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Original Article

Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric and Young Adult Patients with Chronic Myeloid Leukemia in Tyrosine Kinase Inhibitor Era: A Study of the Korean Blood and Marrow Transplantation Registry

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Purpose Chronic myeloid leukemia (CML) in children, adolescents, and young adults is rare and differs from older adults. This study evaluated the outcomes of allogeneic hematopoietic stem cell transplantation (HSCT) in young Korean CML patients during the tyrosine kinase inhibitor (TKI) era.

Materials and Methods A retrospective analysis of 35 CML patients aged < 40 years who underwent allogeneic HSCT from 2009 to 2019 was conducted using Korean Blood and Marrow Transplantation Registry data. Patients were grouped by age < 20 years at HSCT (group 1, n=15) and 20-40 years at HSCT (group 2, n=20). Survival outcomes including overall survival (OS), relapse-free survival (RFS), and event-free survival (EFS) were analyzed using the Kaplan-Meier method.

Results The median time between diagnosis and HSCT was 8.9 months. All the patients achieved engraftment but platelet recovery was significantly slower in group 1 (p=0.034). Acute and chronic graft-versus-host disease occurred in 54.3% and 34.3%, respectively. Five-year OS, RFS, and EFS rates of total patients were 66.8%, 50.8%, and 47.6%, with better OS was observed in group 1 by multivariable analysis (p=0.048). Disease status at HSCT was a significant predictor of OS (p=0.028), RFS (p=0.003), and EFS (p=0.004). Disease progression occurred in 13 out of 35 patients (37.1%); treatment-related mortality accounted for 63.6% of deaths (7 out of 11).

Conclusion When performed at a younger age, allogeneic HSCT result in superior outcome in CML. Achieving remission before HSCT is critical for improved outcomes, highlighting the importance of pretransplant remission via optimal TKI strategies and minimal residual disease monitoring.

Key words Chronic myeloid leukemia, Child, Young adult, Tyrosine kinase inhibitors, Hematopoietic stem cell transplantation, Treatment outcomes

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm originating from the *BCR::ABL1* fusion gene, accounting for 2%-3% of leukemia cases in children younger than 15 years and 9% of leukemia cases in adolescents between 15 and 19 years of age [1,2]. Most cases of CML occur in adults, with the average and median age of onset being > 60 years [1,3].

The discovery of tyrosine kinase inhibitors (TKIs) in the late 1990s revolutionized the treatment of patients with CML [4,5]. The success of TKI therapy has significantly changed the therapeutic algorithm for CML, transforming it from a fatal disease to a manageable condition with near-normal life expectancy [6-8].

Given the low incidence of CML in young age, current practice guidelines are primarily derived from those established for adult patients. However, evidence suggests that pediatric and young adult CML differ genetically from CML in the adult population and tend to manifest clinically more aggressively at diagnosis [1,9].

Some studies have indicated that children and young adult patients have lower rates of complete cytogenetic and major molecular responses than older adults, along with a potentially higher risk of transformation to the accelerated phase (AP) and blast phase (BP) [10].

Before the development of TKI, drug therapy for CML was limited to nonspecific agents, such as busulfan, hydroxyurea, and interferon-alpha, whereas allogeneic hematopoietic stem cell transplantation (HSCT) was the only method used to cure CML [11]. Although the use of HSCT has declined since the introduction of TKI, it remains beneficial for

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patients with CML in the BP or AP, as well as for those who are unresponsive or intolerant to TKI treatment [12-14].

As treatment-free remission is currently becoming a clinical goal, only a minority of patients can discontinue TKIs [15,16]. Therefore, HSCT may play a critical role in children and adolescents/young adults to avoid prolonged exposure to TKIs. Despite the effectiveness of TKIs in managing CML, the unique challenges associated with treating pediatric and young adult patients necessitate a nuanced approach [16]. The potential long-term side effects of TKIs, including effects on growth and development, highlight the importance of optimizing treatment strategies to balance disease control and quality of life [17-19]. Moreover, the genetic differences and aggressive clinical presentation of pediatric and young adult CML underscore the need for tailored therapeutic protocols and the integration of novel agents to improve outcomes [9].

This study evaluated the outcomes of pediatric, adolescent, and young adult patients with CML who underwent allogeneic HSCT in the TKI era. This study aimed to evaluate the impact of age at the time of HSCT on treatment outcome by comparing patients younger than 20 years with those aged 20 to 40 years. In an effort to provide insights into improving treatment strategies for this specific patient population, additional clinical characteristics associated with survival outcomes after HSCT in CML were examined.

