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# The role of stem cell transplantation in the management of Philadelphia chromosome-positive acute lymphoblastic leukemia

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***Abstract:*** The concurrent administration of tyrosine kinase inhibitors (TKIs) with standard chemotherapy together with allogeneic hematopoietic stem cell transplantation (alloHSCT) has improved the outcome of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). Although to date, no study has shown alloHSCT to be inferior to chemotherapy plus TKIs in any subgroup of adult Ph+ ALL, there is some evidence suggesting no additional benefit of alloHSCT in patients with deep molecular responses to intensive chemotherapy with a second-generation, and especially, third-generation TKI. As none of these positive and negative studies are controlled, randomized trials are needed to fully define the role of alloHSCT in Ph+ ALL, especially in those with deep molecular response. However, if studies combining TKIs with new approaches such as immunotherapy lead to durable responses, alloHSCT in the first complete remission could be avoided in the near future in the majority of patients with Ph+ ALL.

***Keywords:*** acute lymphoblastic leukemia, allogeneic, autologous, Philadelphia chromosome, stem cell transplantation

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## Introduction

The Philadelphia (Ph) chromosome results from a reciprocal translocation of the *ABL1* gene on chromosome 9 to the breakpoint cluster region (*BCR*) gene on chromosome 22. This particular subtype of B-cell precursor acute lymphoblastic leukemia (ALL) involves 5% of children, 25–30% of young adults and approximately 50% of adults aged 60 years or more.[1] Depending on the translocation breakpoint, p190 *BCR-ABL1* or p210 *BCR- ABL* oncoproteins are generated, being the former more frequent (around 80% of cases). Both oncoproteins act on the signaling pathways of cell proliferation, survival and self-renewal, leading to leukemogenesis.

Prior to the era of tyrosine kinase inhibitors (TKIs) the treatment in both children and adults consisted of standard chemotherapy followed by allogeneic hematopoietic stem cell transplantation (alloHSCT) in all eligible patients. As an example, the beneficial effects of alloHSCT in this disease were demonstrated in the MRC ALLXII/ECOG2993 trial, in which patients who did not undergo this procedure had a significantly poorer outcome [overall survival (OS) at 5 years of 44% in patients receiving a matched sibling donor (MSD) alloHSCT, 36% following a matched unrelated donor (MUD) alloHSCT, and 19% following chemotherapy].[2] Similar results were observed in the French LALA94 trial, that showed that MSD alloHSCT improved the duration of remission.[3]

The concurrent administration of TKIs (formerly imatinib and later dasatinib or nilotinib, and most recently, ponatinib) with standard chemotherapy and the systematic assessment of minimal residual disease (MRD) opened a new era in the therapy of Philadelphia chromosome-positive (Ph+) ALL.[4] The complete remission (CR) rate improved to 90–100% and the depth of response increased, the rate of early relapses decreased, and consequently, the frequency of alloHSCT realization rose to 70% or more in patients in the first CR (Table 1). Currently around 80% of children

**Table 1.** Results of selected therapeutic trials with imatinib, dasatinib, nilotinib and ponatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia.

