Clinical Pediatric Hematology-Oncology  Volume 24  Number 1  April 2017

Myeloablative Hematopoietic Stem Cell Transplantation with a Non-total Body Irradiation Regimen for Treating Pediatric Acute Lymphoblastic Leukemia

Young Tae Lim, M.D., Kyu Ho Lee, M.D., Saeyoon Kim, M.D., Ph.D.1, Sun Young Park, M.D., Jeong Ok Hah, M.D., Ph.D., and Jae Min Lee, M.D.1
1Department of Pediatrics, College of Medicine, Yeungnam University, 2Department of Pediatrics, Daegu Fatima Hospital, Daegu, Korea

Background: Total body irradiation (TBI) has been traditionally used as a conditioning regimen prior to hematopoietic stem cell transplantation (HSCT) in patients with pediatric leukemia. However, TBI can cause late sequelae such as growth impairment, cataract, hormone abnormalities, infertility, neurocognitive effects, and secondary malignancy in pediatric patients.

Methods: This single center retrospective study included 22 patients with acute lymphoblastic leukemia who were aged <18 years and underwent HSCT between May 1999 and December 2014; seven patients received a TBI-based regimen and 15 received a non-TBI regimen.

Results: The overall survival and event-free survival rates in the TBI group were not significantly different from those in the non-TBI group (overall survival rate 71% vs. 73%, respectively; P=0.906; event-free survival rate 71% vs. 73%, respectively P=0.923).

Conclusion: Our results indicate that non-TBI conditioning regimens can be an alternative treatment option of the treatment of pediatric acute lymphoblastic leukemia undergoing HSCT.

Key Words: Hematopoietic stem cell transplantation, Total body irradiation, Acute lymphoblastic leukemia, Children

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, constituting one-third of all pediatric cancers, and is the most frequent cause of cancer-related death in patients aged less than 20 years. Because of recent advancements in ALL therapy, the overall survival (OS) rate of patients with ALL has increased from <10% in the 1960s to over 90% at present [1]. Treatment of pediatric ALL varies depending on clinical features such as the biologic features of leukemia cells and response to treatment. Combined chemotherapy is used for treatment of patients with standard risk, whereas hematopoietic stem cell transplantation...
(HSCT) is performed in case of relapse or high-risk patients, including those with t(4;11)(q21;q23), t(9;22)(q34;q11.2), hypodiploidy, and hyperleukocytosis [2,3].

Since its introduction about 50 years ago, HSCT has been established as an important therapeutic modality for various diseases such as hematological malignancies, and diseases related to bone marrow failure and immunodeficiency [4]. An HSCT course mainly consists of a conditioning phase followed by stem cell infusion. The conditioning phase removes cancer cells and simultaneously induces immunosuppression for successful engraftment of stem cells. A myeloablative conditioning regimen, which consists of total body irradiation (TBI) and cyclophosphamide, is commonly used as a conditioning method for HSCT in pediatric ALL [5]. TBI has unique advantages over chemotherapy, such as a therapeutic effect on sanctuary sites such as the testes and central nervous system, a homogenous dose regardless of blood supply, and no extrication- or detoxification-associated challenges [6]. However, TBI can cause various adverse effects such as growth impairment, cataract, hormone abnormalities, infertility, neurocognitive effects, and secondary malignancy in pediatric patients [7-10]. Therefore, non-TBI-based conditioning methods have been developed; conditioning regimens combining busulfan and other anti-tumor agents are commonly used as representative non-TBI-based regimens. Busulfan-based regimens do not induce the adverse effects associated with TBI-based regimens, but have a higher rate of relapse after transplantation than TBI-based conditioning regimens do [11]. In addition, busulfan-based regimens have a weak anti-tumor effect on sanctuary sites, including the testes, compared to TBI-based regimens. For pediatric patients with ALL, a conditioning regimen should be carefully selected after considering the advantages and disadvantages of TBI.

