ORIGINAL ARTICLE

Management of Philadelphia chromosome-positive B-acute lymphoblastic leukemia in Tunisia

La prise en charge de la leucémie aigue lymphoblastique B avec chromosome Philadelphie positif en Tunisie

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Abstract

Introduction: The management of Philadelphia-chromosome positive B-cell acute lymphoblastic leukemia (Ph+ B- ALL) is continuously progressing. However, Tunisian data are limited.

Aim: The objective was to describe the clinical and prognostic profile as well as the therapeutic outcomes of Ph+ B- ALL.

Methods: This was a retrospective and descriptive study conducted in the adult clinical hematology department of Aziza Othmana hospital over a period of 12 years. We included patients aged between 18 and 60 years, diagnosed with de novo or secondary Ph+ B- ALL and treated with a combination of chemotherapy and a tyrosine kinase inhibitor (TKI).

Results: We collected data on 36 patients with initial central nervous system involvement in only one case. The GRAAPH-2005 protocol was the most used regimen (n=29). Thirty-four patients received TKI: imatinib (n=28) and dasatinib (n=6). After induction, all patients achieved cytological remission. Molecular response was assessed in 21 of whom 52% achieved a molecular response. After consolidation, 17 had molecular response evaluation, with 13 achieving a molecular response. Seven patients underwent allogenic hematopoietic stem cell transplantation, and two underwent autologous stem cell transplantation. In terms of disease progression ,14 patients relapsed with a median time to relapse of 18 months [4-42] after TKI initiation. The 5- year overall survival in our series was 25%. The 5-year relapse free survival and event-free survival were 22% respectively.

Conclusion: Our study highlighted the various obstacles encountered in the management of Ph+ B-ALL in Tunisia. Addressing these obstacles could improve therapeutic outcomes.

Keywords : Acute lymphoblastic leukemia, Philadelphia chromosome, Tyrosine kinase inhibitor, Prognostic, Clinical profile, Chemotherapy

Résumé

Introduction : La prise en charge de la leucémie aiguë lymphoblastique B avec chromosome Philadelphie positif (LAL B Ph+) est en progression. Les données tunisiennes sur ce sujet restent limitées.

Objectif : Notre objectif était de décrire le profil clinique et pronostique ainsi que les résultats thérapeutiques de la LAL B Ph+.

Méthodes : Il s'agissait d'une étude rétrospective et descriptive menée au service d'hématologie clinique adulte de l'hôpital Aziza Othmana sur 12 ans. Nous avons inclus les patients âgés entre 18 et 60 ans, diagnostiqués LAL B Ph+ de novo ou secondaire, et traités par une association chimiothérapie et inhibiteur de tyrosine kinase (ITK).

Résultats : Nous avons colligé 36 patients avec une atteinte initiale du système nerveux central dans un cas. Le GRAAPH-2005 était le protocole le plus utilisé (n=29). Trente-quatre patients ont reçu un ITK : imatinib (n=28) et dasatinib (n=6). Après l'induction, tous étaient en rémission cytologique. Une réponse moléculaire était obtenue chez 52 % des 21 patients évalués. Après consolidation, 17 avaient une évaluation de la réponse moléculaire, avec 13 en rémissions moléculaires. Sept étaient allogreffés et deux autogreffés. Quatorze ont rechuté, avec un délai médian de 18 mois [4-42] de début de l'ITK. La survie globale, la survie sans rechute et la survie sans événements à 5 ans étaient respectivement de 25 %, 22% et 22%.

Conclusion : Notre étude a souligné les obstacles rencontrés dans la prise en charge de la LAL B Ph+ en Tunisie. Leur résolution pourrait améliorer les résultats thérapeutiques.

Mots clés: Leucémie aigüe lymphoblastique, Chromsome Philadelphie, inhibiteurs de tyrosine kinase, pronostic, Profil clinique, chimiothérapie

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What is known" and "What this article adds?

The management of Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia (Ph+ B-ALL) has seen significant progress, with a marked improvement in prognosis. Our study described the clinical and prognostic profile, as well as the therapeutic outcomes of Ph+ B-ALL in Tunisia. It also highlighted the various obstacles encountered in the management of this disease, thereby emphasizing the need to find solutions to improve therapeutic outcomes.