| Study | *N* | Age, y, median [range] | Chemotherapy regimen | CMR rate, % | AlloHSCT rate, % | RFS rate | OS rate |
|---|---|---|---|---|---|---|---|
| **Imatinib** | | | | | | | |
| Lee and colleagues[6] | 87 | 41 [16–71] | Intensive | 66% (at remission) | 68% | 39% (5 years) | 33% (5 years) |
| Yanada and colleagues[7] | 80 | 48 [15–63] | Intensive | 50% (day 63) | 49% | — | 76% (1 year) |
| Bassan and colleagues[8] | 59 | 45 [20–66] | Intensive | — | 72% | 39% (5 years) | 38% (5 years) |
| Fielding and colleagues[9] | 169 | 42 [16–64] | Intensive | — | 72% | 50% (4 years) | 38% (4 years) |
| Daver and colleagues[10] | 54 | 51 [17–84] | Intensive | 45% (overall) | 30% | 43% (5 years) | 43% (5 years) |
| Chalandon and colleagues[11] | 133 | 45 [21–59] | Intensive (randomized) | 23% (2 cycles) | 65% | — | 46% (5 years) |
| | 135 | 49 [18–59] | Low intensity (randomized) | 29% (2 cycles) | 62% | — | 46% (5 year) |
| Wetzler and colleagues[12] | 34 | 45 [24–57] | Intensive | — | 44% | 46% (5 years) | 51% (5 years) |
| Motllo and colleagues[13] | 68 | 39 [19–60)] | Intensive | 85% (2 cycles)[a] | 85% | - | 52% (5 years) |
| **Dasatinib** | | | | | | | |
| Foà and colleagues[14] | 53 | 54 [24–77] | Corticosteroids | 15% (day 85) | 42% | 22% (20 months) | 31% (20 months) |
| Ravandi and colleagues[15] | 72 | 55 [21–80] | Intensive | 65% (overall) | 17% | 44% (5 years) | 46% (5 years) |
| Ravandi and colleagues[16] | 97 | 44 [20–60] | Intensive | — | 42% | 62% (3 years) | 69% (3 years) |
| Rousselot and colleagues[17] | 71 | 69 [55–83] | Low intensity | 24% (consolidation) | 10% | 28% (5 years) | 36% (5 years) |
| **Nilotinib** | | | | | | | |
| Kim and colleagues[18] | 90 | 47 [17–71] | Intensive | 77% (3 months) | 63% | 72% (2 years) | 72% (2 years) |
| Chalandon and colleagues[19] | 60 | 47 [18–59] | Intensive | 80% (2 months)[a] | 73% | - | 96% (1 year) |
| **Ponatinib** | | | | | | | |
| Jabbour and colleagues[20] | 37 | 51 [27–75] | Intensive | 78% (overall) | 24% | — | 80% (2 year)[b] |
| Martinelli and colleagues[21] | 42 | 68 [27–86] | Corticosteroids | 46% (24 weaks) | - | - | 62% (2 years) |

[a]Major molecular response; [b]Updated results with 76 patients with a median age of 47 years (range, 21–80) showed a CMR rate 83% and a 3-year OS of 76%.
CMR, complete molecular response; LFS, leukemia-free survival; OS, overall survival.

and 50% of young adults are expected to be cured, whereas the curability of elderly (nontransplantable) patients is less than 30%.[5]

The improved outcomes with TKIs have raised several important questions, including the selection of the best TKI for the treatment of Ph+ ALL, the role of less intensive chemotherapy regimens for remission induction, the requirement of alloHSCT in the first CR for all patients, the optimal strategy for TKI therapy in the post-HSCT setting, the best method for MRD assessment and the role of novel nonchemotherapeutic approaches in the treatment of this disease, among others.[5,22] This article will discuss the role of HSCT in the management of this disease.

## The role of HSCT in patients treated with imatinib

Currently, alloHSCT is considered the standard consolidation therapy in Ph+ ALL in patients concurrently treated with chemotherapy and imatinib. Several nonrandomized studies have demonstrated a survival benefit for post-induction alloHSCT compared with a chemotherapy-imatinib combination. In the Ph+ arm of the aforementioned UKALLXII/ECOG2993 trial, the addition of imatinib to an intensive induction therapy improved survival, and this improvement resulted in a higher number of patients undergoing alloHSCT, their outcome being better than that of those who did not undergo this procedure (OS at 4 years of 50% compared with 19% for consolidation chemotherapy).[9] Unfortunately, this study did not provide information on the depth of molecular response before proceeding to consolidation therapy/transplantation and did not allow knowing if there is a subset of patients in molecular remission (MRD-negative) before proceeding to alloHSCT who might have low risk disease and improved survival without transplantation. In one study from the Northern Italy Leukemia Study Group, brief imatinib pulses were administered together with standard chemotherapy.[8] This study demonstrated a 5-year survival of close to 40% in 59 adult patients with Ph+ ALL, being the best OS observed in patients subsequently submitted to either MRD or MUD alloHSCT, in whom a significantly lower cumulative incidence of relapse (CIR) was observed. Other studies have also shown similar results (Table 1).[6,7,11,23–26] On the other hand, the dose intensity of imatinib of over 90% had a favorable impact on OS and on CIR in patients who underwent alloHSCT in the first CR, as demonstrated in a study from Korea.[27] This points out the importance of maintaining imatinib dose intensity during the initial phase of treatment of patients with Ph+ ALL.

To determine the impact of TKI given pre- and post-alloHSCT on the long-term outcome of patients allografted for Ph+ ALL, the Acute Leukemia Working Party (ALWP) of the European Blood and Marrow Transplantation (EBMT) performed a retrospective analysis in 473 patients in the first CR who underwent MRD or MUD-HSCT between 2000 and 2010, of whom 390 received TKIs before transplant.[28] Kaplan–Meier estimates of leukemia-free survival (LFS), OS, CIR, and nonrelapse mortality (NRM) at 5 years were 38%, 46%, 36% and 26%, respectively. On multivariate analysis, TKIs given before alloHSCT were associated with a better OS [hazard ratio (HR) = 0.68; $p = 0.04$] and a lower CIR (HR = 0.5; $p = 0.01$). In the post-transplant period, multivariate analysis identified prophylactic TKI administration to be a significant factor for improved LFS (HR = 0.44; $p = 0.002$) and OS (HR = 0.42; $p = 0.004$), as well as for lower CIR (HR = 0.40; $p = 0.01$).