Results of previous studies have indicated that TBI-based conditioning regimens are superior to non-TBI-based conditioning regimens in terms of therapeutic outcome [5,12]. However, most of these studies were performed in patient populations that included both adults and children with various kinds of cancers. Therefore, in this study, we retrospectively compared survival outcomes and late complications between a TBI group and non-TBI group.

### Materials and Methods

#### 1) Patient eligibility

This retrospective study was conducted in 22 pediatric patients with ALL who were aged <18 years and who underwent HSCT at the Department of Pediatrics of Yeungnam University Medical Center in Daegu, South Korea between May 1999 and December 2014. The following parameters were retrospectively compared between the two groups and included in our analysis: age at transplantation, time from diagnosis to transplantation, white blood cell (WBC) count at transplantation, patient sex, disease status, donor status, stem cell source, time of neutrophil engraftment, time of platelet engraftment, frequencies of acute graft-versus-host disease (GVHD) and chronic GVHD, overall survival (OS), event free survival (EFS), relapse after transplantation, and death. OS was defined as the period from stem cell injection to death or last follow-up observation, whereas EFS was defined as survival with no event, i.e., relapse or death. The patients were divided into a TBI and a non-TBI group: in the TBI group, cyclophosphamide and melphalan were used as conditioning regimens with TBI, whereas, in the non-TBI group, busulfan was used as the primary agent in conjunction with other agents such as melphalan, fludarabine, and cyclophosphamide. The best available source of stem cells was selected from among bone marrow, peripheral blood, and umbilical cord blood. Regarding donor status, a related full-matched donor was considered the top priority; if unavailable, an unrelated donor or mismatched donor was also considered. If no donor was available, autologous stem cell transplantation was considered. Cyclosporine and methotrexate were mainly used for GVHD prophylaxis, and anti-thymocyte globulin was added in cases with an unrelated donor. Neutrophil engraftment time was defined as the number of days required after transplantation to achieve an absolute neutrophil count of at least 0.5×10^9 cells/L, and platelet engraftment time was defined as the number of days required to achieve a platelet count of at least 20.0×10^9 cells/L without platelet transfusion. For GVHD, acute GVHD was graded by degree of invasion into skin,
Table 1. Patient characteristics