Introduction

Philadelphia chromosome-positive (Ph+) B-cell acute lymphoblastic leukemia (B-ALL) accounts for 20% to 25% of adult ALL cases (1). It is historically associated with a poor prognosis, with an overall survival (OS) rate rarely exceeding 20% (2).

However, its management has significantly evolved in recent decades. The emergence of successive generations of tyrosine kinase inhibitors (TKI), the integration of minimal residual disease (MRD) monitoring, advancements in hematopoietic stem cell transplantation (HSCT) techniques, and the development of chemotherapy-free protocols for unfit patients have all contributed to improve the prognosis of this disease (3).

In Tunisia, several limitations persist in the management of this leukemia, such as the unavailability of third generation (3G) TKI, limited access to second generation (2G) TKI and allogeneic HSCT (allo-HSCT), and the absence of immunotherapy. Few studies have reported on the clinical, prognostic, and therapeutic features of Ph+ B-ALL in Tunisia. Given the practical importance of such data, we conducted this study.

Our objective was to describe the clinical and prognostic characteristics as well as the therapeutic outcomes, of adult patients with Ph+ B-ALL

Methods

Study design and patients

This was a 12-year retrospective descriptive study conducted from January 2011 to December 2022. We included patients aged between 18 and 60 years with de novo Ph+ B-ALL, as well as cases of Ph+ B-ALL secondary to chronic myeloid leukemia and treated with a combination of systemic polychemotherapy (SP) and TKI. Diagnosis was confirmed by bone marrow aspiration, immunophenotyping, cytogenetic analysis, and BCR-ABL transcript detection (4,5). We excluded patients ineligible for intensive treatment at diagnosis. Patients treated with pediatric protocols were excluded.

Treatments

Three SP protocols were used: GRAAPH-2005 (Arm A), GRAAPH-2014 (Arm A), and EWALL-Ph01(6) (7) (8). The application of these protocols was adapted based on the patient's general condition and chemotherapy (CT) availability.

A combination of SP and TKI was administered depending on healthcare coverage and drug availability: either imatinib (800 mg/day) or dasatinib (140 mg/day).

For patients under 55, HLA-matched donor search was systematically performed at the start of treatment. All patients were considered for allo-HSCT due to the high relapse risk. An autologous hematopoietic stem cell transplantation (auto-HSCT) was proposed in the absence of an HLA-matched donor after achieving a major molecular remission (MMR).

Assessments

Therapeutic response was assessed in all patients at the end of induction, after the first consolidation cycle, prior to HSCT if indicated, and at 3 months post-transplant. MRD was evaluated by quantitative PCR for the BCR-ABL transcript. When RT-PCR was unavailable- as was the case for patients monitored in 2022 -flow cytometry (FCM) was used as an alternative.

Response definitions

Cytologic remission (CR) was defined as the presence of 5% or less blasts in the bone marrow, with a granulocyte count of 1 G/L or over, a platelet count of 100 G/L or over, and no extramedullary disease (9). Induction failure was defined as the absence of CR criteria at the end of the induction (9). Cytogenetic remission (CyR) was defined by a normal bone marrow karyotype, with the absence of the t(9;22) and the disappearance of additional cytogenetic abnormalities (ACA), if initially present. Complete molecular remission (CMR) was defined by RT-PCR for BCR-ABL transcript indetectable or <0,01% (10). MMR was defined by RT-PCR for BCR-ABL transcript <0.1% (10). Molecular failure was defined by RT-PCR for BCR-ABL transcript >=0.1%. Relapse was defined as > 5% bone marrow blasts or reappearance of extramedullary disease after achieving CR (9).

Statistical analysis

Data were analyzed using IBM SPSS Statistics 25. We used Kaplan-Meier survival curves to determine OS, event-free survival (EFS), and relapse-free survival (RFS). OS was calculated from diagnosis to last follow-up (11). RFS was calculated from CR to relapse or death from any cause (11). EFS was calculated from diagnosis to the first event defined as the following: induction failure, relapse or death (12).