Materials and Methods

1. Study population

To investigate the utilization and outcomes of allogeneic HSCT in Korean children, adolescents, and young adults with CML, we retrospectively analyzed patients enrolled in the Korean Blood and Marrow Transplantation Registry (KBMTR) between 2009 and 2019. The KBMTR is a registry established and maintained by the Korean Society of Blood and Marrow Transplantation, containing data on 10,500 HSCTs from 45 hospitals in South Korea.

A total of 81 patients with CML who had undergone allogeneic HSCT within these 10 years were included in this study. For a more comprehensive analysis, we selected 35 individuals under 40 years of age at the time of HSCT. This age-based stratification enabled a detailed retrospective investigation. We categorized these patients into two groups based on their age at the time of HSCT: those younger than 20 years (group 1) and those 20 years or older (group 2). The disease status at HSCT was classified as complete remission (molecular and/or cytogenetic remission), or active disease (including partial response, refractory/relapsed disease, and untreated disease). Neutrophil engraftment was defined as the first day of consecutive 3 days with the absolute neutrophil count is > 500/mm^3. Platelet engraftment was defined as the first of three consecutive days with sustained platelet count of > 20×10^9/L without transfusion.

2. Statistical analysis

Descriptive statistics are presented as frequencies with percentages for categorical variables and medians with ranges for continuous variables. Differences in variables between the groups were assessed using Fisher's exact test with a p-value approximation by Monte Carlo simulation (for categorical variables) and the Kruskal-Wallis test (for continuous variables).

Overall survival (OS) was defined as the interval between HSCT and death or last follow-up. Relapse-free survival (RFS) was defined as the time from HSCT to the first occurrence of relapse, death, or last follow-up. Event-free survival (EFS) was defined as the time from HSCT to the first occurrence of an event (relapse, disease progression, second malignant neoplasm [SMN], or death) or the last follow-up.

The Kaplan-Meier method was used to estimate the OS, RFS, and EFS rates with 95% confidence intervals (CIs). A log-rank test was used to compare the survival curves for each group. All p-values were two-sided, and $p < 0.05$ was considered statistically significant. For univariable and multivariable analysis, Cox regression was used to explore the impact of clinical characteristics on OS. Factors with a p-value below 0.1 by univariable analysis were further examined using multivariable analysis. All statistical analyses were performed using STATA/MP 17.0 (StataCorp LLC).

Results

1. Patient characteristics

During the study period, 81 patients diagnosed with CML were included in the KBMTR database for allogeneic HSCT. Among these, 35 patients under the age of < 40 years were examined retrospectively. Of these, 23 were male and 12 were female. The median age at diagnosis of all patients was 20.3 years (range, 4.0 to 36.7 years), and the median time from CML diagnosis to HSCT was 8.9 months (range 3.0 to 137.5 months). A total of 15 patients were under 20 years of age at the time of HSCT (group 1), and 20 patients were 20 years old or older (group 2). There were no significant differences in clinical characteristics between the two groups, except for age ($p < 0.001$) and sex ($p=0.006$). At diagnosis, seven patients were in BP, one in the AP, and 26 in the chronic phase (CP). One patient's disease phase was not reported. Total patients' clinical characteristics and HSCT data are summarized in Table 1.

