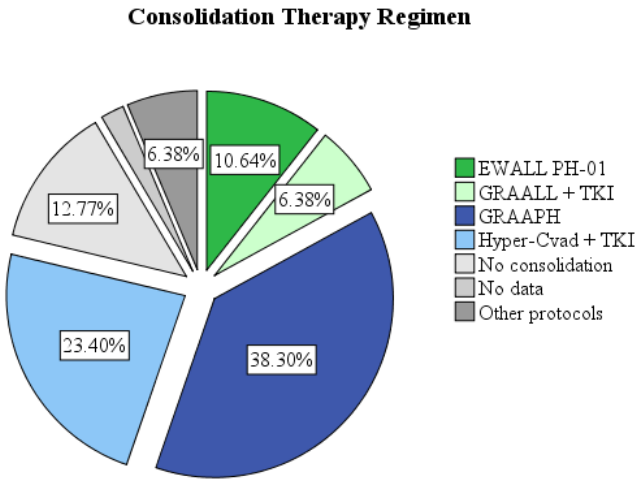

Figure 7 *Consolidation therapy regimen*

At the end of the induction protocol, 76.6% (n=36) of patients achieved complete morphological remission. There are multiple techniques that can evaluate the minimal residual disease (MRD) in Ph+ ALL, and each has their own advantages. We have been evaluating MRD by flow cytometry, and real-time quantitative PCR (RTQ-PCR) (6). Following the induction protocol, measurable residual disease was undetectable in 46,81% (n=22) of patients, while for 36,17% (n=17) it was positive. (sensitivity of the method is 10-4 by immunophenotyping).

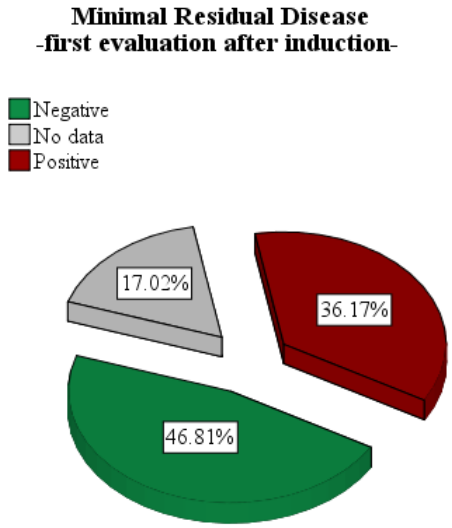

Figure 8 *Measurable residual disease post-induction (immunophenotyping)*

During a median follow-up period of 18 months (range from 2 to 54 months), 51% of patients experienced at least one relapse. Relapses were observed at both medullary and extramedullary sites within the study cohort, highlighting the diverse patterns of disease recurrence.

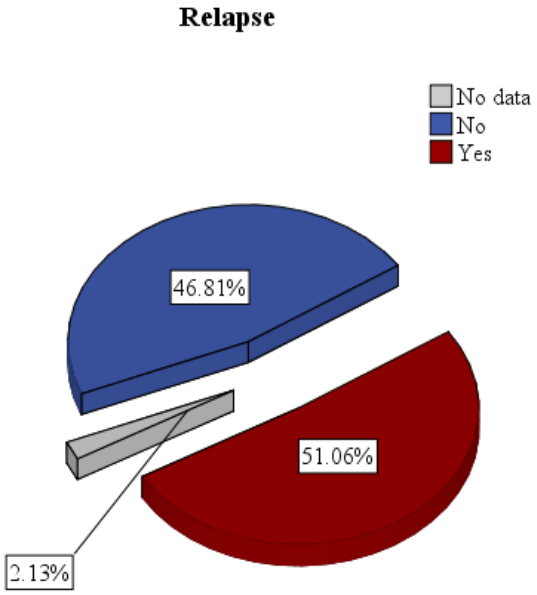

Figure 9 *Fractions of patients who relapsed*

A Pearson correlation analysis was conducted to evaluate the relationship between measurable residual disease (MRD) levels, monitored via immunophenotyping, and relapse in acute lymphoblastic leukemia (ALL). The analysis yielded a correlation coefficient with a p-value of 0.23, which was not statistically significant within this study.

