Outcome and prognostic factors of children with Philadelphia chromosome-positive acute lymphoblastic leukemia treated with imatinib followed by allogeneic hematopoietic cell transplantation in first remission

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Background
Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) is a subset of ALL with poor prognosis. Here, we analyzed the outcomes and prognostic factors of children with Ph+ ALL who received imatinib and chemotherapy followed by allogeneic hematopoietic cell transplantation (HCT) in first complete remission (CR).

Methods
Thirty-one Ph+ ALL patients (female 10) diagnosed from January 2005 to December 2016 were included in the study. All patients were treated with imatinib and chemotherapy before HCT. Bone marrow (BM) evaluations included real-time quantitative polymerase chain reaction (RQ-PCR) study of the BCR-ABL1 fusion transcript. All patients received HCT with total body irradiation (TBI)-based conditioning at a median of 6.4 (range, 4.2–47.1) months from diagnosis.

Results
Compared to values at diagnosis, the median decrement of RQ-PCR value post-consolidation, and prior to HCT was -3.7 Log and -4.8 Log, respectively. The 5-year event-free survival (EFS) and overall survival of the patients were 64.5±9.4% (20/31) and 75.0±8.3% (23/31) respectively. Events included relapse (N=5) and death in CR post-HCT (N=6). The 5-year incidence of molecular relapse was 30.9±9.1% (9/31). An RQ-PCR decrement of at least -4 Log post-consolidation significantly predicted lower incidence of molecular relapse: 7.7±7.7% for ≥-4 Log decrement, 50.0±13.8% for < -4 Log decrement (P=0.027).

Conclusion
Decrement in RQ-PCR for the BCR-ABL1 transcript that was determined after consolidation was the only significant prognostic factor for incidence of molecular relapse. In the post-induction TKI initiation setting, steadfast imatinib treatment during consolidation may allow for optimum post-HCT outcomes.

Key Words
Acute lymphoblastic leukemia, Philadelphia chromosome, Children, RQ-PCR

INTRODUCTION
Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) comprises about 3-5% of pediatric ALL and is known to have inferior outcomes compared to other ALL subtypes [1]. Prior to the incorporation of targeted therapy, in the form of tyrosine kinase inhibitors (TKIs), such as imatinib, into the treatment scheme, the long-term event-free survival (EFS) reported from key studies was approximately 30%, with allogeneic hematopoietic cell transplant (HCT) recipients having superior outcomes compared with patients treated with chemotherapy only [2, 3]. Subsequently, the introduction of imatinib therapy con-
currently with conventional chemotherapy significantly improved the survival of pediatric Ph+ ALL patients, as has been shown in several prospective studies [4-7]. Furthermore, an update of the initial Children’s Oncology Group (COG) trial showed that patients who completed treatment with imatinib and chemotherapy only had an EFS comparable to those who subsequently underwent allogeneic HCT [8].

Our institution’s strategy for the Ph+ ALL subgroup is to classify the patients as very high risk, administer imatinib with chemotherapy, and undertake allogeneic HCT in first complete remission (CR) from a matched sibling (MSD) or unrelated donor (MUD) [9]. Regarding imatinib and chemotherapy combination, studies from adult Ph+ ALL patients show that the decrement in minimal residual disease (MRD) as measured by real-time quantitative polymerase chain reaction (RQ-PCR) for the BCR-ABL1 fusion transcript significantly influences outcomes [10, 11]. Prognostic factor studies in pediatric Ph+ ALL patients who were treated in the TKI era are few, with one study reporting that patients with additional cytogenetic abnormalities have lower survival [8].

Here, our aim was to show the outcomes of Ph+ ALL patients who were administered imatinib combined with chemotherapy, followed by allogeneic HCT in first CR at our institution, and to determine factors with prognostic significance. As well as clinical and transplant-related factors, we studied whether sequential RQ-PCR measurement of the fusion transcript identified patients with poor outcomes.