Table 1. Patient and HSCT characteristics

Characteristic	Total patients (n=35)	Age at HSCT < 20 yr (group 1, n=15)	Age at HSCT ≥ 20 yr (group 2, n=20)	p-value
Sex				
Male	23 (65.7)	6 (40.0)	17 (85.0)	0.006
Female	12 (34.3)	9 (60.0)	3 (15.0)	
Age at diagnosis (yr)	20.3 (4.0-36.7)	16.4 (4.0-18.6)	26.1 (19.2-36.8)	< 0.001
Age at HSCT (yr)	24.5 (4.6-38.4)	17.7 (4.6-19.0)	31.1 (22.8-38.3)	< 0.001
Status at diagnosis				
Chronic phase (CP)	26 (74.3)	9 (60.0)	15 (75.0)	0.449
Accelerated phase (AP)	1 (2.9)	1 (6.7)	0	
Blast phase (BP)	7 (20.0)	4 (26.7)	5 (25.0)	
N/A	1 (2.9)	1 (6.7)	0	
Status at HSCT				
In remission	28 (80.0)	12 (80.0)	16 (80.0)	> 0.99
Active disease	7 (20.0)	3 (20.0)	4 (20.0)	
Indication for HSCT				
High risk at diagnosis (BP, etc.)	10 (28.6)	5 (33.3)	5 (25.0)	0.694
Suboptimal TKI response	12 (34.3)	6 (40.0)	6 (30.0)	
Transformation (CP to others)	6 (17.1)	1 (6.7)	5 (25.0)	
TKI intolerance	3 (8.6)	1 (6.7)	2 (10.0)	
T351I mutation	1 (2.9)	0	1 (5.0)	
Physician's choice	2 (5.7)	1 (6.7)	1 (5.0)	
N/A	1 (2.9)	1 (6.7)	0	
Donor type				
Matched sibling	14 (40.0)	6 (40.0)	8 (40.0)	0.861
Matched unrelated	8 (22.9)	3 (20.0)	5 (25.0)	
One or two-mismatched	8 (22.9)	4 (26.7)	4 (20.0)	
Haploidentical	4 (11.4)	1 (6.7)	3 (15.0)	
N/A	1 (2.9)	1 (6.7)	0	
Conditioning intensity				
MAC	19 (54.3)	10 (66.7)	9 (45.0)	0.203
RIC/NST	16 (45.7)	5 (33.3)	11 (55.0)	
Stem cell count				
TNC ($\times 10^8$/kg)	9.05 (1.10-31.85)	7.37 (1.10-31.85)	11.53 (2.25-21.77)	0.229
CD34+ cells ($\times 10^6$/kg)	5.23 (1.20-30.63)	4.55 (1.20-15.95)	6.53 (2.32-30.63)	0.191
Acute GVHD	19 (54.3)	8 (53.3)	11 (55.0)	0.922
Chronic GVHD	12 (34.3)	4 (26.7)	8 (40.0)	0.293
Post-HSCT TKI				
Yes	13 (37.1)	5 (33.3)	8 (40.0)	0.618
No	19 (54.3)	9 (60.0)	10 (50.0)	
N/A	3 (8.6)	1 (6.7)	2 (10.0)	

Values are presented as number (%) or median (range). GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MAC, myeloablative conditioning; N/A, not available; NST, non-myeloablative conditioning; RIC, reduced-intensity conditioning; TKI, tyrosine kinase inhibitor; TNC, total nucleated cell.

2. Pretransplant treatment and HSCT indications

Among the 32 patients with sufficient clinical data, 27 started treatment with imatinib, four with dasatinib, and one with nilotinib. Subsequently, 18 patients were switched to other TKIs due to resistance, intolerance, or other clinical reasons (Fig. 1). At the time of HSCT, 28 patients were in complete remission, while seven had active diseases. Regarding graft sources, 33 patients were transplanted with peripheral blood stem cells and two with bone marrow. The indications for HSCT were as follows: high-risk at diagnosis (including