Table 2. Correlations		
		Relapse
Minimal Residual Disease at first evaluation after induction	Pearson Correlation	.230
	Sig. (1-tailed)	.060
	N*	47

Table 2 Pearson Correlation analysis between MRD and relapse

The table below provides a comparative analysis of relapse frequencies among patients stratified by their MRD status. Among the 25 MRD-negative patients, 9 experienced relapse, corresponding to a relapse frequency of 36%. Conversely, 11 of the 17 MRD-positive patients relapsed, resulting in a significantly higher relapse frequency of 64.7%. These findings demonstrate that the relapse frequency in MRD-positive patients is nearly double that observed in MRD-negative patients, underscoring the prognostic significance of MRD status in predicting relapse risk. This observation aligns with existing literature, which highlights the critical role of MRD as a predictive biomarker in acute lymphoblastic leukemia.

	Total Patients	Relapsed Patients	Relapse Frequency
MRD Negative	25	9	**36%**
MRD Positive	17	11	**64,7%**
• Frequency of relapsed patients is double in the fraction that have a positive Minimal Residual Disease			

Table 3. *Comparative Evaluation of Relapse Frequencies in the Patient Cohort*

The series of figures below illustrate various aspects of treatment strategies and interventions for patients with R/R Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). The first figure highlights the distribution of new therapeutic approaches used when clasical chemotherapy protocols fail, with the majority of patients (82.98%) not receiving any additional treatment. Among the remaining patients, 12.77% received Blinatumomab, 2.13% received CAR-T cell procedure, and an equal percentage received Inotuzumab Ozogamicin. The second figure shows the proportion of patients who underwent radiotherapy prior to transplantation, with 82.98% not receiving radiotherapy for different conditions as shown below. The next figure provides information on patients who underwent the transplant procedure, indicating that a smaller fraction proceeded to transplantation, while the majority did not. Together, this data emphasizes the variability in treatment responses and the critical role of interventions such as allogeneic stem cell transplantation in managing Ph+ ALL cases, especially when initial chemotherapy is unsuccessful (Fig 10-12).