|                          | Total n (%) | TBI group n (%) | Non-TBI group n (%) | P-value |
|--------------------------|-------------|-----------------|---------------------|---------|
| Number of patients       | 22 (4.0-15.8)| 8 (2.9-15.8)    | 15 (4.0-15.8)       | 0.098   |
| Median age at diagnosis (years) (range) | 5.9 (0.4-15.8) | 8.2 (2.9-15.8) | 3.8 (0.4-13.1) | 0.098   |
| Age 1-10                 | 14 (63.6)   | 4 (57)          | 10 (66.7)           |         |
| Age <1 and >10           | 8 (36.4)    | 3 (43)          | 5 (33.3)            |         |
| WBC count at diagnosis (range) | 35,705 (1,140-836,000) | 5,800 (3,400-774,000) | 50,100 (1,140-836,000) | 0.503   |
| <50,000                  | 12 (55)     | 5 (71)          | 7 (47)              |         |
| >50,000                  | 10 (45)     | 2 (29)          | 8 (53)              |         |
| Risk groups              |             |                 |                     | 0.356   |
| Standard risk            | 8 (36)      | 3 (43)          | 5 (33)              |         |
| High risk                | 14 (64)     | 4 (57)          | 10 (67)             |         |
| Median age at transplant (years) (range) | 8.4 (0.9-17.6) | 9.6 (6.7-17.6) | 6.6 (0.9-14.8) | 0.072   |
| Time from diagnosis to transplant (years) | 1.4 (0.5-6.4) | 2.4 (0.8-4.9) | 1.4 (0.5-6.4) | 0.572   |
| Sex                      |             |                 |                     | 0.083   |
| Male                     | 13 (59)     | 6 (86)          | 7 (47)              |         |
| Female                   | 9 (41)      | 1 (14)          | 8 (53)              |         |
| Disease status           |             |                 |                     | 0.029   |
| CR1                      | 7 (32)      | 0 (0)           | 7 (47)              |         |
| CR2                      | 15 (68)     | 7 (100)         | 8 (53)              |         |
| Immunophenotype          |             |                 |                     | 0.724   |
| B                        | 17 (77.3)   | 6 (85.7)        | 11 (73.3)           |         |
| T                        | 4 (18.2)    | 1 (14.3)        | 3 (20)              |         |
| Biphenotype              | 1 (4.5)     | 0 (0)           | 1 (6.7)             |         |
| Donor status             |             |                 |                     | 0.103   |
| Related full match       | 5 (22.7)    | 4 (57.1)        | 1 (6.7)             |         |
| Related mismatch         | 3 (13.6)    | 0 (0)           | 3 (20)              |         |
| Unrelated full match     | 6 (27.3)    | 1 (14.3)        | 5 (33.3)            |         |
| Unrelated mismatch       | 5 (22.7)    | 1 (14.3)        | 4 (26.7)            |         |
| Auto                     | 3 (13.6)    | 1 (14.3)        | 2 (13.3)            |         |
| Stem cell source         |             |                 |                     | 0.061   |
| Bone marrow              | 5 (22.7)    | 4 (57.1)        | 1 (6.7)             |         |
| Peripheral blood         | 8 (36.4)    | 2 (28.6)        | 6 (40)              |         |
| Cord blood               | 8 (36.4)    | 1 (14.3)        | 7 (46.7)            |         |
| Bone marrow+cord blood   | 1 (4.5)     | 0 (0)           | 1 (6.7)             |         |
| TNC×10^{6}/kg, median (range) | 5.6 (0-19.9) | 2.6 (1-5.7)    | 8.2 (0.6-20.0)      |         |
| CD34+×10^{6}/kg, median (range) | 3.2 (0.2-12.4) | 1.1 (0.4-3.6) | 3.4 (0.2-12.4)      |         |
| Neutrophil engraftment (days) | 15 (10-27)    | 18 (11-26)      | 14 (10-27)          | 0.803   |
| Platelet engraftment (days) | 40 (11-180)  | 39 (33-102)     | 47 (11-180)         | 0.792   |
| Relapse after transplant |             |                 |                     | 0.311   |
| No                       | 21 (95.5)   | 7 (100)         | 14 (93.3)           |         |
| Yes                      | 1 (4.5)     | 0 (0)           | 1 (6.7)             |         |
| Death after transplant   |             |                 |                     | 0.655   |
| No                       | 16 (72.7)   | 5 (71.4)        | 11 (73.3)           |         |
| Yes                      | 6 (27.3)    | 2 (28.6)        | 4 (26.7)            |         |
| Acute GVHD (Grade 2-Grade 4) | 9 (40.9)    | 4 (57.1)        | 5 (33.3)            |         |
| Chronic GVHD             |             |                 |                     | 0.783   |
| Limited                  | 6 (27.3)    | 2 (28.6)        | 4 (26.7)            |         |
| Extensive                | 1 (4.5)     | 0 (0)           | 1 (6.7)             |         |

CR, complete remission; GVHD, graft-versus-host disease; TBI, total body irradiation; TNC, total neutrophil count; WBC, white blood cell.
liver, or gastrointestinal and other organs [13], whereas chronic GVHD was classified as limited or extensive invasion [14].

The study protocol was also approved by the Institutional Review Board of Yeungnam University Hospital.

2) Statistical analysis

Mean values were compared using the Mann-Whitney test, OS and EFS were analyzed using Kaplan-Meier curve analysis, and P-values <0.05 were considered statistically significant. Analyses were conducted using IBM SPSS Statistics 23.0 software (SPSS Inc., Chicago, IL, USA).

Results

A significant difference in disease status at the time of HSCT was observed between the two groups (Table 1). All patients in the TBI group underwent HSCT at CR2, whereas of the 15 patients in the non-TBI group, seven underwent HSCT at CR1 and eight underwent HSCT at CR2. Among the seven patients in the non-TBI group who underwent HSCT at CR1, MLL gene rearrangement was detected in three patients; induction failure, and T cell lineage were detected in one patient each; one patient was aged less than 12 months at the time of HSCT; and positive minimal residual disease was consistently confirmed in one patient after chemotherapy (TEL-AML1 PCR positive).