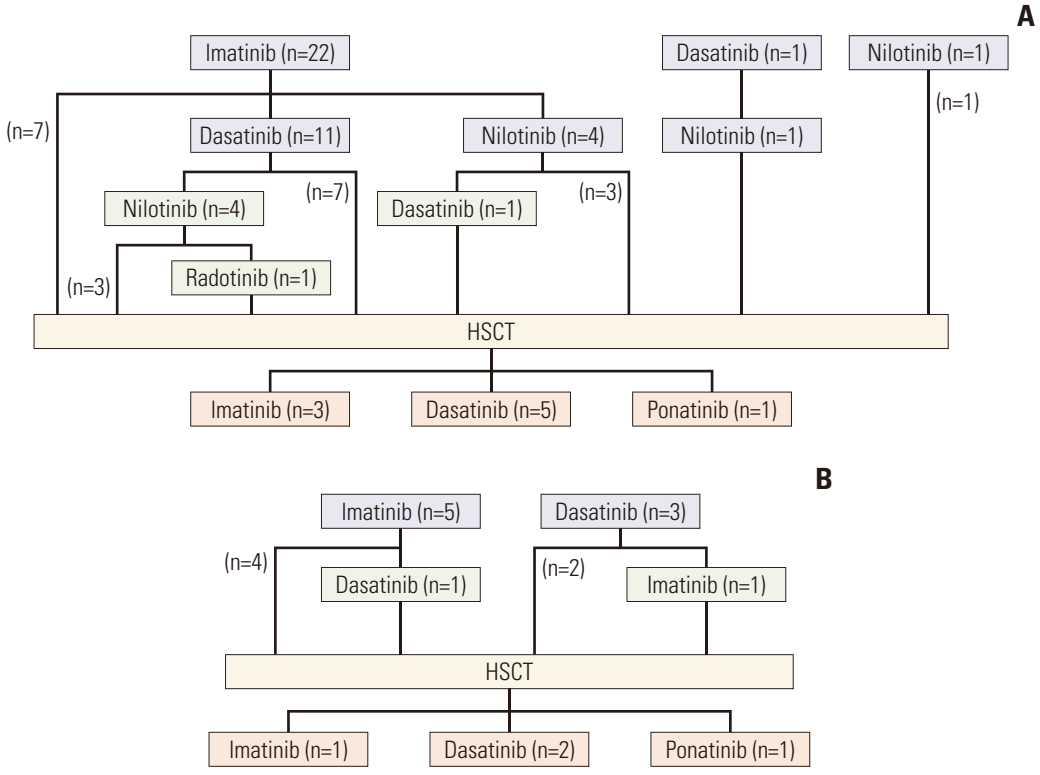

Fig. 1. Treatment flow before and after hematopoietic stem cell transplantation (HSCT) (Three patients with insufficient data were excluded.). (A) Patients initially diagnosed with chronic-phase chronic myeloid leukemia (CML). (B) Patients initially diagnosed with accelerated or blast-phase CML.

BP) in 10 patients (28.6%), suboptimal response to TKI in 12 patients (34.3%), transformation from CP to other phases in six patients (17.1%), TKI intolerance in three patients (8.6%), T351I mutation in one patient (2.9%), physician's choice in two patients (5.7%), and unknown reason (N/A) in one patient (2.9%).

3. Transplantation, engraftment, and post-HSCT management

Myeloablative regimens were used in 19 patients (54.3%), including total body irradiation in six patients (17.1%). Reduced-intensity conditioning (RIC) or non-myeloablative stem cell transplantation (NST) regimens were used in 16 patients (45.7%). Details regarding the conditioning regimens are summarized in S1 Table. The types of HSCT donors were as follows: matched sibling donors for 14 patients (40.0%), matched unrelated donors for eight patients (22.9%), one or two mismatched donors for eight patients (22.9%), haploidentical donors for four patients (11.4%), and none reported in one patient (2.9%). All 35 patients successfully achieved engraftment. The neutrophil engraftment was achieved at a median of 12 days (range, 7 to 29 days). Platelet engraftment occurred at a median of 22 days (interquartile range, 7 to 63 days). There was no significant difference in neutrophil engraftment between groups 1 and 2. However, platelet recovery was delayed in group 1 (27.5 days) compared to that in group 2 (17 days) (p=0.034). Acute graft-versus-host disease (GVHD) occurred in 19 of 35 patients (54.3%) and chronic GVHD in 12 patients (34.3%).

Post-HSCT TKI therapy was administered to 13 patients (4 with imatinib, 7 with dasatinib, and 2 with ponatinib). The reasons for post-HSCT TKI administration were morphologic relapse in seven patients, molecular relapse in five, and prophylaxis in one. Donor lymphocyte infusion was performed in four patients for the treatment of relapse or for the prophylaxis of relapse (S2 Table).

4. Survival outcomes, relapse, and prognostic factors

The 5-year OS, RFS, and EFS rates of the 35 patients were 66.8% (95% CI, 47.9 to 80.2), 50.8 % (95% CI, 33.2 to 66.0), and 47.6 % (95% CI, 30.3 to 63.1), respectively. The median follow-up duration post-HSCT was 91.4 months (range, 28.5 to 160.1 months).