Ethical considerations

The study was approved by the local ethics committee of Aziza Othmana Hospital on december 28, 2024, under reference number 09/2024.

Results

Patient characteristics and treatment

We collected data on 36 patients diagnosed with Ph+ B-ALL, with a median age of 48 years [25–59]. In three patients, Ph+ B-ALL was secondary to a prior hematologic malignancy: chronic myeloid leukemia (n=2) and Hodgkin lymphoma (n=1).
The median white blood cells count was 27 G/L [1-450]. One patient had central nervous system involvement.
Table 1 describes the baseline disease characteristics

Table 1. Initial disease characteristics of patients

Parameter	N (%)
BCR-ABL1 transcript	
P190	22 (56%)
P210	14 (44%)
Cytogenetics	
ACA[a] associated with Ph[b]	20 (60%)
Isolated presence of Ph[b]	7 (20%)
Culture failure	5 (15%)
Normal karyotype	2 (5%)
Most frequent ACA[a]	
Monosomy 7	9 (25%)

[a] Additional cytogenetic abnormalities, [b] Philadelphia chromosome

Figure 1 summarizes the distribution of CT protocols used in our study.

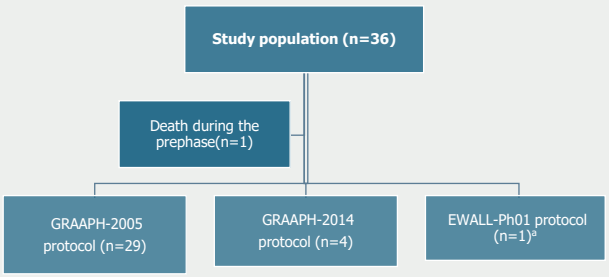


Figure 1. Chemotherapy protocols used in the management of our patients

[a] He received induction therapy per GRAAPH-2005, then switched to EWALL-Ph01 due to advanced age (58 years), prior cerebral ischemic stroke, and hemiplegia during induction, which contraindicated high-dose cytarabine.

Figure 2 illustrates the choice of TKI and the corresponding treatment protocols applied.

Therapeutic response

Four deaths were observed during the induction, all occurring in the setting of hypoxemic pneumonia. After the induction, a CR was obtained in 31 patients. Due to limited access to PCR and/or FCM, seven patients did not undergo MRD assessment.
Table 2 summarizes the therapeutic response in post-induction.

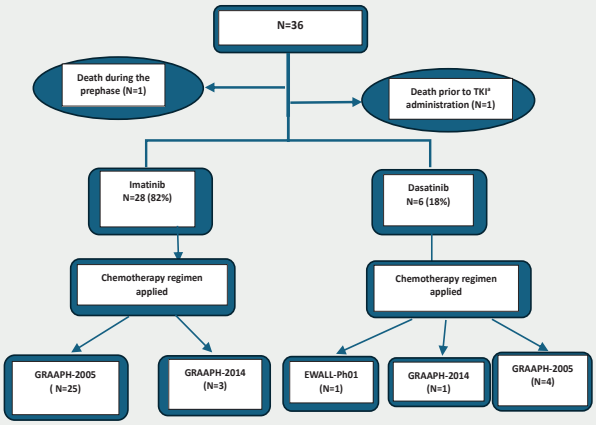


Figure 2. Distribution of tyrosine kinase inhibitors types and corresponding treatment regimen

[a] Tyrosine kinase inhibitor

Table 2. Post-induction therapeutic response

Cytogenetic response	
CyR[a]	21
Cytogenetic failure	6
Culture failure	4
MRD[e] by PCR	N=21
MMR[d]	5
CMR[b]	6
Molecular failure	10
MRD[e] by FCM[c]	N=3
>10-3	2
<10-3	1

[a] cytogenetic remission, [b] complete molecular remission , [c] flow cytometry, [d] major molecular remission , [e] minimal residual disease

Given the small sample size, it was not possible to analyze the association between molecular response and factors such as TKI type, treatment protocol, delay in TKI initiation, or delay in protocol adaptation. Two patients did not receive consolidation therapy (patient refusal, history of Parkinson's disease). Thus, 29 patients (80%) received the first consolidation cycle. Among them, five patients did not undergo post-consolidation evaluation, and one patient died during consolidation. As a result, post-consolidation response was assessed in only 23 patients. This evaluation was performed after a median delay of 2.5 months [1.5–4] from TKI initiation. Twenty-two patients were still in CR while one relapsed. CyR was noted in 22 patients, including those who were not in CyR after induction. Among the 10 patients who had molecular failure post-induction, five achieved CMR post-consolidation. Post-consolidation MRD results are summarized in table 3.