A retrospective single center study recently published by Wang and colleagues[29] reviewed the outcomes of 145 Chinese patients aged 14–65 years who received imatinib with intensive chemotherapy in induction and post-induction therapy in whom alloHSCT was performed by patient or physician choice. Patients proceeding to alloHSCT fared better than those receiving imatinib with chemotherapy alone, with a 4-year disease-free survival (DFS) of 71.3% *versus* 43.9% ($p < 0.001$) and 4-year OS of 82.6% *versus* 45.6% ($p < 0.001$), respectively.

The first group to suggest that alloHSCT could be omitted in Ph+ ALL patients was the Children's Oncology Group. In their study, AALL0031, imatinib was administered in increasing numbers of consecutive days to five cohorts of children with Ph+ ALL in order to assess toxicity.[30] The total imatinib exposure during the initial therapy for cohort 5 was 280 days, and the 3-year event-free survival (EFS) for this cohort was 80.5%, which was significantly better than that of their historical cohort. Interestingly, there was no difference in 3-year EFS between patients in cohort 5 and patients who received an alloHSCT from a MSD or MUD. A longer follow

up of this study demonstrated a similar DFS at 5 years for the chemotherapy plus imatinib group (70%) compared with those who underwent alloHSCT (65% for MSD and 59% for MUD donor).[31] Based on these data, the role of alloHSCT in first CR has been re-evaluated by several pediatric groups. In the adult setting, long-term follow up of the study from the MD Anderson Cancer Center combining hyperCVAD (hyperfractioned cyclophosphamide, vincristine, adriamycin and dexamethasone) with imatinib reported a 5-year OS of 43% in an older cohort (median age 51, range 17–84 years), including 30% who underwent alloHSCT.[10] No significant improvement in the median OS was observed among patients who underwent alloHSCT in the first CR. However, although the difference was not statistically significant, probably because of small numbers, alloHSCT seemed to be beneficial in patients younger than 40 years of age.

The achievement of molecular response is considered the best prognostic factor for outcome in patients with Ph+ ALL.[18,32] This is especially important at intermediate time points, especially after consolidation/before alloHSCT. The kinetics of MRD reduction during induction and consolidation has also shown to be important for prognosis assessment in some studies.[33] The use of MRD monitoring by quantitative polymerase chain reaction for *BCR-ABL1* will probably help to select patients in whom alloHSCT is not needed in CR1 (mirroring what occurs in Ph-negative ALL). The French-Belgium-Swiss Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) conducted a clinical trial randomizing the intensity of chemotherapy concurrent with imatinib (800 mg/day) in the first induction cycle.[11] In this trial, MRD was systematically assessed. In the whole cohort of 254 patients who achieved CR with induction therapy, those who received alloHSCT ($n = 161$) had a significantly improved relapse-free survival (RFS; 48.3%, HR 0.69, 95% CI 0.49–0.98, $p = 0.036$), and OS (56.7%, HR 0.64, 95% CI 0.44–0.93, $p = 0.02$) compared with patients who did not undergo alloHSCT. However, on analysis of the transplant benefit according to pre-transplant MRD status, patients in molecular remission did not seem to benefit from alloHSCT in terms of RFS ($p = 0.96$), whereas patients with positive MRD status did ($p = 0.034$). Although this trial was not designed to assess the role of HSCT in adult patients with Ph+ ALL, its results seem to indicate that a subset of patients in good molecular response could be successfully treated without HSCT.

Another important point refers to how the depth of molecular remission influences on the results of alloHSCT with myeloablative (MAC) or reduced-intensity conditioning (RIC) regimens. Using the Center of International Blood and Marrow Transplant Research data set, Bachanova and colleagues[34] studied the influence of the presence of MRD before transplant on the outcomes according to the intensity of the conditioning regimen. Overall, 49% of patients transplanted using the MAC regimen and 39% of those with RIC were MRD-negative before transplantation. The CIR at 3 years was highest in the MRD-positive patients who underwent RIC (61%) compared with similar relapse risks for MRD-negative patients after RIC (31%) or MAC (21%). The lowest rates of relapse occurred in patients treated with pre-HSCT TKI who were also MRD-negative before HSCT. For these patients, the conditioning regimen intensity did not influence the risk of relapse (RIC, 17%; MAC, 20%), and the OS rate was 55%.

