

# Tyrosine Kinase Inhibitor for Treatment of Adult Allogeneic Hematopoietic Stem Cell Transplantation Candidate with Philadelphia-Positive Acute Lymphoblastic Leukemia

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Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) accounts for approximately 25–33% of all adult ALL cases. Its prognosis was dismal until the introduction of tyrosine kinase inhibitors (TKIs) in clinical applications. TKIs combined with chemotherapy resulted in higher rates of complete remission (CR) and complete molecular remission (CMR) compared with chemotherapy alone. However, allogeneic stem cell transplantation (allo-SCT) has been considered the only potentially curative option once the patient achieves CR. There are still questions that remain unanswered regarding the use of TKIs prior to or after allo-SCT. Imatinib was the first TKI used for induction and maintenance therapy in combination with chemotherapy. What is its optimal dosage and how long should it be maintained? Does the second generation of TKIs result in a better outcome in terms of induction and maintenance? Is there a cured fraction of patients who might achieve long-term survival without allo-SCT, and if yes, how could these patients be identified? What is the role of TKIs use after allo-SCT? Herein, evidence regarding the use of TKIs prior to and after allo-SCT is discussed.

## USE OF TYROSINE KINASE INHIBITORS PRIOR TO ALLOGENEIC STEM CELL TRANSPLANTATION

### Efficacy of induction and maintenance

Before the era of TKIs, 60–90% of Ph+ ALL patients achieved CR after induction chemotherapy, and <20% of patients achieved long-term leukemia-free survival (LFS).<sup>[1]</sup> The long-term LFS after allo-SCT was 30–50%.<sup>[2,3]</sup> The international ALL trial MRC UKALL XII/ECOG2993 enrolled 267 Ph+ ALL patients (<55 years old) who received

allo-HSCT with sibling or matched unrelated donors from 1993 to 2004. The 5-year overall survival (OS) was 44% after sibling allo-SCT, 36% after matched unrelated allo-SCT, and 19% after chemotherapy.<sup>[3]</sup>

The introduction of TKIs in clinical applications induced dramatic changes in the patient outcomes of Ph+ leukemia. Thomas *et al.*<sup>[4]</sup> showed that the rate of CR was 96% in newly diagnosed Ph+ ALL patients treated with imatinib combined with chemotherapy. Sixty percent of the patients achieved CMR. The 2-year LFS was 85%, and there was no unexpected toxicity related to the use of imatinib. This study was the first large study on the treatment of adult Ph+ ALL with TKI combined chemotherapy. The results suggested that this combination strategy resulted in a higher CR rate, a deeper molecular remission, and a similar tolerance, compared with chemotherapy alone. The improved CR and CMR rates provide efficient time for patients to find a suitable donor and to complete the preparation procedures for allo-SCT. The doses of imatinib varied substantially, and the effect of its dose intensity on outcomes has not been well explored in the setting of Ph+ ALL. Lim *et al.*<sup>[5]</sup> showed that a dose intensity of 600 mg imatinib daily during the initial 7–8 weeks was strongly correlated with longer CR duration and superior OS. The intensity of the combined chemotherapy, either for induction or consolidation

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after CR, has been recommended as the same as that for Ph-negative ALL without L-asparaginase, such as vindesine, daunorubicin, cyclophosphamide, and prednisone.<sup>[6]</sup> This strategy is aimed at the achievement of rapid and deep CR. Reduced-intensity chemotherapies, such as vindesine and prednisone, should be avoided except in the cases of unfit, elder patients.

There were very little data regarding using second-generation TKIs for Ph+ ALL. Dasatinib was approved to be effective in imatinib-resistant Ph+ ALL.<sup>[7]</sup> Oral administration of dasatinib achieves a therapeutic concentration in the cerebrospinal fluid, showing that it is advantageous for the treatment of acute leukemia in comparison with imatinib. Ottmann *et al.*<sup>[8]</sup> reported that 42% of 36 imatinib-resistant Ph+ ALL patients achieved hematological remission with dasatinib treatment combined with chemotherapy. Ravandi *et al.*<sup>[1]</sup> conducted a phase II study combining the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen with dasatinib in newly diagnosed patients (median age of 53 years, range: 21–79). With a median follow-up of 14 (range: 4–37) months, 94% of the patients achieved CR, and the 2-year survival rate was 64%. More recent data suggest that dasatinib treatment resulted in deeper complete hematologic remission and cytogenetic remission compared with imatinib regimen. In the GIMEMA LAL 1205 protocol from multiple centers in Italy, patients with newly diagnosed Ph+ ALL, older than 18 years of age, received dasatinib induction therapy for 84 days combined with steroids for the first 32 days and intrathecal chemotherapy for the remaining days. Totally 53 patients (median age of 54 years) achieved CR. At 20 months, the OS was 69.2% and the LFS was 51.1%. The LFS was significantly higher in patients who showed a decrease in the breakpoint cluster region and the Abelson leukemia virus (*BCR-ABL*) levels to  $<10^{-3}$  at day 85 compared with patients who did not reach these levels.<sup>[9]</sup> A report from the European Working Group on Adult ALL group showed the outcomes of elder patients ( $n = 71$ , all  $>55$  years, median age: 69 years) with dasatinib (140 mg/d, 100 mg/d over 70 years) with low-intensity chemotherapy. The CR rate was 96%, the CMR rate was 65% during consolidation, and the 5-year OS was 36%.<sup>[10]</sup>

### Is there a subgroup that might achieve long-term survival without allogeneic stem cell transplantation?

TKIs combined with chemotherapy results in CMR in some adult Ph+ ALL patients. This fact has raised the question of whether some of these patients with CMR could be cured without allo-SCT. There were a few small cohort studies showing that the prognosis of patients treated with imatinib-combined chemotherapy was similar to those who received allo-SCT in CR1. In the report by Thomas *et al.*,<sup>[4]</sup> six of the ten patients who did not receive allo-SCT were still alive without recurrence of disease after a median follow-up of 20 months. Kuang *et al.*<sup>[11]</sup> reported the clinical results of sustaining integrating imatinib and interferon (IFN)- $\alpha$  in maintenance therapy in patients ineligible for allo-SCT.