**MATERIALS AND METHODS**

**Patient group**

Ph+ ALL patients diagnosed at the Department of Pediatrics, The Catholic University of Korea from January 2005 to December 2016, and treated with imatinib and chemotherapy, followed by allogeneic HCT in first CR were included in the study (N=31) (Table 1). Patients who completed treatment without transplant, or who received HCT in second CR or later were excluded. The median age and white blood cell (WBC) count at diagnosis were 12.7 years and 72,200/μL, respectively. None of the patients had central nervous system (CNS) involvement at diagnosis. Twenty-four (77%) of the patients had additional cytogenetic abnormalities besides the Ph chromosome according to Giemsa band karyotyping (Supplementary Table 1).

**Chemotherapy**

Remission induction and subsequent chemotherapy until transplant, was based on an institutional regimen [9]. Consolidation chemotherapy duration in our regimen was 8 weeks (Supplementary Table 2). Patients diagnosed until December 2008 were administered dexamethasone during all phases of steroid treatment (CMCP-ALL2005); subsequent patients received prednisolone (CMCP-ALL2009). Notably, the initial 7 patients here were administered 1–5 courses of anthracycline (idarubicin or daunorubicin) and high dose cytarabine combination after remission induction instead of our ALL post-induction treatment. All but 4 patients started imatinib after initial remission induction at a dose of 340 mg/m²/day and were treated with the TKI continuously until conditioning for HCT; the remaining 4 patients were administered imatinib during remission induction. Five of the patients (16%) failed to achieve CR after initial remission induction and achieved CR after second induction chemotherapy or consolidation. Routine TKI therapy post-transplant was not done; only patients who showed an increase in the BCR-ABL1 RQ-PCR transcript post-HCT re-started TKI therapy.

**BCR-ABL1 evaluation**

Ph+ ALL was diagnosed by reverse-transcription polymerase chain reaction (RT-PCR) for the fusion transcript and bone marrow (BM) karyotyping. Leukemic burden was assessed by RQ-PCR measurement of the BCR-ABL1 transcript at diagnosis, post-consolidation, just prior to HCT, and at 1, 3, 6, 9, and 12 months post-HCT with a BM specimen, and utilizing a quantification kit for each fusion transcript (BioSewoom Inc., Seoul, Korea). The relative expression level of the gene was calculated using the 2−∆∆Ct method by normalizing to the geometrical mean of ABL1 as a stable reference gene and presenting it relative to the control.

**Study outcomes**

The first objective of our study was to determine the 5-year EFS, overall survival (OS), incidence of relapse and non-relapse mortality (NRM) post-transplant of our study group. We also calculated incidence of molecular relapse; while considering an increase in BCR-ABL1 RQ-PCR value post-transplant which required the re-initiation of TKI therapy, regardless of BM morphology, an event. Isolated extra-
medullary relapse was also considered an event in the incidence of molecular relapse calculation. EFS was defined as the time from HCT to last follow-up in CR, or the first event, which included relapse or death from any cause; OS was defined as the time from HCT to last follow-up, or death from any cause.

Additionally, we attempted to define clinical and chemotherapy-related (age and WBC count at diagnosis, presence of additional cytogenetic abnormalities, steroid response, chemotherapy protocol), transplant-related [donor type, human leukocyte antigen (HLA) disparity, infused TNC and CD34+ cell dose, acute and chronic graft-versus-host disease (GVHD)], and RQ-PCR-based MRD factors [values at diagnosis, log decrement post-induction, post-consolidation, just prior to HCT, and achievement of molecular remission (RQ-PCR of '0')] which significantly influenced either the EFS or incidence of molecular relapse.

**Statistical analysis**

Continuous variables were dichotomized according to respective median values in order to analyze their impact on outcomes. Disparity in RQ-PCR decrement according to the type of chemotherapy was calculated using the Mann–Whitney test. Survival rates were calculated according to Kaplan-Meier method and comparisons were done with the Log-rank test. The impact of acute and chronic GVHD was diagnosed in 5 patients (16.1%).

**Transplantation**

Patients received HCT in first CR at a median of 6.4 months from diagnosis (range, 4.2–47.1 mo). The majority of patients underwent unrelated donor HCT (Table 2). All patients underwent total body irradiation (TBI)-based myeloablative conditioning. Median infused cell doses were as follows: total nucleated cell (TNC) 13.6×10^8/kg (0.5–23.2), mononuclear cell 10.0×10^8/kg (0.3–19.8), CD34+ cell 5.0×10^6/kg (0.1–29.3), CD3+ cell 40.3×10^6/kg (0.6–133.0).

