Outcome of Allotransplants in Patients with Chronic-phase Chronic Myeloid Leukemia Following Imatinib Failure: Prognosis Revisited

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Abstract. *Background: The outcome of allotransplants in patients with chronic -phase (CP) chronic myeloid leukemia (CML) who progressed to accelerated phase (AP) or blast phase (BP) following imatinib failure, especially those without preceding suboptimal response, remains unclear. Patients and Methods: One hundred and five patients with newly-diagnosed CML-CP were retrospectively reviewed. Sixty-six patients received first-line imatinib therapy, 26 received interferon followed by imatinib, and 13 received front-line allotransplants. Results: No significant differences were found in overall survival (p=0.57) and blast-free survival (p=0.25) between different first-line therapies. Among 66 imatinib-treated patients, 18 (27.3%) developed imatinib failure, 14 (21.2%) progressed to AP/BP, including eight without preceding suboptimal response. Compared to front-line allotransplant, patients with imatinib failure had a significantly worse overall survival after allotransplants (p=0.015), mainly due to an increase of treatment-related mortality. Conclusion: Early recognition of imatinib-treated patients who should receive an allotransplant is important rather than waiting until imatinib failure with disease progression.*

Treatment of patients with newly-diagnosed chronic myeloid leukemia (CML) in chronic phase (CP) has changed following the introduction of tyrosine kinase inhibitors (TKI) (1-3). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a confirmed curative approach which has benn widely applied as front-line therapy before the TKI era. Allo-HSCT is currently reserved as a second- or third-line therapy for patients in the accelerated phase (AP) or blast phase (BP) at diagnosis after TKI pre-treatment, those with imatinib failure with progression to AP/BP after second-generation TKI therapy, those with the breakpoint cluster region–Abelson (BCR–ABL) kinase domain T315I mutation, and those who failed second-generation TKI therapy (3-5). However, approximately 15-25% patients fail imatinib therapy due to primary resistance, loss of initial response, or intolerance (4, 5). Identification of the causes of imatinib failure is important when determining choosing treatment. Although disease progression to AP/BP has been less commonly seen in imatinib-treated CP patients with regular cytogenetic and molecular monitoring, it can be found in some patients at the time of imatinib failure without their having a preceding suboptimal response. Allo-HSCT remains an important treatment option in patients who progress to AP/BP following imatinib failure; however, the outcomes of allo-HSCT under such conditions, especially for those without preceding suboptimal response, remain poorly-reported.

Patients and Methods

One hundred and five patients with newly-diagnosed CML-CP with regular follow-up at the Kaohsiung Medical University Hospital from 1999 to 2011 were retrospectively reviewed. Informed consent and approval was obtained from the Institutional Review Boards of Kaohsiung Medical University Hospital (KMUH-IRB-20110202). Patients with AP or BP at diagnosis were excluded. Sixty-six patients received imatinib as first-line therapy, 26 patients who were diagnosed before 2003 initially received interferon therapy and then were administered imatinib,

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Key Words: Chronic myeloid leukemia, hematopoietic stem cell transplantation, tyrosine kinase inhibitor, imatinib, allotransplantation.