Among the seven patients in the TBI group, five showed successful neutrophil and platelet engraftment; one girl died due to sepsis 4 days after HSCT whereas one boy showed successful neutrophil engraftment 11 days after HSCT, but expired because of the occurrence of sepsis before platelet engraftment. Among the 15 patients in the non-TBI group, 12 showed successful neutrophil and platelet engraftment. Among the remaining three patients, one expired because of acute GVHD after transplantation, whereas two showed successful neutrophil engraftment after transplantation but failed to achieve platelet engraftment; one of them died because of Pneumocystis jirovecii pneumonia whereas the other died because of relapse after transplantation. Conditioning regimens used for the patients in the two treatment groups are described in Table 2.

Transplant characteristics of patients are provided in Table 3. Among the 22 patients, relapse occurred in one patient in the non-TBI group. He was BCR-ABL-positive and experienced a relapse in the bone marrow after transplantation (patient #3).

Death occurred in six of the 22 patients: two in the TBI group and four in the non-TBI group. Among the two patients in the TBI group, one girl (patient #18) died because of sepsis on day 1 after HSCT whereas one boy (patient #22) expired because of sepsis, despite successful neutrophil engraftment but platelet engraftment failure after transplantation. Among the four patients in the non-TBI group who died, one girl (patient #9) died because of P. jirovecii pneumonia after transplantation, two boys (patient #8, #12) died because of severe acute GVHD, and the other boy (patient #3) died after relapse.

The 5-year OS rate in the TBI group was not significantly different from that in the non-TBI group (Fig. 1A). The 5-year EFS rate in the TBI group was not significantly different from that in the non-TBI group (Fig. 1B). In analyzing only CR2 patients, the 5-year OS and EFS did not show significant differences between the TBI group and the Non-TBI group (Fig. 2A, B).

Regarding late complications, two of the seven patients in the TBI group died during therapy. Among the remaining five patients, three had short stature whereas two had testicular hypogonadism. In addition, Type 1 diabetes mellitus occurred in one patient 17 months after transplantation. No endocrine complications such as short stature or

Table 2. Conditioning regimens

| Conditioning regimen                        | Number of patients |
|--------------------------------------------|--------------------|
| Total body irradiation                     |                    |
| Total body irradiation/cyclophosphamide    | 1                  |
| Total body irradiation/melphalan           | 1                  |
| Total body irradiation/cyclophosphamide/melphalan | 5             |
| Non-total body irradiation                 |                    |
| Busulfan/melphalan/fludarabine             | 6                  |
| Busulfan/melphalan/cyclophosphamide       | 6                  |
| Busulfan/melphalan                         | 1                  |
| Busulfan/fludarabine                       | 1                  |
| Busulfan/cyclophosphamide                 | 1                  |
Table 3. Transplant characteristics of Non-TBI patients