Cumulative incidence of acute GVHD grade II–IV and chronic GVHD were 74.2±8.2% (23/31) and 48.4±9.7% (15/31) respectively, with 13.0±6.2% (4/31) incidence for at least moderate chronic GVHD. Severe chronic GVHD was diagnosed in 5 patients (16.1%).

**Fusion transcript RQ-PCR**

The median RQ-PCR value for the BCR-ABL1 transcript at diagnosis was 1.09 (range, 0.21–9.13) (Table 3), and the median decrement of the RQ-PCR value post-consolidation was -3.72 Log. The difference in post-consolidation RQ-PCR decrement according to the type of consolidation chemotherapy (that is, between patients who received institutional CMCP-ALL regimen and the seven patients who received anthracycline and high dose cytarabine) was not significant (P=0.210). Twelve (39%) and 15 (48%) patients achieved...
molecular remission (RQ-PCR value of ‘0’) post-consolidation and prior to HCT respectively.

Overall, 8 patients (26%) showed an RQ-PCR value increase after transplant at a median time post-HCT of 9.2 months (range, 2.9–51.8 mo), requiring the initiation of imatinib with or without chemotherapy. Mean duration of subsequent TKI therapy was 7.4 months (range, 0.2–20.3). Three of the patients showed morphological relapses concurrent with the increase in the RQ-PCR value and received both imatinib and chemotherapy; two received a second HCT after achieving second CR and currently survive event-free, while the remaining patient showed a second relapse and died. Of the five patients who started imatinib for an RQ-PCR value increase without experiencing overt relapse, three achieved molecular remission and survived event-free; the remaining two patients, however, died from subsequent relapse and refractory disease, and veno-occlusive disease after second HCT, respectively.

Survival outcomes

With a median duration of 61.8 months follow-up for surviving patients, the 5-year EFS and OS of the study group were 64.5±9.4% (20/31, relapse (N=5) and NRM (N=6)] and 75.0±8.3% (23/31) (Fig. 1A, B). The 5-year incidence of relapse was 18.3±7.9% (5/31); sites of relapse in the 5 patients were BM (N=3), BM+CNS (N=1), and isolated testis (N=1). Three of these patients currently survive disease-free, including 2 who received second transplants. The 5-year incidence of molecular relapse was 30.3±7.3%; causes of NRM included chronic GVHD (N=2), cerebral aspergillosis (N=1), thrombotic microangiopathy (N=1), veno-occlusive disease (N=1), and pulmonary hemorrhage (N=1).

Prognostic factors

None of the factors studied proved to significantly influence EFS. Importantly, the steroid type utilized during chemotherapy and donor type for HCT did not affect EFS (5-year EFS 75.0±15.3% for matched related donor vs. 60.2±11.6% for unrelated donor; P=0.443) (Table 4). Patients who received a transplant from an HLA mismatched donor had

![Figure 1](image_url)
lower 5-year EFS, although the difference was not significant (HLA matched donor transplant 80.0±8.9% vs. HLA mismatched donor transplant 39.8±16.3%; \( P=0.100 \)). Also, patients who had additional cytogenetic abnormalities besides Ph had inferior 5-year EFS (56.8±11.7% vs. 85.7±13.2% for those with Ph only; \( P=0.157 \)). Variables related to RQ-PCR value of the fusion transcript, such as extent of RQ-PCR decrements at any of the time points studied and the achievement of molecular remission prior to HCT, did not have a significant impact on EFS (Table 4).

Regarding the incidence of molecular relapse, MRD status after consolidation chemotherapy was the only significant factor, with those achieving ≥4 Log reduction of the BCR-ABL1 transcript having significantly lower incidences of molecular relapse compared to those with less reduction (7.7±5.7% vs. 50.0±13.8%; \( P=0.027 \)) (Table 4). Patients with additional cytogenetic abnormalities had higher incidences of molecular relapse compared to patients with Ph only (36.9±11.6% vs. 14.3±14.3%; \( P=0.329 \)), although without statistical significance.