Table 3. Post-consolidation minimal residual disease assessment

MRD[d] by PCR	N=17
MMR[c]	1
CMR[a]	12
Molecular failure	4
MRD[d] by FCM[b]	N=5
<10-4	3
>10-4	2

[a] complete molecular remission, [b] flow cytometry , [c] major molecular remission , [d] minimal residual disease

Fourteen patients (39%) relapsed with a median time of 14 months [2-38] from achieving CyR and 18 months [4-42] from TKI initiation. Thirteen received the GRAAPH-2005 protocol. Regarding the type of TKI, 12 patients received imatinib and two received dasatinib. The T315i mutation was tested in two patients and returned positive in one case.

Given the small sample size and unequal distribution of TKI types and protocols, comparison between groups was not possible.

Post-consolidation molecular status was available for only nine relapsed patients. After consolidation, eight were in molecular response (CMR or MMR)

Eighteen patients (50%) did not undergo HLA typing for the following reasons: age over 55 years (n=10), death during treatment (n=6), absence of siblings (n=1), and refusal to continue treatment after induction (n=1).

Eighteen patients had an HLA typing, revealing an HLA-matched donor in 12 cases (67%). Among those with a matched donor, five patients did not undergo allo-HSCT for the following reasons: donor refusal (n=1), donor age and comorbidities (n=1), toxic death prior to transplant admission (n=1), incidental finding of lung adenocarcinoma during pre-transplant workup (n=1), and patient refusal (n=1).

Seven patients received allo-HSCT: two in CR2 and five in CR1. All were in CMR at last follow-up. Two toxic deaths related to allo-HSCT were reported.

Auto-HSCT was performed in two patients (5%) using a conditioning regimen based on busulfan+cyclophosphamide+prophylactic cranial radiotherapy, due to the unavailability of total body irradiation. One patient was in MMR and the other in CMR at the time of transplantation. Both received maintenance therapy with dasatinib. One maintained MMR for 44 months, while the other relapsed four months after transplantation.

Survival Analysis

Given the small sample size and the unequal distribution of patients according to the type of TKI used and the treatment protocol, it was not possible to perform survival comparisons based on these variables.

Similarly, the limited number of patients with MRD quantification by PCR precluded any meaningful comparison of survival based on molecular response after induction and consolidation therapy.

We noted eight cases of treatment-related death and seven cases of death related to disease progression.

In our cohort, the 5-year OS, RFS and EFS rates were 25%, 22% and 18% respectively.

Discussion

This study was undertaken to describe clinical and prognostic characteristics as well as the therapeutic outcomes of adult patients with Ph+ B-ALL.

Table 4 compares the diagnostic features observed in our study with those reported in the literature.

Table 4. Comparison of diagnostic features between our study and existing literature

	Our series	GRAAPH-2005 trial (6) (n=268)	PONALFILtrial (10) (n=30)	Trial of Daver et al (9) (n=54)
Initial CNS[b] involvement	1	9/268	1 (3%)	7 (13%)
Median WBC[c] count	27 G/l	22,4 G/l	6,4 G/l	16,7 G/l
Initial karyotype :				
- Culture failure	5 (15%)	15 (6%)	0	5 (9%)
- t(9,22)	7 (20%)	247 (92%)	18 (60%)	10 (19%)
-t(9,22)+ACA[a]	20(60%)	176 (66%)	12 (20%)	35 (65%)
-Normal	2 (5%)	21 (8%)	0	4 (7%)
BCR-ABL1 transcripts:	18 (56%)	195 (73%)	20 (67%)	36 (67%)
P190	14 (44%)	69 (26%)	9 (30%)	18 (33%)
P210				

[a] Additional cytogenetic abnormalities, [b] central nervous system, [c] white blood cells

In our cohort, CR was achieved in 100% of patients in post-induction with CyR and molecular response observed respectively in 52% and 51% of patients. Post-consolidation MRD quantification was performed in 17 patients, 13 of whom showed molecular response.