| Patient No | Sex | Age at diagnosis (years) | Age at HSCT (years) | Disease status at HSCT | Immuno-phenotype | Cytogenetics | Donor | HLA match | Stem cell source | Conditioning regimen | The reason for HSCT | Relapse after HSCT | Outcome (years)
|------------|-----|--------------------------|---------------------|-----------------------|------------------|--------------|-------|-----------|------------------|-------------------|--------------------|-----------------|-----------------|
| 1          | F   | 2.1                      | 2.8                 | CR1                   | B                | t(4;11)(q21;q23);MLL | MUD         | Full match | PB               | Bu-Mel-Flu        | MLL rearrangement    | No               | NED (0.7)       |
| 2          | M   | 12.4                     | 13.3                | CR1                   | T                | Normal karyotype   | MRD         | Full match | BM               | Bu-Mel-Cy          | T-ALL              | No              | NED (2.3)       |
| 3          | M   | 3.3                      | 4.8                 | CR2                   | B                | t(9;12)(q34;q11.2);B CR-ABL1 | MMRD 2 MM | Full match | PB               | Bu-Flu            | BCR-ABL1           | Yes             | Death (0.9)     |
| 4          | M   | 13.1                     | 14.3                | CR1                   | B                | t(12;21)(p13;q22);TEL-AML1 | MUD       | Full match | PB               | Bu-Mel-Flu        | Positive MRDs      | No              | NED (2.5)       |
| 5          | M   | 1.4                       | 5.8                 | CR2                   | B                | MLL rearrangement  | MMURD      | 2 MM       | PB               | Bu-Cy             | CR2                | No              | NED (1.9)       |
| 6          | F   | 1.7                      | 5.7                 | CR2                   | B                | t(12;21)(p13;q22);TEL-AML1 | MMURD 2 MM | BM + CB    | Bu-Mel-Flu        | MRD               | No                 | NED (3.0)       |
| 7          | F   | 0.7                      | 1.6                 | CR1                   | B                | t(4;11)(q21;q23);MLL | MUD         | Full match | CB               | Bu-Mel-Flu        | MLL rearrangement    | No               | NED (6.0)       |
| 8          | M   | 6.0                       | 8.7                 | CR2                   | B                | t(9;12)(q34;q11.2);BCR-ABL1 | MMURD 1 MM | Full match | CB               | Bu-Mel-Flu        | BCR-ABL1           | No              | Death (0.4)     |
| 9          | F   | 1.8                       | 3.1                 | CR2                   | T                | del(16q)           | MMURD      | 2 MM       | CB               | Bu-Mel-Flu        | T-ALL              | No              | Death (0.2)     |
| 10         | F   | 11.9                      | 13.5                | CR2                   | B                | Normal karyotype   | Auto       | Full match | PB               | Bu-Mel-Cy          | CR2                | No              | NED (6.7)       |
| 11         | M   | 8.4                       | 14.8                | CR2                   | B                | Normal karyotype   | Auto       | Full match | PB               | Bu-Mel-Cy          | CR2                | No              | NED (7.8)       |
| 12         | M   | 5.8                       | 6.6                 | CR1                   | T                | del(9q)            | MMURD      | 2 MM       | CB               | Bu-Mel-Cy          | T-ALL              | No              | Death (0.1)     |
| 13         | F   | 3.8                       | 9.4                 | CR2                   | B                | Biphentphenotype   | MMURD      | 2 MM       | CB               | Bu-Mel-Cy          | CR2                | No              | NED (10.7)      |
| 14         | F   | 0.4                       | 0.9                 | CR1                   | B                | Hyperdiploidy      | MMURD      | 1 MM       | CB               | Bu-Mel            | Infant ALL         | No              | NED (9.4)       |
| 15         | F   | 6.6                       | 7.4                 | CR1                   | B                | 11q23 rearrangement | MMURD      | Full match | CB               | Bu-Mel-Cy          | MLL rearrangement    | No              | NED (9.7)       |
| 16         | M   | 2.9                       | 6.7                 | CR2                   | B                | Normal karyotype   | MMURD      | 2 MM       | CB               | TBI-Mel-Cy         | CR2                | No              | NED (10.0)      |
| 17         | M   | 6.2                       | 8.6                 | CR2                   | T                | Normal karyotype   | MMURD      | 2 MM       | CB               | TBI-Mel-Cy         | CR2                | No              | NED (10.3)      |
| 18         | M   | 15.8                      | 16.6                | CR2                   | B                | Normal karyotype   | MURD       | Full match | PB               | TBI-Cy            | CR2                | No              | Death (0.5)     |
| 19         | M   | 8.2                       | 9.6                 | CR2                   | B                | Normal karyotype   | MRD        | Full match | BM               | TBI-Mel-Cy         | CR2                | No              | NED (13.1)      |
| 20         | M   | 11.7                      | 12.6                | CR2                   | B                | T(4;11)(q21;q23)   | MRD        | Full match | BM               | TBI-Mel-Cy         | CR2                | No              | NED (13.0)      |
| 21         | M   | 5.0                       | 8.1                 | CR2                   | B                | Normal karyotype   | MRD        | Full match | BM               | TBI-Mel-Cy         | CR2                | No              | NED (13.2)      |
| 22         | F   | 12.8                      | 17.6                | CR2                   | B                | 45,XX,t(9;12)(q34; q11.2), -15 | Auto       | Full match | PB               | TBI-Mel-Cy         | CR2                | No              | Death (0.01)    |

