Current treatment strategies for Philadelphia chromosome-positive adult acute lymphoblastic leukemia

Han-Seung Park

Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Abstract
Acute lymphoblastic leukemia (ALL) is an aggressive hematological disease. The incorporation of tyrosine kinase inhibitors (TKIs) into the standard treatment regimen for Philadelphia (Ph)-positive ALL significantly improved clinical outcomes. TKI-based induction chemotherapy, followed by allogeneic hematopoietic cell transplantation (HCT) during the first complete remission (CR), is the standard of care for ALL patients. However, treatment with TKIs alone or TKIs plus low-intensity chemotherapy can achieve CR in some patients. Although this strategy is not enough to induce a deeper molecular response, it can reduce the incidence of treatment-related mortality. Despite promising results from pediatric trials, allogeneic HCT remains an important component of the treatment strategy for Ph-positive adult ALL. However, improving the highly sensitive BCR-ABL1 assays and introducing immunotherapy may decrease the demand for allogeneic HCT. Nevertheless, the treatment of Ph-positive ALL is still challenging, especially in cases with relapsed and refractory disease. Potent TKIs and monoclonal antibodies, such as blinatumomab and inotuzumab, have improved patient outcomes in relapse and refractory cases of ALL. The introduction of effective agents, such as potent TKIs and monoclonal antibodies, may improve the possibility of remission in Ph-positive ALL patients and hopefully cure this disease.

Key Words Adult acute lymphoblastic leukemia, Philadelphia positive

INTRODUCTION
Acute lymphoblastic leukemia (ALL) is an aggressive hematological disease [1-4]. Combining high-dose chemotherapy and allogeneic hematopoietic cell transplantation (HCT) improved treatment outcomes in ALL patients [5-10]. Historically, Philadelphia chromosome (Ph)-positive cases of ALL, which comprise about 30% of all adult ALL cases, had a very poor prognosis. The incorporation of tyrosine kinase inhibitors (TKIs) in the treatment of ALL significantly improved treatment outcomes [6]. Nevertheless, the treatment of Ph-positive ALL is still challenging, especially in cases of relapsed and refractory disease. In this review, we will focus on the management of newly diagnosed Ph-positive ALL and highlight recent advances in the treatment of relapsed and refractory ALL.

CURRENT STANDARD TREATMENT STRATEGIES FOR TRANSPLANT-ELIGIBLE PATIENTS

TKI-based treatments improve the rates of complete remission (CR) in Ph-positive ALL patients. After the introduction of TKIs, an allogeneic HCT is performed in up to 80% of patients [11]. Despite the limitations of allogeneic HCT, such as severe graft-versus-host disease (GVHD) and other complications, it remains the standard of care for the treatment of Ph-positive ALL [12, 13]. The UKALLXII/ECOG 2993 study revealed that adult Ph-positive ALL exhibited a significant response to allogeneic HCT [6, 14]. The GRAAPH-2005 trial compared the treatment outcomes after allogeneic HCT with those after autologous stem cell transplantation. The rates of five-year event-free survival and overall survival (OS) were 37% and 46%, respectively. Furthermore, allogeneic HCT showed better survival outcomes in relapse-free survival (hazard ratio of 0.69) and OS (hazard ratio of 0.64) [15]. Other trials suggested a role...
for allogeneic HCT in the treatment of younger adult patients. [6, 16]. All patients who were eligible for transplantation underwent allogeneic HCT after CR, and they reported high rates of survival.

Using RT-PCR to assess the minimal residual disease (MRD) in cases of BCR-ABL1 provides a useful method to identify high-risk patients. Early and deeper molecular responses before allogeneic HCT are associated with better clinical outcomes. A negative MRD score before allogeneic HCT was associated with a significantly improved survival rate and an incidence rate of 8% for disease relapse over a five-year period. In contrast, 39% of patients who did not undergo allogeneic HCT experienced relapse [17]. Kim et al. [8] reported that patients who achieved deeper molecular response during treatment with multiple chemotherapy drugs plus nilotinib before allogeneic HCT showed better long-term outcomes. The outcomes of MRD-positive patients at the time of allogeneic HCT were poorer than those of the MRD-negative cases [18-21].