When survival compared according to age at diagnosis,

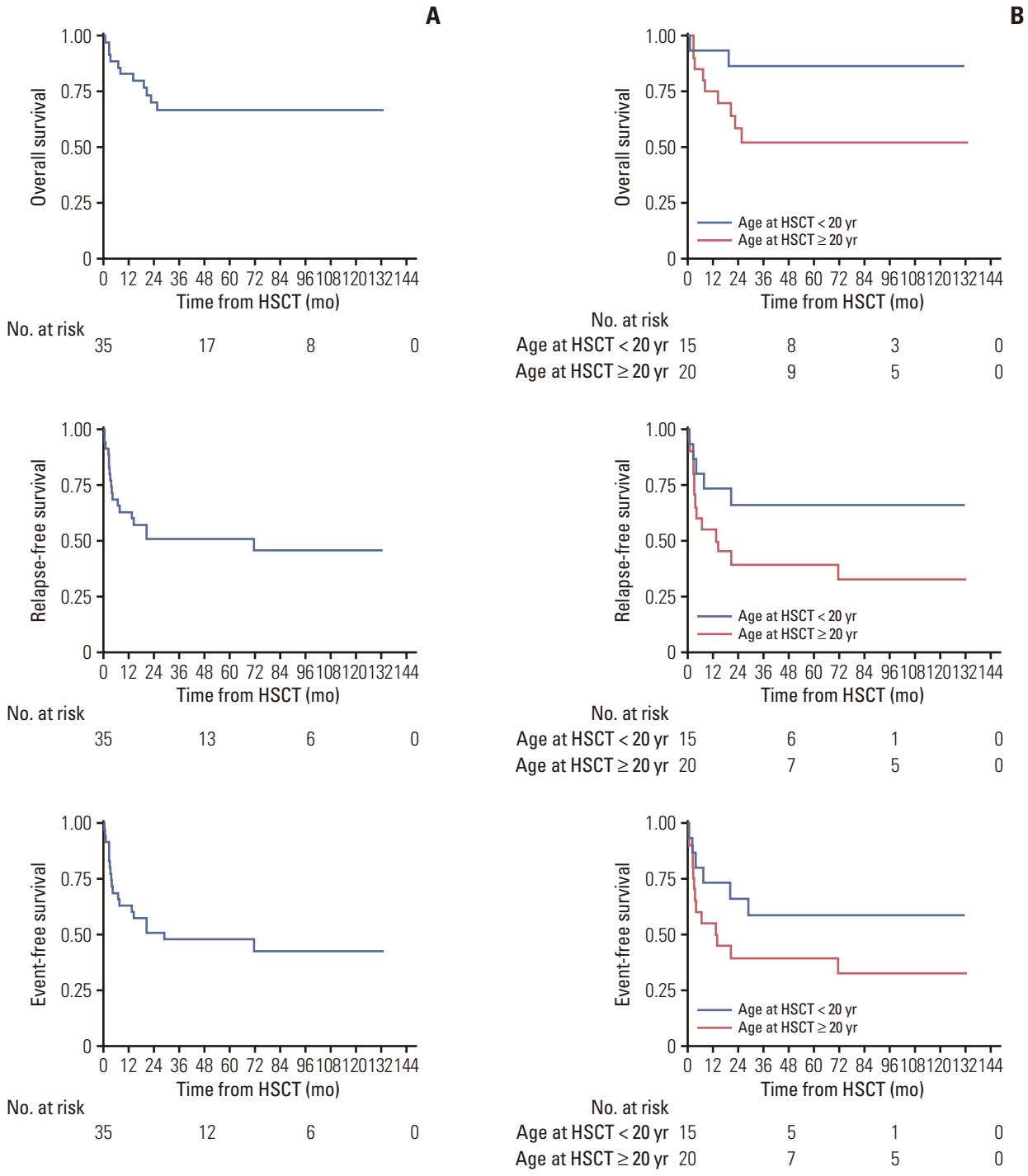

Fig. 2. Kaplan-Meier survival curve. (A) Overall survival, relapse-free survival, and event-free survival of total patients. (B) Overall survival, relapse-free survival, and event-free survival based on age at the time of hematopoietic stem cell transplantation (HSCT) (group 1; patients who underwent HSCT at the age of less than 20 years old, group 2; patients who underwent HSCT at the age of 20 years or more).
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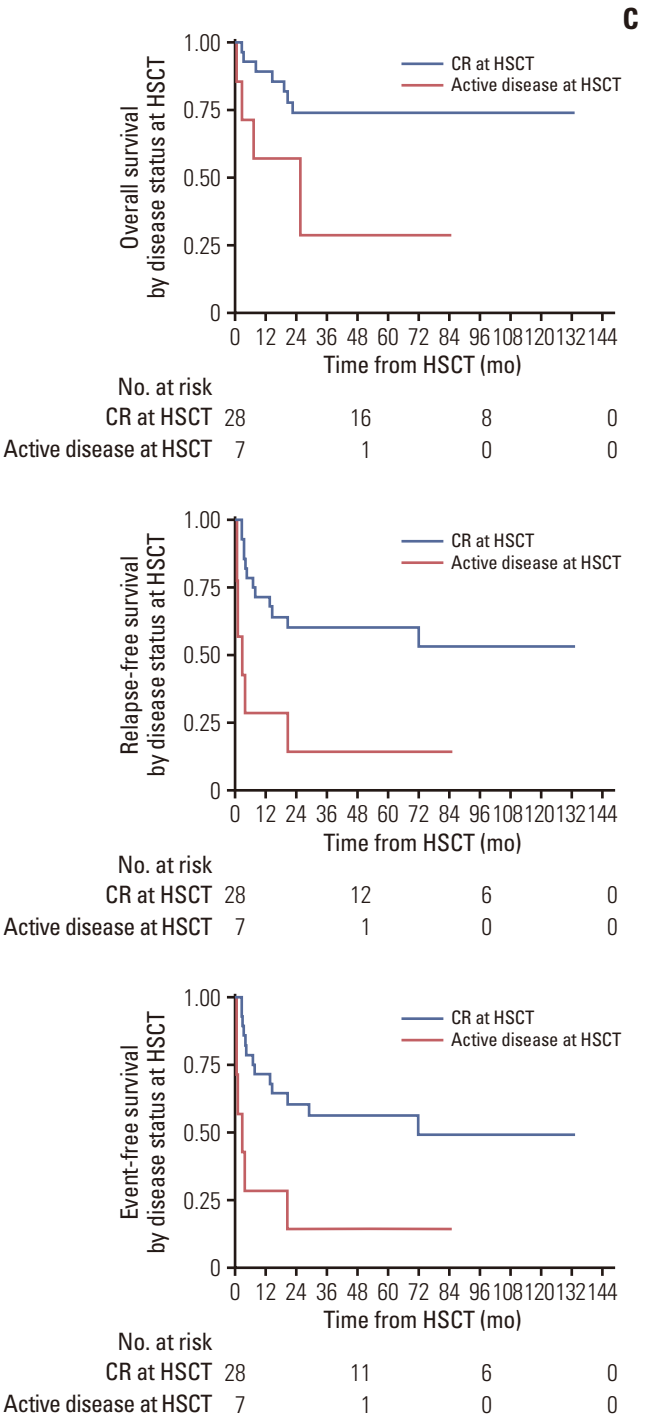

Fig. 2. *(Continued from the previous page)* (C) Overall survival, relapse-free survival, and event-free survival by the disease status at the time of HSCT (status 1; complete remission, status 2; active disease).

patient diagnosed CML under 20 years had 5-year OS, RFS, and EFS rates of 74.6% (95% CI, 45.4 to 89.7), 57.8% (95% CI, 31.1 to 77.3), and 51.3% (95% CI, 25.7 to 72.1), compared to those diagnosed at 20 years and older with rates of 59.8% (95% CI, 33.4 to 78.6), 44.4% (95% CI, 21.6 to 65.1), and 44.4% (95% CI, 21.6 to 65.1), respectively. The p-values were 0.277, 0.223, and 0.340, respectively.