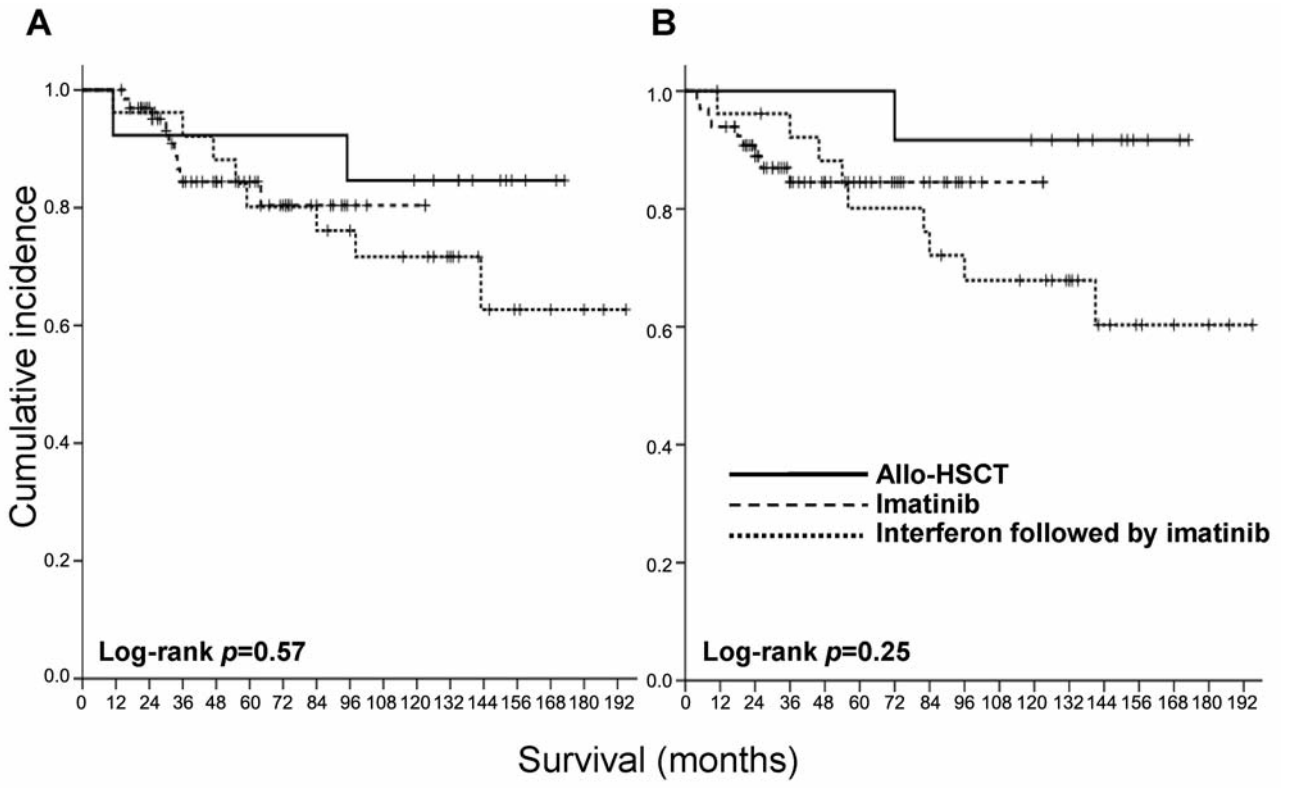

Figure 1. *Comparison of overall survival (A) and blast-free survival (B) in all patients with newly-diagnosed chronic-phase chronic myeloid leukemia categorized by first-line treatment.*

and 13 patients treated with an intention-to-cure received allo-HSCT as front-line therapy with short-term pre-transplant interferon without imatinib. In patients receiving first-line imatinib, cytogenetic and molecular responses were evaluated regularly according to the European Leukemia Net recommendations (3). *BCR–ABL* kinase domain mutation was performed by direct sequencing when imatinib failure occurred.

Twenty-two (21.0%) patients received allo-HSCT, including 13 as front-line therapy and nine following imatinib failure. No significant difference was noted between front-line therapy group and imatinib failure group in terms of age, sex, donor type, sex-mismatch, stem cell source, conditioning regimen, graft-*versus*-host disease (GVHD) prophylaxis and $(CD34)^+$ cell number. Patients with imatinib failure and disease progression had a higher European Group for Blood and Marrow Transplantation (EBMT) risk score ($p=0.03$) due to a more advanced disease status at allo-HSCT and a longer duration from CML diagnosis to allo-HSCT.

The categorical variables were analyzed by chi-square tests and Fisher's exact tests. Kaplan–Meier analysis was performed to estimate survival outcomes, including overall survival (OS) and blast-free survival (BFS), and these were compared by log-rank tests. Cox proportional hazards regression was performed for multivariate analysis. All analyses were performed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). A *p*-value of <0.05 indicates a statistically significant difference.

Results

Regarding the first-line treatment in all CP patients (n=105), no significant difference was found in OS ($p=0.57$) and BFS ($p=0.25$) in patients receiving imatinib, interferon followed by imatinib, and front-line allo-HSCT (Figure 1). Disease progression to BP was found in 19 (18.1%) patients, conferring a significantly worse OS when compared with those without progression to BP ($p<0.001$). Among the patients progressing to BP, there was no significant difference in OS between patients receiving first-line imatinib or interferon followed by imatinib ($p=0.57$), and between patients receiving or not receiving subsequent allo-HSCT ($p=0.39$).