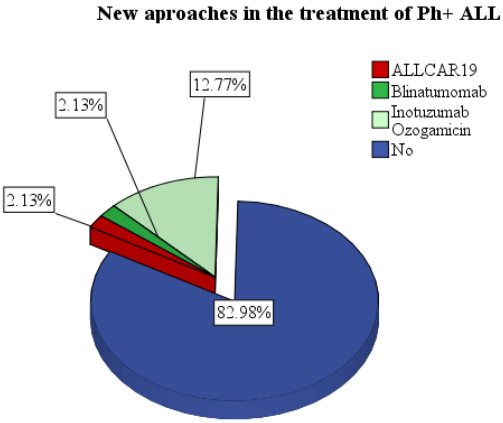

Figure 10 *Treatment options for R/R Ph positive ALL*

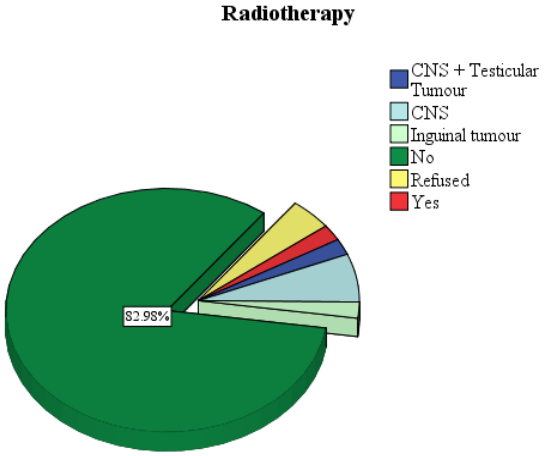

Figure 11 *Patients that underwent radiotherapy prior to transplant*

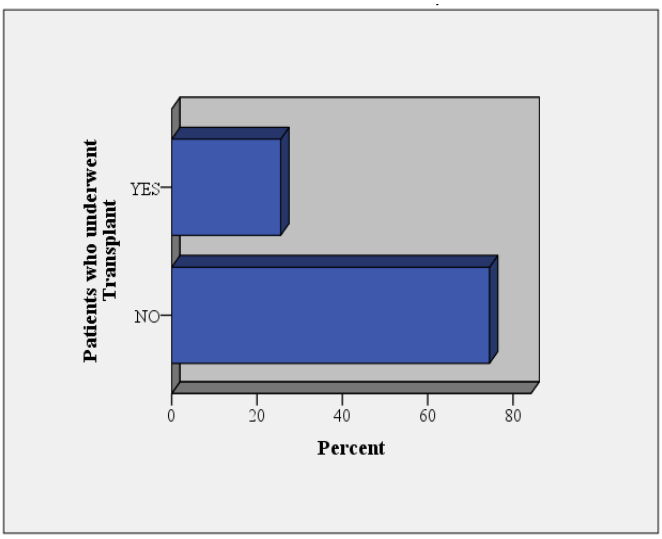

Figure 12 *Patients that underwent the Transplant Procedure*

The Kaplan-Meier survival curve illustrates the overall survival function for patients over time, measured in days. The curve begins at 1.0, representing 100% survival at the study's start, and gradually declines as the duration of survival increases, indicating the occurrence of events such as relapse or death. The curve declines are observed in the early phases, suggesting higher mortality during the initial period. As time progresses, the slope of the curve becomes less steep, indicating fewer events occurring later in the follow-up period. The censored data points, marked along the curve, represent patients who were lost to follow-up or whose outcomes were not observed within the study timeframe.

Notably, one female patient included in the study was diagnosed at the beginning of 2020 and has survived for over 1600 days. She continues to visit our clinic regularly for check-ups, suggesting an extended survival for the patients who underwent transplant and were treated prior to the procedure and after with a tyrosine kinase inhibitors. Improved outcomes in patients with Ph-positive ALL and the key role of tyrosine kinase inhibitors in both inducing remission and maintaining treatment following allo-HSCT were also observed by Enache et al (7).

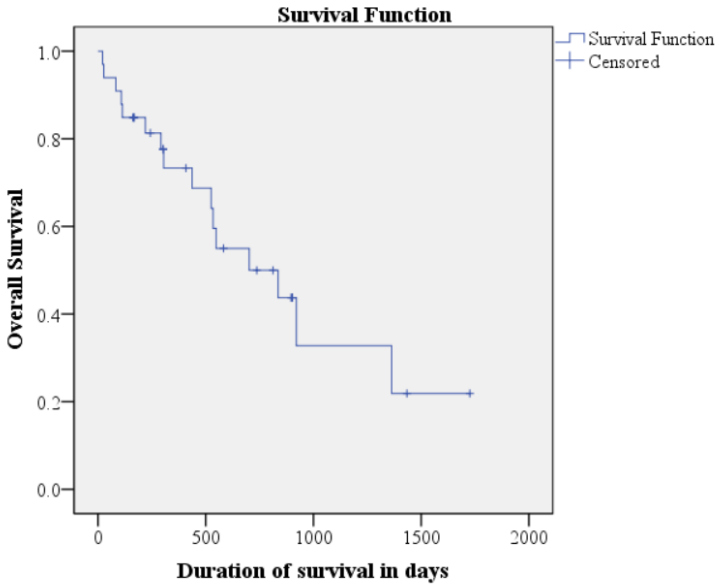

Figure 13 *Kaplan Meier survival analysis*

The data indicates the outcomes of patients included in the study, with a total of 47 participants. Among them, 25 patients are currently alive, while 22 patients have deceased. The leading cause of death in relapsed patients is sepsis, accounting for 44.44% of the cases. Carcinomatous meningitis (associated with breast cancer), gastrointestinal hemorrhage, and stroke each contribute equally, with each accounting for 11.11% of the deaths. We also highlighted SARS-CoV-2 infection, which was responsible for 22.22% of deaths, given the recent history of the COVID-19 pandemic. This suggests the significant impact of this virus on the patients that have a compromised immune system.

Discussions

The above findings highlight the complexity involved in managing patients with Philadelphia-positive acute lymphoblastic leukemia and underscore the critical need for personalized therapeutic strategies to optimize outcomes in individuals receiving tyrosine kinase inhibitor therapy.