Although TKI monotherapy and TKIs plus low-intensity chemotherapy have clinical benefits in Ph-positive adult ALL patients, many patients relapsed after treatment. This finding may be due to the high incidence of TKI-resistant T315I mutations among patient populations [9, 23, 25]. TKIs with a higher potency, such as ponatinib, may be effective in treating patients that screen positive for these mutations. Unfortunately, only limited data regarding these findings are available [26]. Combining a TKI with immunotherapy can be a good choice for treatment. Recently, Chiaretti et al. [24] reported the results of a Phase II study focusing on treatment with dasatinib plus blinatumomab, a bispecific T-cell engager. In total, 63 patients were enrolled in the study; each patient received two to three cycles of blinatumomab treatment. Among these patients, the CR rate was 47% and the OS rate was 95% at 10 months.

**IS ALLOGENEIC HCT MANDATORY FOR LONG-TERM SURVIVAL?**

Allogeneic HCT is a long-established strategy for treating patients with Ph-positive ALL. However, this treatment modality has numerous potential adverse effects such as GVHD, veno-occlusive disease, and infection. Younger patients without comorbidities can expect benefits from allogeneic HCT whereas older patients have an increased risk of treatment-related mortality. Although allogeneic HCT is generally considered to be immune to adverse genetic and cytogenetic mutations, some studies concluded that the results of allogeneic HCT in cases of T315I mutation and deletions of CKND2A/2B, PAX5 genes were poor despite allogeneic HCT [27-29].

The AALL0031 study reported the long-term outcomes of Ph-positive pediatric ALL patients after allogeneic HCT. Survival outcomes were similar in patients with and without allogeneic HCT (five-year rates of disease-free survival were 70±12% in the without transplant group, 65±11% in the allogeneic HCT from related donor group, and 59±15% in the allogeneic HCT from unrelated donor group; P=0.60) [30]. Slayton et al. [31] reported positive outcomes for Ph-positive pediatric ALL patients, with five-year OS rates of 86%. In this study, the clinical outcomes of patients who underwent allogeneic HCT were comparable with those of patients who received chemotherapy alone. Despite promising results in pediatric studies, the application of this strategy to Ph-positive adult ALL patients is still being debated. In the UKALLXII/ECOG 2993 study, some patients who did not undergo transplantation sustained a long-term disease-free status after treatment. However, the majority of patients who underwent allogeneic HCT after CR achieved better outcomes (four-year OS rates of 50% in myeloablative conditioning transplant group compared with 39% in the reduced-intensity conditioning transplant group and 19% in the chemotherapy-only group) [6]. Ravandi et al. [16] conducted a U.S. intergroup multicenter trial focusing on 97 patients with Ph-positive adult ALL.
This study reported better survival rates in patients who underwent allogeneic HCT [relapse-free survival (RFS) and OS, P=0.038 and 0.037, respectively].

Although limited data exists regarding the efficacy of the third-generation multi-TKI, ponatinib, Jabbour et al. [32] reported promising clinical results using Hyper-CVAD plus ponatinib treatment. Patients who underwent allogeneic HCT did not show a difference in OS whereas the three-year OS rate was 70% for the allogeneic HCT group versus 87% for the TKI maintenance group. Meanwhile, patients treated with deeper molecular responders had better long-term outcomes; the three-year OS rate for patients with a complete molecular response (CMR) was 81% after 3 months. This study introduced the possibility of a transplantation-free treatment strategy using a third-generation TKI. Furthermore, allogeneic HCT may benefit only MRD-positive patients; however, this question requires further investigation.

NEW CHALLENGES IN RELAPSED PH-POSITIVE ALL TREATMENT

Adding TKIs to chemotherapy regimens and following this with allogeneic HCT improved patient outcomes; unfortunately, the prognosis of relapsed and refractory cases of Ph-positive ALL is still very poor. Kadia et al. [33] reported a phase II study focusing on the use of MTX, vincristine, pegylated-asparaginase, and dexamethasone in relapsed and refractory ALL cases. This treatment regimen yielded a CR rate of 30 to 40% after the first round of salvage chemotherapy [34-36]. Survival outcomes among relapsed and refractory Ph-positive ALL cases of Ph-positive ALL patients is [9, 25]. However, relapse may also occur without ABL1 mutations. In addition to ABL1 mutations, various signaling abnormalities may contribute to relapse.