Among the patients treated with first-line imatinib (n=66), 18 (27.3%) developed imatinib failure, 14 (21.2%) already progressed to AP/BP, including eight (12.1%) who had progressed to AP/BP when imatinib failure was documented. These patients were of great concern since disease progression was found the first time imatinib failure occurred without any preceding suboptimal response. Further analysis of these patients revealed clonal evolution in four (50%) [multiple chromosome abnormalities, additional t(8;21), additional trisomy 8, and t(9;15;22), respectively] and *BCR–ABL* mutations in two (25%)

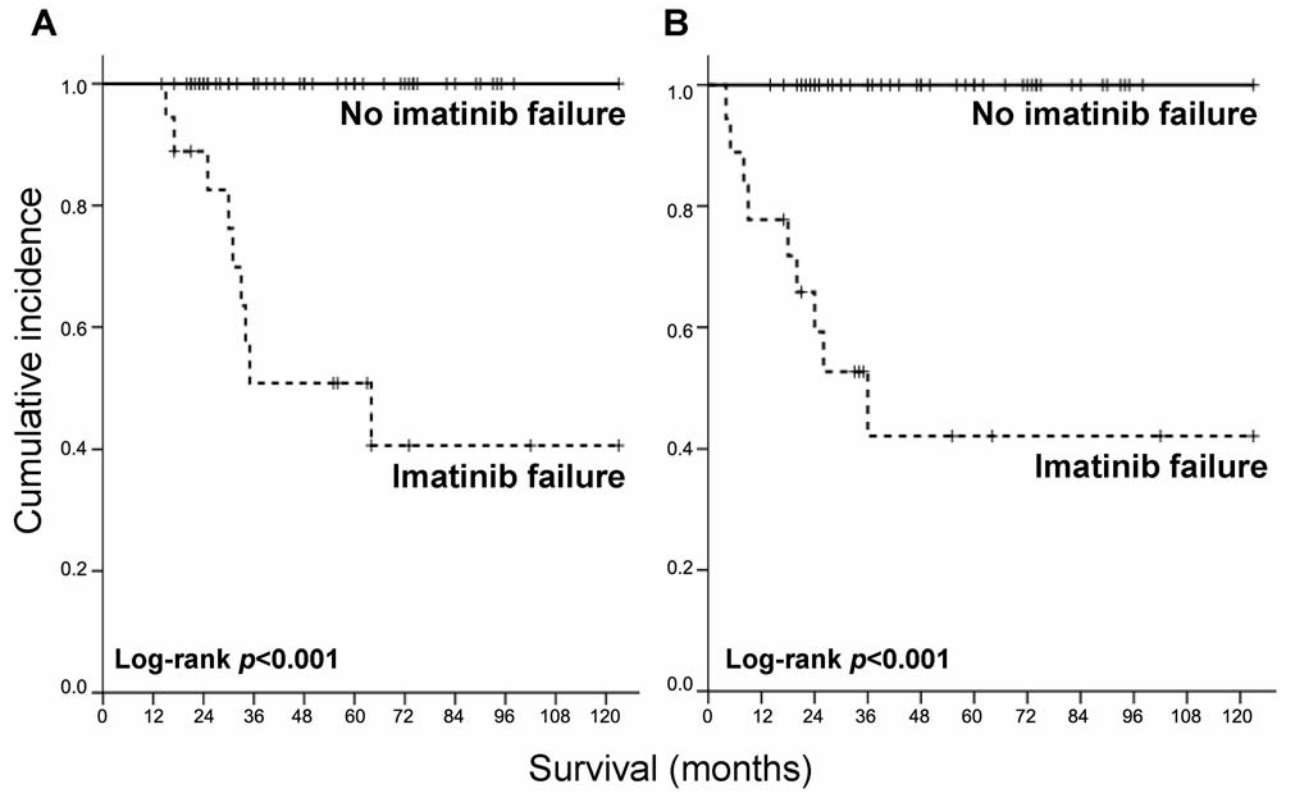

Figure 2. *Comparison of overall survival (A) and blast-free survival (B) in patients with chronic-phase chronic myeloid leukemia receiving imatinib as first-line treatment.*

(T315I/E255K and T315I, respectively). Patients developing imatinib failure had a significantly poor OS ($p<0.001$) and short BFS ($p<0.001$) when compared with those who did not develop imatinib failure (Figure 2).

Allo-HSCT was performed in nine out of 18 patients with imatinib failure, including eight with disease progression to AP/BP when imatinib failure occurred. Failure of second-generation TKI therapy was found in 67.7% prescriptions (median treatment duration=5.5 months, range=4-8 months). There were no relapses (median follow-up=31 months, range=1-116 months) following allo-HSCT in patients developing imatinib failure with disease progression, with a 3-year survival rate of 50% (95% CI=10-31 months). Causes of death were chronic GVHD (n=2), acute GVHD (n=1), and infection complications (n=1), indicating an increased rate of treatment-related mortality (TRM). Among the nine patients who failed imatinib therapy and did not subsequently receive allo-HSCT, increasing imatinib dosage and second-generation TKIs were used but six eventually progressed to the AP/BP and five (55.6%) died of disease.