Our therapeutic outcomes are similar to those reported in the GRAAPH-2005 study (98.5% CR arm A). Post-consolidation evaluation showed that 65% achieved a MMR and 26% achieved a CMR (6). However, survival outcomes were lower than in the GRAAPH-2005 study, with 5-year OS, EFS and RFS rates of 25%, 18%, and 22%, respectively, compared to 46% and 37% in the GRAAPH-2005 study. These discrepancies may be explained by the low rate of HSCT in our series. Indeed, the GRAAPH-2005 study demonstrated better OS and RFS in transplanted patients (6).

Before TKI, the prognosis of Ph+ B-ALL was poor (CR < 70% and OS < 20%). Imatinib showed short-lived molecular responses as monotherapy (13). Later studies revealed synergistic effects when combined with CT agents like cyclophosphamide, vincristine, doxorubicin, and etoposide, leading to its integration into treatment protocols and improved outcomes (14,15,16). The primary goal was to achieve a deep molecular response after induction, increasing the chances of allo-HSCT in CR1 (17). Dasatinib , a more potent BCR-ABL inhibition , has shown efficacy in imatinib intolerant or resistant patients with a 58% of hematologic response rate (2,18). In a study by Ravandi et al., hyper-CVAD plus dasatinib led to 96% CR rate with MMR and CMR rates of 83% and 65%, respectively. Five-year RFS and OS were 44% and 46%, respectively (19) .

In our study, 28 patients received imatinib (GRAAPH-2014 (n=3) and GRAAPH-2005 (n=25)). Six received dasatinib in combination with CT (GRAAPH-2014 (n=1), EWALL-Ph01 (n=1), and GRAAPH-2005 (n=4)). CR was achieved in all patients (100%). Due to the small sample size, a comparative analysis between the two groups was not feasible, and no definitive conclusions can be drawn. However, based on data from the literature, improved access to dasatinib could potentially enhance therapeutic

outcomes.

Although the introduction of 1G and 2G TKI has significantly improved long-term survival now reaching 40–65%, relapse remains a major challenge, especially in patients not consolidated with allo-HSCT. These relapses are primarily associated with the T315I mutation (3), which accounts for approximately 65% of kinase domain mutations and confers resistance to both 1G and 2G TKI (2,20).

Ponatinib, a 3G TKI with broad BCR-ABL inhibitory activity, is effective against T315I (2,21). In a study by Jabbour et al (n=37, median age=51), Hyper-CVAD + ponatinib led to 100% CR, 97% MRD negativity and 78% CMR (22). A meta-analysis of 26 studies confirmed ponatinib's superiority in OS and CMR to 1G and 2G TKI (2,23). These findings support ponatinib as a more effective first-line option (2,23). However, ponatinib is currently unavailable in Tunisia, limiting treatment options for patients with T315I or those relapsing after dasatinib. In our cohort, two of the 14 relapsed patients were already receiving dasatinib, and one of them was found to harbor the T315I mutation relapsed. Due to the unavailability of ponatinib, both patients continued salvage therapy with dasatinib.

Before TKI, allo-HSCT was the standard consolidation for Ph+ B-ALL, given dismal survival without it (OS<10%) (24). The UKALL/ECOG2993 study showed 5-yar OS of 44% with matched sibling donor transplants, 36% for haploidentical transplants, and only 19% for non-transplanted patients (25).

The introduction of TKI has significantly improved the prognosis of Ph+B-ALL, leading to higher rates of MRD negativity and lower risk of relapse (26). Given the limited access to allo-HSCT and its associated toxicity, its necessity in the TKI era especially with more potent options like ponatinib- is increasingly debated (27,28). Several studies showed no clear survival benefit when adding allo-HSCT to TKI+CT regimens (9,14,27).