### DISCUSSION

Here, we analyzed the outcome and risk factors for Ph+ ALL who underwent a joint imatinib-chemotherapy treatment, with subsequent allogeneic HCT in first CR. Our 5-year EFS and OS rates of 64.5±9.4% and 75.0±8.3% were similar to those reported by recent studies on this ALL subtype [8, 12].

Favorable prognostic factors for children with Ph+ ALL treated in the pre-TKI era included clinical factors such as younger age, lower WBC count and favorable early BM response to remission induction chemotherapy [13, 14]. However, variables which influence patient outcomes after treatments combining TKI and chemotherapy remain unclear, with limited previous studies on this issue. The most recent report of the COG AALL0031 trial showed that patients with additional cytogenetic abnormalities besides the Ph chromosome had lower EFS while the level of MRD post-induction, as detected by flow cytometry, had no impact on survival [8].

Although the analysis was undertaken on a small number of patients, we found that none of the factors studied had a clear impact on EFS, while the decrement of the fusion transcript measured by RQ-PCR post-consolidation was the only significant factor for incidence of molecular relapse post-transplant, with patients achieving at least a -4 Log decrease while having lower incidence of relapse. Molecular relapse was analyzed as an endpoint here because an increase in the fusion transcript RQ-PCR value post-HCT, though does not correspond with a clear, morphological relapse, translates into the re-initiation of TKI therapy with both TKI-related complication and future relapse risks. The significance of the post-consolidation RQ-PCR value found in our study is similar to the transcript level prognostic value that was detected after the first 4 weeks of imatinib therapy after remission induction, which was reported to be important in a study of adult Ph+ ALL patients [11].

Regarding other prognostic factors, we found that patients with additional cytogenetic abnormalities had lower EFS and greater incidence of relapse than those with the Ph chromosome only, although not to the significant extent found in the COG study [8]. Variables that did not affect EFS or incidence of relapse significantly were also meaningful. For example, as with the COG study, we found that end-induction MRD did not affect outcomes [8], and that RQ-PCR value prior to HCT, and whether the patient achieved molecular remission prior to HCT did not affect post-transplant outcome. Donor type did not influence EFS, supporting a previous study on the acceptable outcomes of alternative donor transplant for pediatric Ph+ ALL [15]. Importantly, however, patients who received transplant from an HLA mismatched donor had inferior EFS, possibly due to an increase in NRM.

A clear limitation of our retrospective study is the differing consolidation chemotherapy treatment undertaken in a minority of patients, resulting in a lack of uniformity regarding the post-consolidation time point at which the RQ-PCR study was undertaken. We also draw attention to the high incidence of chronic GVHD, especially the 32.4% incidence of at least moderate chronic GVHD among our patients. Ph+ ALL may be susceptible to a graft-versus-leukemia effect, lowering the risk of relapse [16]. However, the undertaking of allogeneic HCT for cure of Ph+ ALL may have resulted in long-term morbidity in a subset of our patients.

Further research is necessary to improve the outcome of this poor prognosis ALL subtype. TKI therapy may be started during remission induction, as exemplified in the Spanish Cooperative Group SHOP study in which imatinib was administered from day 15 of remission induction onwards [5]. One study found that the introduction of TKI at day 22 of induction produced a major decrease in MRD levels and improved EFS, underscoring the utility of early TKI initiation in decreasing leukemic burden [17]. Another modification that may improve EFS is the administration of TKI post-HCT as maintenance treatment, a regimen that resulted in a 73% 5-year EFS in one pediatric study [18].

Second generation TKIs allow for better CNS penetration than imatinib. A recent study on dasatinib combined with chemotherapy for the treatment of Ph+ ALL showed survival outcomes similar to a cohort of patients treated with imatinib [19]. Importantly, this study showed that a subgroup of patients with IKZF1 deletion had significantly worse survival, emphasizing the role of this genetic mutation as a possible prognostic factor.

Finally, regarding methods to improve survival of Ph+ ALL patients, reduced intensity conditioning for transplant may be considered. A report on a small series of patients showed that non-myeloablative conditioning may be a valid option, with four out of five patients surviving disease-free [20]. Validity of reduced intensity conditioning becomes important when one considers the 5-year incidence of NRM of 17% in our study.
In summary, for our Ph+ ALL patients who started imatinib with chemotherapy post-induction and subsequently underwent allogeneic HCT in first CR, the magnitude of fusion transcript decrement during post-consolidation was the only significant factor for the incidence of molecular relapse after transplant. In the post-induction TKI initiation settings, steadfast treatment with imatinib during consolidation may allow for optimum post-HCT outcomes.