When stratified by age at HSCT, group 1 (under 20 years) had 5-year OS, RFS, and EFS rates of 86.2% (95% CI, 55.0 to 96.4), 66.0% (95% CI, 36.5 to 84.3), and 58.7% (95% CI, 30.0 to 79.0), respectively. Group 2 (HSCT done at 20 years or later) resulted in 5-year OS, RFS, and EFS rates of 52.4% (95% CI, 28.1 to 71.9), 39.4% (95% CI, 18.6 to 59.7), and 39.4% (95% CI, 18.6 to 59.7), respectively. The corresponding p-values were 0.057, 0.098, and 0.168.

According to disease status at the time of HSCT, 5-year OS, RFS, and EFS rates were 74.0% (95% CI, 53.0 to 86.7) vs. 28.6% (95% CI, 1.4 to 69.1), 60.3% (95% CI, 39.8 to 75.7) vs. 14.3% (95% CI, 0.7 to 46.5), and 56.3% (95% CI, 35.9 to 72.4) vs. 14.3% (95% CI, 0.7 to 46.5) for those in complete remission versus those with active disease, respectively. The p-values that corresponded to this were 0.028, 0.003, and 0.004 (Fig. 2).

Among the total 35 patients, 13 patients experienced relapse after HSCT. Relapse occurred in six patients in group 1 and seven patients in group 2, with the time to relapse ranging from 1 to 72 months (median, 4 months) post-HSCT.

Patients who received TKIs following HSCT demonstrated inferior survival outcomes compared to those who did not, potentially due to the administration of post-HSCT TKIs primarily in the context of relapse management. (5-year OS, 88.9% vs 65.8%; p=0.035) Another patient in group 1 was diagnosed with mucosa-associated lymphoid tissue (MALT) lymphoma as SMN at 29 months post-HSCT, which was successfully treated, and the patient was alive without disease at the last follow-up.