## The role of HSCT in patients treated with dasatinib

Theoretically, second-generation TKIs such as dasatinib, hold promise to overcome resistance to imatinib, with the achievement of deeper responses and potentially avoiding the need for alloHSCT (Table 1). However, some trials continue to support the superiority of alloHSCT. The US Intergroup conducted a trial with dasatinib combined with intensive chemotherapy in 94 adult patients aged 20–60 years.[16] AlloHSCT was recommended if a matched donor was available. A landmark analysis showed a superior RFS ($p = 0.038$) and OS ($p = 0.037$) with alloHSCT compared with no HSCT. The 3-year RFS and OS after alloHSCT were 71% and 87%, respectively. The GIMEMA LALA1205 study evaluated the induction with dasatinib and minimal therapy (prednisone) followed by investigator choice of consolidation in 53 patients with Ph+ ALL.[14] The CR rate was 100% with no induction deaths. With a short follow up, the relapse rate was 100% with no further therapy, 74% with dasatinib alone, 36% with dasatinib plus chemotherapy, and 11% with alloHSCT.

In contrast, the MD Anderson Cancer Center (MDACC) group published their long-term

experience using the hyperCVAD regimen combined with dasatinib in 72 patients 12 of whom underwent alloHSCT in the first CR.[15] The 5-year OS probabilities of transplanted *versus* nontransplanted patients were 33% and 49%, respectively. According to a comparison of the outcomes of patients above and below the age of 40 years, it appeared that patients younger than 40 years benefited from HSCT in the first CR, although the numbers were very small.

The European Working Group on Adult ALL (EWALL) group carried out a phase II trial with low intensity induction and consolidation therapy combined with intermittent doses of dasatinib in elderly patients with Ph+ ALL.[17] Overall, 67 (96%) out of 71 patients (median age 69 years) achieved CR, of whom only 7 (median age 60 years) underwent allogeneic HSCT (3 relapsed and 4 were alive in CR). This study shows that deintensification of chemotherapy combined with TKIs could allow some fit elderly patients to proceed to RIC alloHSCT.

Central nervous system involvement (CNS) is especially frequent in Ph+ ALL both at diagnosis or at relapse.[35] Although it is not per se an adverse prognostic factor, its adequate management is important before and during the HSCT procedure. Triple intrathecal therapy with methotrexate, cytarabine and dexamethasone or liposomal cytarabine depot have been shown useful. Whether dasatinib, that crosses the blood–brain barrier and reaches therapeutic concentrations in the CNS,[36] could be used instead of imatinib and contribute to a safer or better CNS prophylaxis schedule, should be evaluated in a clinical study.

## The role of HSCT in patients treated with nilotinib

The experience with nilotinib upfront in Ph+ ALL is very limited (Table 1). The Adult Acute Lymphoblastic Leukemia Working Party of the Korean Society of Hematology conducted a phase II trial with nilotinib combined with intensive chemotherapy in 90 patients aged 17–71 years.[18] The CR rate was 91% with a complete molecular response (CMR) rate of 61%. When compared with nonrecipients, alloHSCT recipients had a lower CIR (19% *versus* 41%) and higher 2-year RFS (78% *versus* 49% $p = 0.045$). However, for patients achieving a CMR, the 2-year RFS was not different between the groups (65% no alloHSCT *versus* 53% alloHSCT, $p = 0.78$). At 2 years, no OS benefit was observed with allogeneic HSCT (80% alloHSCT *versus* 72% no alloHSCT, $p = 0.23$). The GRAALL group is conducting a clinical trial [ClinicalTrials.gov identifier: NCT 02611492] with nilotinib and chemotherapy in patients with Ph+ ALL aged 18–59 years and the results of the first 60 patients have recently been reported in abstract form.[19] The CR rate was 98% with a major molecular response rate of 80% after induction and 93% after consolidation. Data on the outcomes in transplanted (31 allogeneic and 13 autologous) *versus* nontransplanted patients are not yet available.

The EWALL group has conducted a phase II trial [ClinicalTrials.gov identifier: NCT01528085] with low intensity induction and consolidation therapy combined with concurrent nilotinib in 79 elderly patients with Ph+ ALL. A total of 28 out of 67 patients underwent alloHSCT in the first CR (Ottmann, personal communication). The final results of this trial are pending.