Among patients receiving allo-HSCT (n=22), patients with imatinib failure and disease progression had a significantly worse OS ($p=0.015$, Figure 3A) compared to those receiving allo-HSCT as front-line therapy (median follow-up=134 months, range=6-167 months). Only one patient died of relapse and one of chronic GVHD among patients receiving front-line allo-HSCT, with a 3-year survival rate of 91.7% (95% CI=29-38 months). There was a trend for poor OS in groups with higher EBMT score (log-rank $p=0.11$, 0.07, 0.53, respectively for EBMT score 0-2 *versus* 5-7, score 3-4 *versus* 5-7, and score 0-2 *versus* 3-4), however, the difference was more prominent between front-line therapy and imatinib failure groups (Figure 3B). An interval of less than one year from CML diagnosis to allo-HSCT led to a borderline better OS compared with an interval of one year or more ($p=0.06$). Pre-transplant imatinib had no adverse impact on allo-HSCT in terms of TRM ($p=0.11$), relapse rate ($p=0.99$), grade II-IV acute GVHD ($p=0.67$), and extensive chronic GVHD ($p=0.25$). Among patients receiving allo-HSCT following imatinib failure, no OS difference was found between the AP and second CP status at the time of allo-HSCT ($p=0.46$), between patients with and those without *BCR–ABL* kinase domain mutation ($p=0.75$), and between patients with and those without clonal evolution ($p=0.24$). In multivariate analysis, patients with imatinib failure and disease progression had still a borderline significance of poor OS after allo-HSCT ($p=0.06$).