Among the 11 patients who died after HSCT, the cause of death in seven patients was treatment-related mortality, and in four patients was relapsed or progressive CML. According to the age at HSCT, among those who were less than 20 years old (group 1), one patient died from infection. Among the patients who were older than 20 years (group 2), the causes of treatment-related mortality were pneumonia in two patients, other infection in three patients, and pulmonary toxicity in one patient. Death related to relapsed or refractory CML occurred in one patient in groups 1 and three patients in group 2, respectively.

Conditioning intensity (p=0.913), status at diagnosis (BP vs. AP vs. CP, p=0.681), sex (p=0.65), and age at diagnosis (p=0.275) showed no correlation with OS. Univariable analysis identified the age at HSCT, disease status at HSCT, and transformation from CP to other phase as potential factors

Table 2. Clinical factors related to overall survival

Characteristic	Total (No. of death)	Univariable analysis		Multivariable analysis	
		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Sex					
Male	23 (8)	1.00	0.650	-	-
Female	12 (3)	0.74 (0.20-2.79)			
Age at diagnosis (yr)					
< 20	17 (4)	1.00	0.275	-	-
≥ 20	18 (7)	1.96 (0.57-6.71)			
Age at HSCT (yr)					
< 20	15 (2)	1.00	0.046	1.00	0.048
≥ 20	20 (9)	3.98 (0.86-18.46)		8.38 (1.02-68.65)	
Status at diagnosis[a]					
Chronic phase (CP)	24 (7)	1.00	0.681		
Accelerated phase (AP)	1 (0)	Not estimable			
Blast phase (BP)	9 (3)	1.10			
Status at HSCT					
In remission	28 (7)	1.00	0.058	1.00	0.142
Active disease	7 (4)	3.68		2.87 (0.70-11.80)	
Indication of HSCT					
High risk at diagnosis (BP, etc.)	10 (3)	1.00	0.165	-	-
Suboptimal TKI response	12 (3)	0.927 (0.19-4.62)			
Transformation (CP to others)	6 (4)	3.05 (0.68-13.69)			
TKI intolerance	3 (0)	0 (0-not estimable)			
T351I mutation	1 (0)	0 (0-not estimable)			
Physician's choice	2 (0)	0 (0-not estimable)			
Transformation pre-HSCT					
No	28 (6)	1.00	0.039	1.00	0.082
Yes	6 (4)	4.25		3.12 (0.86-11.28)	
Donor type					
Matched sibling	14 (5)	1.00	0.327	-	-
Matched unrelated	8 (2)	0.58 (0.11-2.99)			
One or two-mismatched	8 (1)	0.30 (0.03-2.53)			
Haploidentical	4 (3)	1.82 (0.43-7.65)			
Conditioning regimen					
MAC	19 (6)	1.00	0.913	-	-
RIC/NST	16 (5)	0.94 (0.28-3.08)			
Stem cell count					
TNC ($\times 10^8$/kg)	-	1.03 (0.95-1.12)	0.477	-	-
CD34+ cells ($\times 10^6$/kg)	-	1.02 (0.93-1.12)	0.651		
Acute GVHD					
No	16 (5)	1.00	0.852	-	-
Yes	19 (6)	1.12 (0.34-3.67)			
Chronic GVHD					
No	19 (4)	1.00	0.711	-	-
Yes	12 (3)	1.33 (0.30-5.96)			

Variables with p-value < 0.1 from univariable analysis were included in the multivariable analysis. CI, confidence interval; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MAC, myeloablative conditioning; MNC, mononucleated cell; NST, non-myeloablative conditioning; RIC, reduced-intensity conditioning; TKI, tyrosine kinase inhibitor; TNC, total nucleated cell. [a]One patient's status at diagnosis was not reported.

affecting OS. However, age at HSCT was the only statistically significant factor in multivariable analysis (Table 2). By univariable analysis, disease status at HSCT was a significant factor for RFS (p=0.003) and EFS (p=0.004) (Fig. 2C).

Discussion

The number of patients undergoing allogeneic HSCT for CML has decreased significantly since the introduction of *BCR::ABL1* TKIs. However, as the prevalence of CML continues to rise and approximately 1%-2% of patients develop resistance to multiple TKIs annually, the need for allogeneic HSCT may increase once again [7]. In this context, our study provides valuable insights into the treatment outcomes of allogeneic HSCT in pediatric and young adult patients with CML, addressing the current gap in data for this population.