## The role of HSCT in patients treated with ponatinib

Despite the high CR rates obtained with the combination of chemotherapy with first and second-generation TKIs, long-term survival in adults remains at 40–50%, with most relapses being attributed to TKI resistance by acquisition of the T315I mutation or clones that confer a high degree of resistance. Ponatinib is a third-generation TKI active against mutated and unmutated *BCR-ABL1*, including T315I. The phase II trial PACE (recently updated[37]), with ponatinib as a single drug showed significant benefit (41% major hematologic response and 47% major cytogenetic response) despite previous intolerance or refractoriness to other TKIs. Consequently, the MD Anderson Cancer Center conducted a phase II trial with ponatinib combined with the hyperCVAD regimen in 37 patients with Ph+ ALL (Table 1).[20] The overall CR, complete cytogenetic response, and CMR rates were 100%, 100%, and 78%, respectively, with 26% achieving CMR after one cycle of therapy. With a median follow up of 26 months in the initial publication, 78% maintained CR, with an estimated 2-year OS of 80%. Interestingly, the OS curves were similar after censoring or not at alloHSCT (analyzed as a landmark at 4 months by HSCT), this fact being confirmed in the most recent update of this trial (Table 1). A retrospective comparison with patients receiving the same

chemotherapy combined with dasatinib showed favorable outcomes for patients treated with ponatinib.[38] Similarly, a meta-regression analysis including 26 Ph+ ALL studies (25 of earlier generation TKIs and 1 of ponatinib) also showed better outcomes for ponatinib *versus* earlier generation TKIs in patients with newly diagnosed Ph+ ALL.[39] The Spanish PETHEMA Group is conducting a trial [ClinicalTrials.gov identifier: NCT02776605] evaluating the efficacy of ponatinib with standard chemotherapy (according to PETHEMA ALL Ph08 trial)[24] in young adults with Ph+ ALL. A phase III trial comparing ponatinib *versus* imatinib, administered in combination with low-dose chemotherapy as a frontline therapy of Ph+ ALL is being conducted (EudraCT Number: 2018-000397-30) and other phase III trials are being planned.

The Italian GIMEMA group conducted a phase II clinical trial with ponatinib (45 mg/day) combined with minimal chemotherapy in 42 evaluable elderly patients (median age 68 years), 40 of whom attained CR. The OS probability at 1 year was 87%. The frequency of patients who underwent alloHSCT as well as their outcomes are not known because of the low follow up at the time of the preliminary publication.[21]

A post hoc, retrospective, indirect comparison of OS among patients who received single-agent ponatinib in the PACE trial with those who underwent allo-SCT as reported to the EBMT registry, showed that ponatinib was associated with shorter OS (although not statistically significant) compared with alloHSCT [HR, 2.77; 95% confidence interval (CI), 0.73–10.56; $p = 0.146$] in patients who had Ph+ ALL.[40]

## TKIs after allogeneic HSCT

The need for systematic use of TKIs after alloHSCT is still a matter of debate. The only randomized trial has shown post-transplant imatinib resulted in a low relapse rate, durable remissions and excellent long-term outcome in patients with BCR-ABL1-positive ALL irrespective of whether it was given prophylactically or MRD-triggered.[41] The EBMT position statement[42] recommends that patients with undetectable MRD after alloHSCT may be treated prophylactically or, alternatively, may be monitored and administered a TKI only after the detection of MRD (preemptive strategy), and patients with detectable MRD after alloHSCT should be started on TKI treatment as soon as possible. Imatinib was recommended as the first-choice TKI, except for patients with early molecular recurrence (i.e. within the 3 months after HSCT) or BCR-ABL transcripts at a level higher than $10^{-4}$ at any time after HSCT for whom a second-generation TKI was recommended.[42] However, in the current clinical practice there is a generalized trend to use TKIs as maintenance therapy after alloHSCT. Their tolerability is an important issue, and dose reductions or intermittent removal are frequent.[41] An unsolved issue is the duration of this maintenance therapy because there is a reluctance of patients and physicians to skip them in patients with sustained molecular response and good TKI tolerability. The EBMT statement recommends one year of continuous MRD negativity for TKI removal.[42] However, as relapses until three years after alloHSCT are being observed, it seems more logical to remove TKIs at least from this moment.