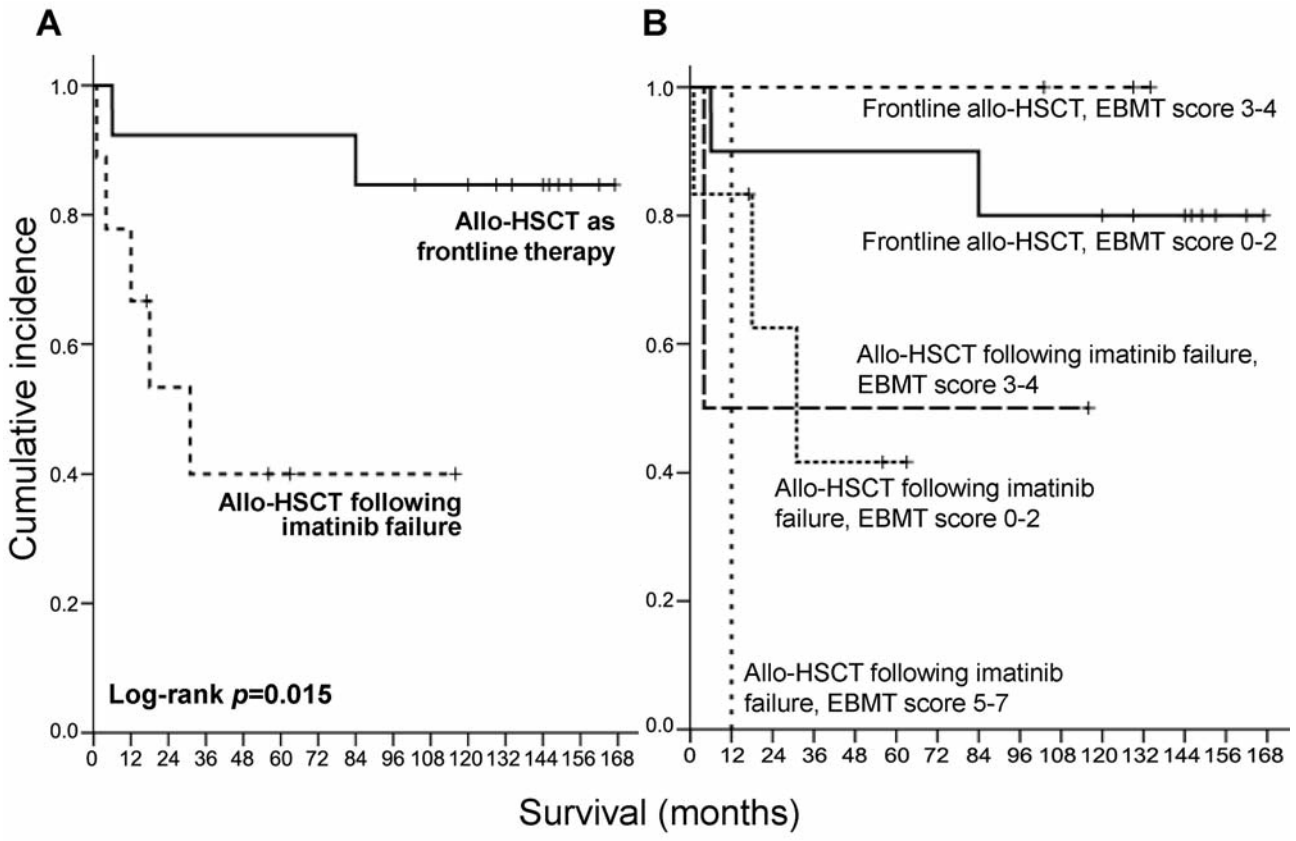

Figure 3. *Comparison of overall survival after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients receiving allo-HSCT following imatinib failure and in patients receiving allo-HSCT as front-line therapy (A) and further categorized by different risk score groups (B).*

Discussion

Currently, the case numbers regarding allo-HSCT in advanced phases of CML (AP, BP, and second CP) after imatinib failure are limited. In an interim analysis of the German CML Study IV, the 3-year OS was 59% for 28 patients receiving allo-HSCT in advanced phases following pre-transplant TKIs (6). In another study analyzing 47 patients receiving allo-HSCT following imatinib failure, including 29 progressing to AP/BP, the 2-year OS rate was 59% in advanced disease and outcomes were worse in patients with *BCR–ABL* mutations (7). In our analysis, the 3-year survival rate after allo-HSCT in imatinib failure with advanced disease was 50%, similar to previous studies, despite no survival disadvantage in the mutation group due to the limited number of cases. However, such a survival rate is much lower than that for patients who traditionally received allo-HSCT as front-line therapy before the TKI era, raising the argument whether allo-HSCT is more beneficial when performed at an early stage than at the stage of disease progression following imatinib failure in certain CP patients, especially those with rapid progression without preceding suboptimal response.

Whether or not patients with imatinib failure should receive allo-HSCT or second-generation TKIs is under debate. Early recognition of a lower probability of benefit from second-generation TKIs and preventing disease progression to AP/BP is important. Several factors have been associated with outcomes after therapy with second-generation TKIs, including failure to achieve major cytogenetic response (CyR) at 12 months (8), lack of CyR and performance status (9), and a combination of low Sokal score, best CyR, neutropenia, and time-to-therapy for second-generation TKIs (10). However, some of our patients who achieved complete CyR developed imatinib failure without a preceding suboptimal response even within 12 months, and 67.7% of these patients failed second-generation TKI therapy, implying the importance of earlier allo-HSCT intervention rather than delaying until the failure of second-generation TKIs with disease progression.

The mechanisms are still unknown for patients with 'abrupt' disease deterioration without preceding suboptimal response, even though they were under regular cytogenetic and molecular monitoring as the European Leukemia Net recommends (3). Clonal evolution and mutations are associated with imatinib failure and were found in most of our

patients, therefore more frequent cytogenetic and molecular monitoring is necessary for earlier detection before disease progression. Furthermore, the interpretation of our findings should be cautious for borderline significance in multivariate analysis, the retrospective study design, and a relatively limited case number. Since patients with imatinib failure and disease progression tend to have a higher EBMT risk score, it is important to recognize such patients early, in order to prevent performing allo-HSCT at a higher EBMT score status.

In summary, patients with CML-CP who received first-line imatinib therapy and developed failure with disease progression had a significantly poorer survival after allo-HSCT compared to patients receiving allo-HSCT as a frontline therapy, mainly due to an increase of TRM. Despite the limited number of cases, the findings suggest that frontline allo-HSCT remains important in certain patients with CML-CP, especially those without preceding suboptimal response. Early recognition of such patients in order to receive allo-HSCT is important rather than delaying until imatinib failure with disease progression. Further studies enrolling more patients are warranted.

Conflicts of Interest

The Authors declare no conflicts of interest.

Acknowledgements

This study was supported by grants from the Kaohsiung Medical University (Q97011) and the Kaohsiung Medical University Hospital (93-KMUH-022).

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Received July 29, 2013
Revised September 13, 2013
Accepted September 16, 2013