Authors’ Disclosures of Potential Conflicts of Interest

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

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### Supplementary Table 1. Results of Giemsa band karyotyping of the bone marrow at diagnosis.

| UPN | Karyotype                                                                 |
|-----|---------------------------------------------------------------------------|
| 1   | 46,XY(t(9;22)[q34;q11.2][1]/45,idem,-7[13]/46,XY[6]                        |
| 2   | 46,XY(t(9;22)[q34;q11.2][1]/45,idem,-7[18]/46,XY[1]                     |
| 3   | 45,XX,der(7;9)[q10q10][t(9;22)[q34;q11.2],der(22)[t(9;22)[9]/46,XX[11] |
| 4   | 45,XX,der(7;9)[q34;q11.2][12]/46,XX[8]                                   |
| 5   | 46,XY(t(9;22)[q34;q11.2][16]/46,XY[4]                                   |
| 6   | 46,XY(t(9;22)[q34;q11.2][1]/45,XX,-7[13]/46,XY[6]                       |
| 7   | 46,XY(t(9;22)[q34;q11.2][4]/48,idem,-7[18]/46,XY[1]                    |
| 8   | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 9   | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 10  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 11  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 12  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 13  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 14  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 15  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 16  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 17  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 18  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 19  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 20  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 21  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 22  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 23  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 24  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 25  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 26  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 27  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 28  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 29  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |
| 30  | 46,XY(t(9;22)[q34;q11.2][12]/46,XX[8]                                   |

### Supplementary Table 2. Remission induction and consolidation for CMCP-ALL.

| Drug                      | Dose                     | Days      |
|---------------------------|--------------------------|-----------|
| Prednisolone (PO)         | 60 mg/m² (max. 80 mg)    | 1–7       |
| Methotrexate/cytarabine/hydrocortisone (IT) | By age
| Vincristine (IV)          | 1.5 mg/m² (max. 2 mg)    | 1, 8, 15, 22 |
| Daunorubicin (IV)         | 45 mg/m²                  | 1         |
| L-asparaginase (IM)       | 6,000 μg/m³ (max. 10,000 μ) | 2, 4, 6, 9, 11, 13, 16, 18, 20 |
| Prednisolone (PO)         | 60 mg/m² (max. 80 mg)    | 1–21      |
| Methotrexate (IT)         | By age                   | 1, 22     |
| Cyclophosphamide (IV)     | 1,000 mg/m³              | 1, 29     |
| Cytarabine (IV)           | 100 mg/m³                | 1–5, 15–19, 29–33, 43–47 |
| Vincristine (IV)          | 1.5 mg/m² (max. 2 mg)    | 15, 22, 43, 50 |
| Prednisolone (PO)         | 45 mg/m² (max. 60 mg)    | 22–26, 50–54 |
| 6-Mercaptopurine (PO)     | 60 mg/m³                 | 1–7, 29–35 |

aFor patients diagnosed and treated from January 2009 onwards, prednisolone was used for treatment. However, for patients diagnosed from January 2005 to December 2008, dexamethasone was used at a dose of 8 mg/m²/day PO (max. 10 mg/day) during all phases of steroid treatment from prephase to end of maintenance treatment. bAge-adjusted doses of triple intrathecal chemotherapy: Methotrexate 6 mg (<1 yr), 7.5 mg (≥1 and <2 yr), 10 mg (≥2 and <3 yr), 12.5 mg (≥3 yr); cytarabine 12 mg (<1 yr), 15 mg (≥1 and <2 yr), 20 mg (≥2 and <3 yr), 25 mg (≥3 yr); hydrocortisone 12 mg (<1 yr), 15 mg (≥1 and <2 yr), 20 mg (≥2 and <3 yr), 25 mg (≥3 yr). cAge-adjusted doses of intrathecal methotrexate: 6 mg (<1 yr), 7.5 mg (≥1 and <2 yr), 10 mg (≥2 and <3 yr), 12.5 mg (≥3 yr).