## Source of allogeneic hematopoietic stem cells

The most therapeutically favorable type of HSCT for ALL is alloHSCT from an HLA-identical sibling donor or a full-MUD, but the availability of these donors is not always possible. The use of haploidentical donors has expanded the scope of alloHSCT but the comparative studies between adult Ph+ ALL patients who have received haploidentical HSCT and patients who have undergone HLA-matched HSCT are scarce. In a study from China the incidences of aGVHD, cGVHD, and cytomegalovirus (CMV) viremia were higher in the patients who received haploidentical HSCT than in those who received HLA-matched HSCT, but there was no difference in NRM and conversely, there was a significant reduction in the relapse rate in Ph+ ALL patients who have received haploidentical HSCT.[43] This suggest that haploidentical HSCT is a promising option for Ph+ ALL patients who lack a suitable HLA-matched donor.

## Role of autologous HSCT

With the feasibility of achieving deep molecular responses with the combination of TKIs and chemotherapy, autologous HSCT (autoHSCT) has become an attractive option. A retrospective review of 177 Ph+ ALL patients from the ALWP of the EBMT compared the outcomes of autoHSCT before and after the TKI era.[44] Improvement in OS and LFS was observed in the

TKI era, especially in MRD-negative patients at the time of transplant. In turn, the Cancer and Acute Leukemia Group B (CALGB) study 10,001 enrolled 58 patients of whom 19 were submitted to autoHSCT, being their OS and LFS similar to the 15 patients who underwent alloHSCT.[12] A recently reported study from the ALWP of the EBMT retrospectively compared the results of myeloablative alloHSCT from MSD or MUD with those of autoHSCT for adults with Ph+ ALL in molecular remission treated between 2007 and 2014.[45] The CIR at 2 years was 47% after auto HSCT, 28% after MSD-HSCT and 19% after MUD-HSCT ($p = 0.0002$), the respective rates of NRM were 2%, 18% and 22% ($p = 0.001$), the probabilities of LFS were 52%, 55% and 60% ($p = 0.69$), while OS rates were 70%, 70% and 69% ($p = 0.58$), respectively. This registry study suggests that in the era of TKIs, outcomes of myeloablative autoHSCT and alloHSCT are comparable in Ph+ ALL adults in first molecular remission.

The most convincing data come from the study by the GRAALL group, in which similar RFS and OS rates were observed in patients in first CR achieving major molecular response (MMR) who received autoHSCT ($n = 29$) and alloHSCT ($n = 90$) (HR, 0.94; 95% CI, 0.53–1.65; $p = 0.82$ and 0.95; 95% CI, 0.51–1.74; $p = 0.86$].[11] It is of note that all patients undergoing autoHSCT received maintenance therapy with imatinib combined with mercaptopurine and methotrexate. The potential role of autoHSCT with the use of more potent TKIs and monoclonal antibodies merits investigation.

## Potential impact of prognostic factors on the decision of HSCT

As mentioned previously, the depth of molecular response is one of the main prognostic factors in Ph+ ALL as observed in several trials (but not in all) with TKIs combined with chemotherapy. However, other prognostic factors could influence the decision to perform HSCT. One of these factors is the white blood cell (WBC) count. In the aforementioned retrospective study by Wang and colleagues,[29] that included patients treated with chemotherapy and imatinib, out of 133 CR patients who completed at least two consolidation cycles, 77 (58%) underwent alloHSCT and 56 (42%) received continuous TKIs with chemotherapy. The baseline characteristics at diagnosis, the hematologic response after a 4-week induction, the BCR-ABL levels after induction, the first and the second consolidation cycles, and the treatment strategy (nontransplant or transplant) were analyzed to identify factors associated with CIR, DFS and OS. Multivariate analysis showed that a WBC $< 30 \times 10^9$/l at diagnosis and a 3-log or greater reduction of BCR-ABL levels from baseline after two consolidation cycles were favorable prognostic factors. In the 'low risk' group of patients (WBC $< 30 \times 10^9$/l and 3-log or greater reduction of BCR-ABL levels from baseline after two consolidation cycles, encompassing 42 patients, 31%) the outcomes after HSCT or continuous TKIs with chemotherapy were not significantly different (OS 96.6% *versus* 83.3%, $p = 0.128$, respectively), whereas in the remaining groups the outcome of transplanted patients was significantly better.

Other prognostic factor refers to the presence of additional cytogenetic abnormalities associated with *t*(9;22), especially some monosomies. This has been observed by several groups in either children[31] or in adults[13,46] and had independent prognostic significance of molecular response in the study by the Spanish PETHEMA Group.[13] Given that almost all patients (93%) from this study underwent alloHSCT in first CR, it is probable that this subset of patients will require additional innovative strategies. In the same sense, in a series of 97 adults with Ph+ ALL treated with TKIs combined with chemotherapy and followed by alloHSCT in first CR, the GMALL group studied the presence of deletions of several genes involved in B-cell development and the cell cycle such as IKZF1, CDKN2A/2B, PAX5, BTG1, EBF1, ETV6 and RB. In this study CDKN2A/2B deletions emerged as a strong new independent prognostic marker for predicting CIR and OS.[47] The poor outcome was primarily attributable to a high relapse rate after alloHSCT. The use of more potent TKIs or immunotherapy could overcome this resistance.