Furthermore, tyrosine kinase inhibitors (TKIs) were utilized across various treatment lines in this cohort. In the first-line setting, the majority of patients were treated with Imatinib, with a median treatment duration of 6 months. One patient received ponatinib in the first line due to mutations in the ABL1 kinase domain, while two others were treated with dasatinib due to the blastic phase of

chronic myeloid leukemia. In the second-line treatment setting, which was administered to 29 patients, Dasatinib demonstrated the most sustained therapeutic use, with an average duration of 12.68 months. In contrast, ponatinib and nilotinib were associated with significantly shorter median treatment durations, at 3.5 months and 1 month, respectively. These differences underscore the variability in therapeutic durability, as well as the potential impact of tolerability or efficacy of these agents in the management of relapsed or refractory disease. In the third-line treatment cohort, 14 patients received therapy with ponatinib demonstrating a median duration of 7.72 months, while dasatinib was administered to one patient, with a treatment duration of 2 months.

Figure 14 highlights the distribution of patients by the number of TKIs used: 27.66% of patients were treated with one TKI, 29.79% with two, 10.64% with three, and 2.13% with four. Additionally, mutations in the ABL1 kinase domain were identified in seven cases, suggesting potential resistance mechanisms that may necessitate switching between multiple TKIs.

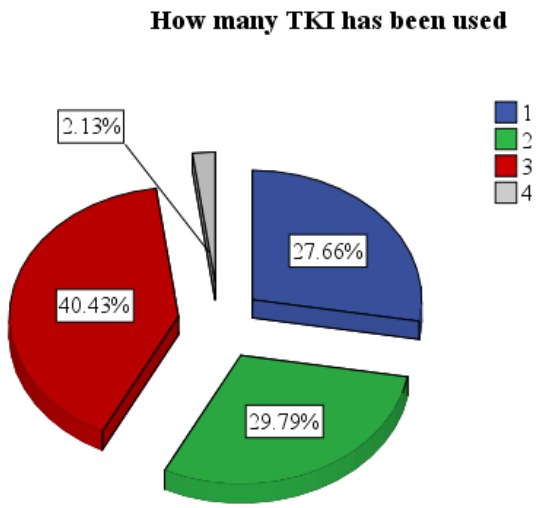

Figure 14 *Fractions of patients by number of Tyrosine-Kinase Inhibitors attempted*

This form of acute lymphoblastic leukemia was associated with a poor prognosis; however, according to specialized literature, patient survival rates have significantly improved following the introduction of tyrosine kinase inhibitors (TKIs). In contrast to chronic myeloid leukemia (CML), patients with acute Philadelphia chromosome-positive leukemia (Ph+ ALL) often develop resistant clones due to mutations within the ABL domain. These resistant clones may already be present at the time of diagnosis. (8) At present, a couple of molecules demonstrate activity against the T315I mutation, with Ponatinib currently available in Romania. Research is also being conducted on the ability of these agents to penetrate the blood-brain barrier, a property that has already been demonstrated in the case of Dasatinib. (9)

Another key area of investigation is the correlation between minimal residual disease (MRD) and the risk of relapse during treatment. According to our findings, the relapse rate is twice as high among patients with positive MRD. Existing literature indicates that achieving deep molecular response at the end of induction therapy is a significantly more robust prognostic indicator than achieving complete morphological remission. These studies highlight improved outcomes in terms of both event-free survival and overall survival. (10;11)

Limitations – This study depends on pre-existing data that was introduced in the Institute database and in some cases some information may be missing. Consequently, this may impact the outcome of our results.

Conclusion

The findings of this real-world investigation are congruent with those reported in clinical studies on the efficacy of TKi therapies combined with low-dose chemotherapy.

Early response to treatment (within the first few weeks of induction therapy) is a critical factor. Patients who achieve minimal residual diseases' negativity after initial therapy have a significantly better prognosis.

Ph + R/R ALL remains a therapeutic challenge, since it is associated with a reduced survival rate and resistant mutations in the BCR-ABL TK domain.

No funding for this study

Conflicts of interest

I certificate that I do not have any financial or personal relationships that might bias the content of this work.
This study was approved by the Institutional Research Board and Ethics Committee.
The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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