The role of allo-HSCT in Ph+ B-ALL has been investigated in two major meta-analyses by Ponvilawan et al. and Zeng et al (27,29). These studies concluded that allo-HSCT continues to confer a survival benefit when combined with imatinib, although this benefit appears to be reduced compared to the pre-TKI era. However, with 2G and 3G TKI, this advantage seems to diminish, due to their superior efficacy compared to imatinib and the significant toxicity related mortality (TRM) associated with allo-HSCT (26,30,31). However, these findings are largely based on small phase 2 studies (26). Currently, allo-HSCT remains recommended for young patients in CR1, particularly in the absence of 3G TKI and when an early CMR is not achieved (28). For those achieving early CMR, the decision to proceed with allo-HSCT must be carefully weighed against its toxicity and the benefits of continued CT alone (28).

In Tunisia, considering the limitations of the local healthcare system, allo-HSCT remains a cornerstone of treatment in Ph+ B-ALL. Several persistent challenges continue to impact patient management, including limited access to dasatinib, restricted availability of MRD monitoring for early relapse detection, and lack of access to salvage therapies such as ponatinib and immunotherapies. These constraints make allo-HSCT an indispensable consolidation approach in our setting.

In our cohort, 12 patients had an HLA-matched sibling donor, but only seven underwent allo-HSCT. All transplanted patients were in CMR at last follow-up. However, two patients experienced TRM.

The low rate of allo-HSCT in our series can be attributed to several factors. In Tunisia, there is a lack of resources to manage allo-HSCT-related complications. Furthermore, the country has only one national bone marrow transplantation center, which has resulted in an upper age limit of 50 years for transplant eligibility. However, Ph+ B-ALL is a disease with increasing incidence in older adults. In our cohort, ten patients were over the age of 55 and were not HLA-typed due to this age-related limitation. Haploidentical transplantation remains poorly developed in our setting, largely due to limited infrastructure and challenges in managing its associated complications further restricting access to allo-HSCT. In fact, in our series, seven patients were not transplanted due to the unavailability of an HLA-matched sibling donor.

Addressing these structural and logistical barriers is essential to expanding access to allo-HSCT and improving treatment outcomes in patients with Ph+ B-ALL.

As an alternative, auto-HSCT followed by maintenance therapy offers a lower TRM but at the cost of a higher relapse risk. This approach has been supported by several studies such as CALGB 10001, which demonstrated the feasibility of auto-HSCT in Ph+ B-ALL (32,33). In this trial, 34 patients received CT+imatinib, followed by either allo-HSCT (n=15) or auto-HSCT (n=19). The study concluded that auto-HSCT is an effective alternative for patients lacking an HLA-matched donor (34).

The GRAAPH-2005 study also demonstrated comparable survival outcomes between auto-HSCT and allo-HSCT in patients achieving CMR prior to transplantation (6). According to Saleh et al., auto-HSCT may be considered a valid therapeutic option for well-selected Ph+ B-ALL patients, particularly those achieving a good molecular response prior to transplantation and lacking a suitable donor (26). Other authors emphasize the importance of verifying BCR-ABL negativity in harvested peripheral blood stem cell before auto-HSCT to optimize outcomes(35).

In our cohort, two patients underwent auto-HSCT, preceded by a conditioning regimen consisting of cyclophosphamide + busulfan+ prophylactic cranial irradiation. Both received post-transplant dasatinib maintenance. One patient relapsed 4 months after transplantation, while the other maintained molecular remission for 103 months. The low number of patients undergoing auto-HSCT may be explained by the limited capacity to assess molecular status pre-transplantation. In 2022, MRD evaluation was based on FCM, which lacks the sensitivity and specificity of PCR. Given the small sample size, no definitive conclusions can be drawn. However, based on current literature, auto-HSCT remains a valid therapeutic option for patients in molecular remission at 3 months post-CR. Improving the availability of PCR-based MRD monitoring could better inform the selection of candidates for auto-HSCT.