The use of immunotherapy to treat relapsed and refractory cases of Ph-positive ALL has been less explored compared to the use of immunotherapy to treat cases of Ph-negative ALL. In the Phase II ALCANTARA study, blinatumomab showed promising results in patients with Ph-positive ALL and yielded a median OS of 7.1 months and RFS of 6.7 months. Sixteen out of the 45 (36%) patients achieved CR with 14 patients achieving CMR regardless of prior TKI therapy. Meanwhile, 4 out of 10 patients (40%) with a T315I mutation experienced CR. The authors concluded that blinatumomab showed effective antileukemic effects in relapsed and refractory Ph-positive cases of ALL [37]. Assi et al. reported the results of a retrospective study on 13 patients with relapsed refractory Ph-positive ALL and chronic myeloid leukemia with reasonable clinical outcomes [38]. On comparing blinatumomab with the standard of care in the treatment of relapsed and refractory cases of Ph-positive ALL, the OS after blinatumomab treatment was superior to that associated with the standard of care (hazard ratio=0.81) [39].

Inotuzumab ozogamicin, a humanized anti-CD22 monoclonal antibody conjugated to calicheamicin, is another promising agent for treating ALL. In the Phase III randomized INO-VATE study, remission rates did not differ significantly between the inotuzumab ozogamicin group and the standard chemotherapy group among patients with Ph-positive ALL [40]. Although this study failed to prove the clinical superiority of inotuzumab ozogamicin over standard chemotherapy regimens in patients with relapsed and refractory Ph-positive ALL, inotuzumab ozogamicin showed favorable rates of CR (78.6% vs. 44.4%, P=0.08). The introduction of powerful drugs, such as blinatumomab and inotuzumab, and innovative prospective clinical trials, such as TKIs with immunotherapy or TKIs with other combinations of targeted therapy, and the adoption of frontline immunotherapy is currently ongoing.

FUTURE DIRECTIONS

The incorporation of TKIs in the treatment of Ph-positive ALL significantly improved clinical outcomes. However, the clinical outcomes in patients with relapsed and refractory Ph-positive cases of ALL are still grave. The rapid development of monoclonal antibodies led to a breakthrough in the treatment of relapsed and refractory cases of ALL. Future studies should reveal the optimal combinations of monoclonal antibodies with or without standard chemotherapy. Currently, studies using monoclonal antibodies to treat newly diagnosed cases of Ph-positive ALL are ongoing. If these potent monoclonal antibodies can reduce the intensity of standard chemotherapy regimens, treatment-related mortality rates may reduce during treatment. Moreover, if these approaches can achieve deeper and durable molecular responses, it may decrease the demand for allogeneic HCT.

There are several issues regarding chimeric antigen receptor (CAR) T-cell therapies for Ph-positive ALL. Currently, the anti-CD19 CAR T-cell is approved for the treatment of relapsed and refractory ALL cases in children and young adults. Long-term follow-up data on CD19 CAR T-cell therapy for treating relapsed ALL cases showed impressive outcomes, especially in 16 Ph-positive adult ALL patients [41]. The positive effects of CAR T-cell treatments are undeniable, but there is debate over whether CAR T-cell therapy can replace allogeneic HCT [42]. Whether CAR T-cell therapy is to be applied before or after immunotherapy is another question because there are concerns about target-antigen modulation after immunotherapy [43].

CONCLUSION

Treatment strategies for Ph-positive ALL patients are rapidly changing. Fortunately, the introduction of effective
agents, such as potent TKIs and monoclonal antibodies, may improve the possibility of remission in Ph-positive ALL patients and hopefully cure this disease.

**Authors’ Disclosures of Potential Conflicts of Interest**

No potential conflicts of interest relevant to this article were reported.

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