## New therapeutic options in Ph+ and their potential impact on HSCT

Immunotherapy constitutes one of the most promising new therapeutic options for patients with ALL. Monoclonal antibodies (MoAbs) and chimeric antigen receptors (CAR) T-cells are the most active immunologic therapies, while programmed cell death (PD)1/programmed death-ligand (PDL)1 inhibitors seem to have a more limited role in ALL. The two most developed MoAbs in both Ph+ and negative ALL are inotuzumab ozogamycin (InO) and blinatumomab.

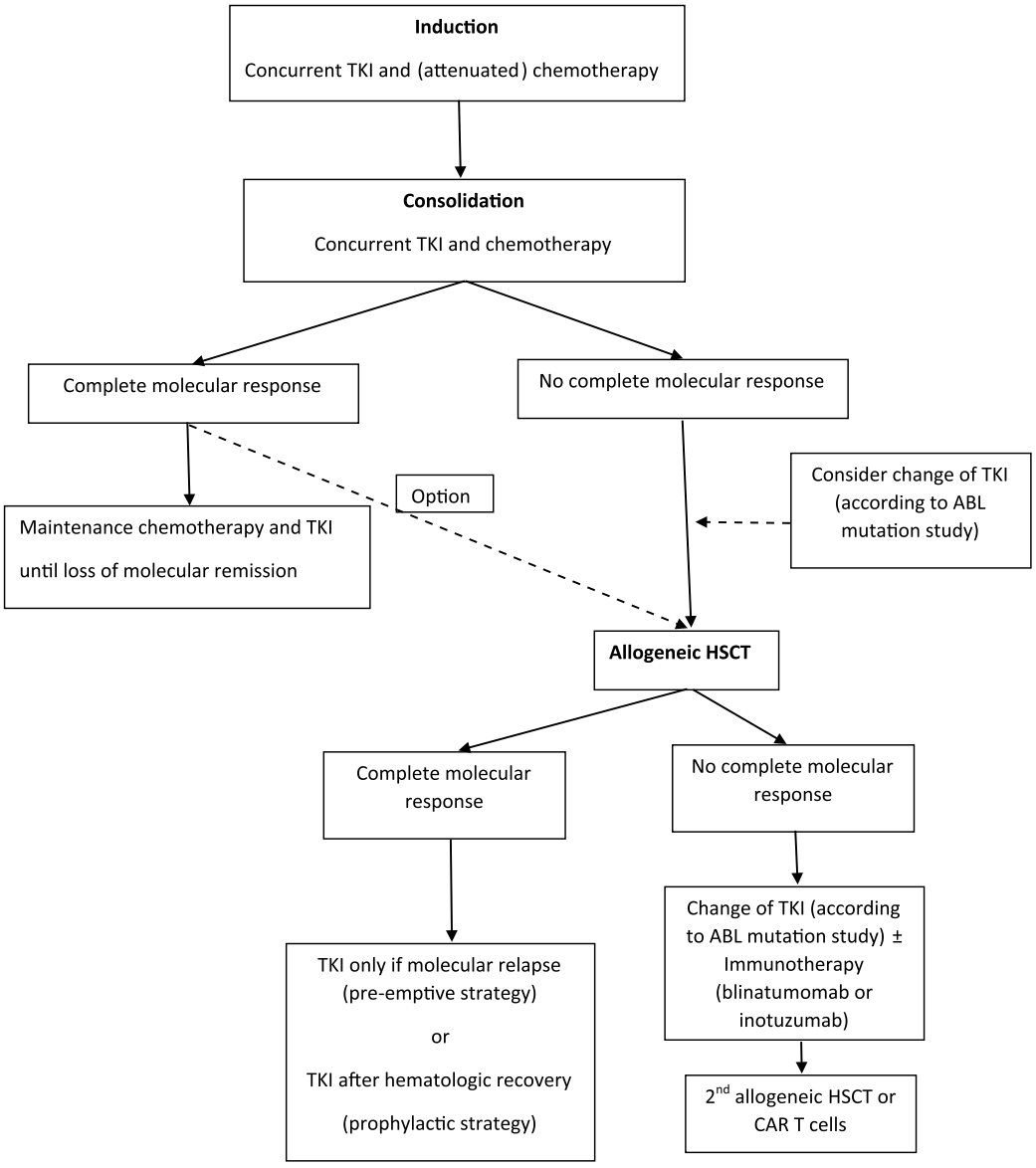


**Figure 1.** Proposed therapeutic algorithm for standard treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia.

Regarding InO, an updated follow up of the subset of 22 patients with relapsed or refractory (R/R) Ph+ ALL included in the phase III study[48] comparing InO with the standard of care showed a superior frequency of CR or CR with incomplete hematologic recovery (CRi; 3% *versus* 56%, $p = 0.1$) and a significant increase in the frequency of MRD negativity (64% *versus* 19%, $p = 0.0006$), that did not translate into a better OS (medians 8.7 *versus* 8.4 months) in spite of a higher frequency of subsequent alloHSCT in CR in the InO group ($n = 9$, 41% *versus* 5, 19%).[49] Blinatumomab has demonstrated activity in a patient population ($n = 45$, median age 55 years) resistant to several lines of TKIs, including patients with the T315I mutation and with prior alloHSCT in 44%.[50] The CR/CRi rate was 36% with 86% of complete MRD response in CR/CRi patients and a median OS of 7.1 months. Overall, 4 out of 16 patients with CR/CRi proceeded to alloHSCT. A step forward consists of the combination of blinatumomab and TKIs in patients with R/R Ph+ ALL. The preliminary results of an ongoing phase II trial involving 12 patients with R/R Ph+ ALL ($n = 9$) or lymphoid blast crisis of chronic myeloid leukemia ($n = 3$) showed complete hematologic, cytogenetic and molecular response rates were 50% (3/6), 71% (5/7), and

75% (9/12), respectively.[51] With a median follow up of 8 months, the median OS was not reached; the 6-month and 1-year OS were 73%. Currently blinatumomab combined with TKIs is being evaluated as initial treatment in patients with *de novo* Ph+ ALL. In addition, the combination of TKIs with InO and blinatumomab should be investigated, in order to achieve a chemotherapy-free regimen to treat patients with Ph+ ALL.