The prognostic and therapeutic relevance of MRD in Ph+ B-ALL has been well documented (36). Ravandi et al. demonstrated that achieving MMR and MRD negativity by FCM ($<10^{-4}$) between 3 and 12 months after treatment was associated with a lower relapse rate and improved OS (37). Similarly, Kim et al. highlighted the positive prognostic impact of achieving CMR within 3 months of CR (38). Short et al. studied 202 patients treated with Hyper-CVAD+TKI, finding that MRD statuts at 3 months were significantly associated with better OS (p=0.005) and EFS (p=0.002), while MRD at CR showed no significant impact on either OS (p=0.11) or EFS (p=0.4) (39). In this study achieving CMR at 3 months was associated with excellent survival outcomes, regardless of the type TKI used or other initial prognostic factors. Short et al. also suggested that the optimal timing for MRD assessment may vary with different TKI, due to their distinct mechanisms and rates of leukemic cell clearance (36). Ravandi et al. further confirmed that MRD monitoring by PCR is a valuable decision-making tool in the management of Ph+ B-ALL. This has led to the development and exploration of more sensitive tools (28). It is important to note that around 20–30% of cases show discordance between PCR and FCM. PCR is highly sensitive but may yield false positives, while FCM is more specific and predictive for relapse. A combined strategy is advised: PCR+FCM during treatment, FCM prioritized around transplant, and PCR for long-term follow-up (40).

In Tunisia, MRD assessment in patients with Ph+ B-ALL is based on FCM and RT-PCR. However, several periods of unavailability of RT-PCR have been reported. In our cohort in 2022, none of the patients underwent MRD quantification using RT-PCR, which negatively impacted patient management. Without molecular response assessment, auto-HSCT could not be considered. Furthermore, due to the lower sensitivity of FCM compared to RT-PCR, response evaluation was incomplete, making treatment adaptation more challenging.

Improved availability of RT-PCR for BCR-ABL quantification is essential for tailoring therapy based on treatment response. In our study, since BCR-ABL transcript quantification was not performed for all patients and due to the small sample size, it was not possible to draw statistical correlations between MRD values and survival outcomes.

The favorable therapeutic outcomes of combining blinatumomab with TKIs in refractory cases have encouraged the use of CT-free protocols, even in first-line. The D-ALBA study included 63 patients treated with dasatinib and blinatumomab, achieving a molecular response in 60% after two cycles. Four-year OS and RFS were 78% and 75%, respectively (41) . In a phase II trial by Jabour et al., patients received ponatinib plus blinatumomab, resulting in CR and MRD negativity rates of 96% and 87%. One-year OS and EFS were both 95% (42). These excellent results support CT-free approaches, reducing CT-related toxicity. Blinatumomab has been also used as a bridge to allo-HSCT in relapsed/refractory Ph+ ALL patients, either alone or in combination with TKIs, to achieve MRD negativity and improve transplant success (43).

It is important to mention certain limitations of our study, including its retrospective design, the small sample size, the use of different treatment protocols across the cohort, the heterogeneity in MRD assessment and the inclusion of patients with transformed chronic myeloid leukemia as well as the absence of mutation analysis in the tyrosine kinase domain.

Our study underscores key challenges in managing Ph+ B-ALL in Tunisia, highlighting the urgent need to improve access to dasatinib, ensure consistent MRD monitoring via RT-PCR, and provide ponatinib for patients with T315I mutations or relapse post-dasatinib. Enhancing RT-PCR availability would also support the use of auto-HSCT in eligible patients lacking a donor. To better define the clinical and therapeutic landscape, multicenter nationwide studies are needed.

Glossary
Ph+: Philadelphia chromosome-positive
B-ALL: B-cell acute lymphoblastic leukemia
OS: overall survival
TKI: tyrosine kinase inhibitors
MRD: minimal residual disease
HSCT: hematopoietic stem cell transplantation
3G: third generation
2G: second generation
Allo-HSCT: allogeneic hematopoietic stem cell transplantation
CT: chemotherapy
SP: systemic polychemotherapy
TRM: toxicity related mortality
Auto-HSCT: autologous hematopoietic stem cell transplantation
MMR: major molecular remission
FCM: flow cytometry
CR: Complete remission
CyR: Cytogenetic remission
ACA: additional cytogenetic abnormalities
CMR: Complete molecular remission
EFS: event-free survival
RFS: relapse-free survival

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