Maintenance therapy lasted for 5 years with an imatinib dose of 400 mg daily, an IFN- $\alpha$  dose of 3 million units at 2–3 doses/week, and chemotherapy that included vindesine and dexamethasone. For 41 patients without allo-SCT with a median follow-up of 32 months, the 3-year LFS and OS were 42.7% and 57.9%, respectively. *BCR/ABL* persistent negativity at 6 and 9 months might be beneficial in choosing suitable patients for the imatinib/IFN- $\alpha$  maintenance strategy.

Ravandi *et al.*<sup>[12]</sup> demonstrated the predictive value of minimal residual disease (MRD) assessment by real-time quantitative polymerase chain reaction (RQ-PCR) and multiparameter flow cytometry (MFC) in Ph+ ALL patients at CR1. With a median follow-up of 383 (range: 232–501) weeks for patients using imatinib ( $n = 54$ ) and 123 (range: 1–235) weeks for dasatinib ( $n = 68$ ), the 3-year OS of patients who were negative for MRD by MFC at 3 months and 12 months after CR1 was 65–70% and over 80%, respectively. For patients with an MRD  $<0.1\%$  by RQ-PCR after 3 or 9 months of CR1, the 3-year OS was over 60%. A long-term follow-up of the Group for Research on Adult Acute Lymphoblastic Leukemia Philadelphia-positive-2003 trial described the outcomes of 45 patients whose postremission therapy was partly decided by MRD results.<sup>[13]</sup> Imatinib doses of 600–800 mg daily were given with consolidation chemotherapy. The OS was 50% after allo-SCT ( $n = 24$ ), 33% for patients without allo-SCT ( $n = 9$ ), and 80% after autologous SCT ( $n = 10$ ). Seven of the ten patients achieved CMR (MRD  $<10^{-4}$ ). Short *et al.*<sup>[14]</sup> showed that patients with Ph+ ALL who achieved CMR at 3 months had superior survival compared with those with less significant molecular responses (median OS: 127 vs. 38 months,  $P = 0.009$ ; relapse-free survival: 126 vs. 18 months,  $P = 0.007$ ), even without allo-SCT. A prospective controlled study is needed to determine whether autologous SCT with CMR should be performed instead of allo-SCT.

## USE OF TYROSINE KINASE INHIBITORS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Recent data suggest that TKI maintenance after allo-SCT could markedly improve outcomes. Chen *et al.*<sup>[15-16]</sup> reported the efficacy of imatinib in preventing hematological relapse and improving LFS when administered to Ph+ ALL patients after allo-SCT with haploidentical or matched unrelated donors without *ex vivo* T-cell depletion. The results demonstrated that the estimated 5-year relapse rate was lower in the imatinib-prophylaxis group compared with the nonimatinib-prophylaxis group (10.2% vs. 33.1%,  $P < 0.001$ ). The 5-year LFS was remarkably higher in the imatinib-prophylaxis group (81.5% vs. 33.5%,  $P < 0.001$ ) compared with the nonimatinib-prophylaxis group. The authors drew similar conclusions from the patients who received prophylactic use of TKIs after haploidentical ( $n = 101$ ) or matched sibling ( $n = 38$ ) allo-SCT. At a median follow-up of 36 months, the 5-year LFS and OS in the haploidentical and matched sibling groups were 65.8% and 74.0%, respectively.<sup>[17]</sup> Pfeifer

*et al.*<sup>[17]</sup> performed a randomized trial of prophylactic or MRD-triggered imatinib after allo-SCT. The early occurrence of MRD positivity or positivity at higher levels identified a subset of patients who did not benefit from imatinib. Due to its advantage for the prevention of disease recurrence, the prophylactic use of TKIs after allo-SCT was recommended recently in the consensus by the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation.<sup>[18]</sup>

In summary, with the introduction of TKIs in the first-line therapy combined with chemotherapy, the outcomes of adult Ph+ ALL patients have been greatly improved compared with chemotherapy alone. Prospective trials are needed to determine the optimal dosage and length of maintenance of TKIs and the indication for the first line use of second-generation TKIs. Allo-SCT remains the only cure option for all patients who achieved CR. Whether the treatment strategy should be allo-SCT or TKIs combined with chemotherapy is controversial when the patients lack a matched sibling or unrelated donor. The right recommendation relies not only on the efficacy of TKIs combined with chemotherapy but also on the safety of allo-SCT from alternative donors. It is important to note that the safety and efficacy of allo-SCT from alternative donors have been improved in recent years, especially in China. When making decisions for individual patients, the physical condition of the patients and the transplantation experience of the medical center should be considered. A subgroup of patients who achieve early and durable CMR might have a potential opportunity for long-term survival with maintenance of TKIs combined with chemotherapy, IFN, or autologous SCT. The monitoring of MRD should be routinely performed for the assessment of relapse risk and adjustment of the therapeutic strategy.

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