In this retrospective study, we examined the outcomes of 35 patients aged < 40 years who were diagnosed with CML and underwent HSCT. Over a median follow-up of 91.4 months, the study observed OS, RFS, and EFS rates of 66.8%, 50.8%, and 47.6%, respectively. Most patients began treatment with imatinib, the standard first-line therapy for CML, and subsequently transitioned to other TKIs as necessary due to resistance or intolerance. At the time of HSCT, a significant proportion of patients achieved complete remission, which is consistent with the clinical practice guidelines that emphasize the importance of disease control before transplantation. Disease status at HSCT emerged as a significant predictor of OS, RFS, and EFS, underscoring the importance of achieving complete remission before transplantation.

This achievement of remission underscores the role of pretransplant treatment in optimizing HSCT outcomes. Multiple reports emphasize that pretransplant status is crucial for transplant success, reinforcing the need for effective pretransplant management and suggesting that transplantation should be considered before progression to BP [20-22].

This emphasizes the necessity of aggressive management of CML to ensure optimal transplant outcomes and enhance treatment efficacy and survival. The pivotal role of TKI therapy in the initial management of CML is well-documented, with previous studies demonstrating that imatinib and other TKIs significantly improve long-term survival rates [23,24].

Younger patients at HSCT (< 20 years at HSCT) generally exhibited better survival outcomes than those aged 20-40 years. This trend may be attributed to generally better health and fewer comorbidities observed in younger patients. Our findings are consistent with other studies suggesting that younger patients often experience better outcomes, although discrepancies with some research highlight the need for further investigation [25].

The impact of disease status during HSCT may be influenced by the distinct biological characteristics of CML in younger patients, including more aggressive disease presentations. The high rates of acute (52.8%) and chronic (36.1%) GVHD observed in our cohort underscores the ongoing challenges associated with allogeneic HSCT. Despite achieving remission prior to transplantation, GVHD remains a significant concern. New immunosuppressive therapies and biological agents are promising for improving GVHD management, which is crucial for enhancing patient outcomes.

The notable relapse rates, with a median time to relapse of 4 months post-transplantation, highlight the need for improved strategies to prevent relapses. The higher mortality rate in older patients (group 2) may reflect decreased treatment tolerance and more complex disease progression. Additionally, the development of MALT lymphoma in one patient emphasizes the necessity for vigilant long-term surveillance of secondary malignant neoplasms.

Considering the importance of HSCT, efforts to reduce mortality and morbidity through advancements in transplantation technologies are essential. These include high-resolution human leukocyte antigen typing, introduction of reduced-intensity conditioning, increased availability of alternative donors, and improved supportive care. Given the high probability of non-relapse mortality after CML HSCT, it is advised to use RIC when transplanting patients who have achieved complete remission and no high-risk factors, although there was no difference in survival outcome according to conditioning regimen [20,26].

This study had a few limitations. First, its retrospective nature and relatively small sample size may limit the generalizability of the findings. The lack of significant differences in survival outcomes between the two age groups may be due to limited statistical power. Second, the T315I mutation, known for its resistance to multiple TKIs [27], was not routinely tested, which may have affected the interpretation of TKI resistance and treatment outcomes. Finally, because this study was based on a registry of patients who underwent HSCT rather than on the entire CML patient population in Korea, the findings may not be fully generalizable to all patients with CML. Consequently, establishing definitive criteria for HSCT selection remains challenging.

In conclusion, this study provides valuable insights into young patients with CML who underwent allogeneic HSCT. While a younger age at HSCT appears to be associated with better survival outcomes, achieving remission at the time of HSCT remains crucial. The ongoing challenges of GVHD and relapse highlight the need for continuous improvements in the management of these patients. Future research should focus on larger, prospective studies to confirm these findings and explore novel strategies to enhance long-term outcomes

in patients with CML undergoing HSCT. Given the emerging evidence on the efficacy of newer agents, such as ponatinib for T315I mutation-positive patients, routine early mutation testing should be considered to facilitate timely therapeutic adjustments or early HSCT when appropriate. Continued investigation into new TKI's application in pediatric populations [28,29] holds promise for evolving treatment paradigms and improving outcomes in younger patients with resistant CML.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (IRB No. X-2204-749-902), and the need for informed consent from each patient was waived because the authors did not have access to any identifying information. All procedures were performed under the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008.

Author Contributions

Conceived and designed the analysis: Choi HS.
Collected the data: Ju HY, Choi HS, Park HJ, Yoo KH, Lyu CJ, Im HJ, Kim MK, Mun YC, Moon JH, Yoon SS, Lee E, Lee JH (Jae Hoon Lee), Lee JH (Je-Hwan Lee), Chong SY, Cheong JW.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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