Regarding the activity of CAR T-cells in patients with R/R Ph+ ALL, the most mature data in adults came from the phase II trial performed in the Memorial Sloan Kettering Cancer Center with the 19–28z construct.[52] Overall, 16 out of 53 infused patients had Ph+ ALL, including 5 patients with the T315I ABL kinase mutation and 10 out of 16 refractory to ponatinib. The CR rate was (93% *versus* 79% in Ph-negative patients) and no differences were observed in the OS probability compared with Ph-negative patients. Subsequent alloHSCT did not have any impact on the OS probability. From the data of this study it seems evident that the Ph status does not influence outcomes after CAR T-cell therapy, at least with this specific construct.

## Conclusion

To date, no study has shown alloHSCT to be inferior to chemotherapy plus TKIs in any subgroup of adult Ph+ ALL, although limited data suggest no additional benefit of allogeneic HSCT in patients with deep molecular responses to intensive chemotherapy with a second-generation and third-generation TKIs. However, none of these positive and negative studies were randomized. Although randomized studies are needed to fully define the role of alloHSCT in Ph+ ALL, especially in patients with deep molecular responses, in practice it is almost impossible to perform large-scale randomized studies of this rare disease especially focusing on alloHSCT. In addition, it is remarkable that there are many confounding factors, especially in patients not undergoing transplant, who may be influenced by donor availability, physician judgment about the appropriateness of alloHSCT, patient choice, or patient ability to proceed to alloHSCT, and this bias could influence DFS and OS. In their absence it seems logical to maintain the indication of alloHSCT in fit patients treated with first or second-generation TKIs, especially for those who do not achieve deep molecular response after induction and consolidation therapy (Figure 1).

The integration of ponatinib into frontline therapy may reduce relapse and, although the current evidence is still limited to one phase II trial with an adequate number of patients and prolonged follow up,[20] it will probably constitute a step forward in the treatment of *de novo* Ph+ ALL. The addition of immunotherapy to TKIs could have an additional favorable impact, but the available data are even more preliminary. If these initiatives could be implemented with little or no treatment-related mortality and could led to durable responses, alloHSCT in first CR could be avoided in the majority of patients with Ph+ ALL. As the second and third-generation TKI administered chronically and the new immunotherapeutic approaches are expensive, economic considerations should also be considered when compared with alloHSCT.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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