NED, no evidence of disease; MRD, matched related donor; MUD, matched unrelated donor; MMRD, mismatched related donor; MMURD, mismatched unrelated donor; MMRDs, minimal residual disease; MM, mismatch; PB, peripheral blood; BM, bone marrow; CB, cord blood; Bu, busulfan; Flu, fludarabine; Cy, cyclophosphamide; Mel, melphalan; TBI, total body irradiation.

*Survival time from HSCT.
Fig. 1. Overall survival (A) and event-free survival (B) after a total body irradiation-based conditioning regimen (n=7) compared with that after a conditioning regimen without total body irradiation (n=15).

Fig. 2. Overall survival (A) and event-free survival (B) after a total body irradiation-based conditioning regimen (n=7) compared with that after a conditioning regimen without total body irradiation (n=8) in CR2 patients.

Discussion

Locatelli et al. argued that most long-term side effects in pediatric patients who have received HSCT are associated with the conditioning regimen performed before transplantation, including radiotherapy-induced toxicity [15]. In their study, growth impairment was observed in most patients in the TBI group, and 30-40% of these patients presented thyroid function abnormalities. In addition, delayed puberty development was observed in some patients in the TBI group. According to Sanders et al., the rates of thyroid function abnormalities and growth hormone deficiency were associated more strongly with a TBI-based conditioning regimen than they were with a non-TBI-based conditioning regimen among pediatric patients who had undergone HSCT [16]. Moreover, demand for synthetic growth hormone therapy in the TBI-based conditioning group was higher than that in the non-TBI-based conditioning group. Park et al. conducted a single institution study consisting of 28 pediatric patients with acute leukemia in order to de-
termine the effect of TBI-based conditioning [17]. The most common chronic complication associated with TBI was short stature, which occurred at a rate of 14.3%. On the basis of height measurements before and after HSCT, Shankar et al. reported that the use of busulfan and cyclophosphamide as a non-TBI-based conditioning regimen had no effect on the growth of pediatric patients [18].

In the present study, five out of the seven total patients in the TBI-based conditioning group were documented as long-term survivors. Three among those five patients were found to have short stature (<3 percentile), and these patients showed no response to growth hormone therapy. However, short stature was not observed in the non-TBI-based conditioning group. Thus, TBI had a negative effect on pediatric patients by causing late sequelae, including growth impairment. Therefore, the potential negative effects of TBI-based conditioning regimens must be carefully considered when selecting a conditioning regimen.

Several studies initiated in the 1970s aimed to develop suitable TBI alternative such as a chemotherapy-based conditioning regimen. After Santos et al. first confirmed the myeloablative effect of busulfan in a murine aplastic anemia model [19], a busulfan+cyclophosphamide regimen became the most frequently used alternative to a TBI-based regimen. Busulfan has high myeloablative and anti-leukemic activities but a weak immunosuppressive effect, which can be augmented by simultaneous use of cyclophosphamide [20]. A busulfan+cyclophosphamide conditioning regimen was first used in pediatric HSCT in the 1980s. Busulfan is especially suitable for a pediatric conditioning regimen because its plasma clearance rate is 4- to 5-fold higher in children than in adults, resulting in lower toxicity [21].

Despite these advantages of busulfan, previous studies have reported that the survival rate of pediatric patients with ALL after transplantation was lower with a busulfan-based conditioning regimen than with a TBI-based conditioning regimen. Ringden et al. conducted a study on 167 patients with leukemia who underwent HSCT using hematopoietic stem cells obtained from HLA-identical donors [22]. The study subjects were randomized into a busulfan-based conditioning group or TBI-based conditioning group for comparison of post-transplantation results. The 3-year survival rate in the TBI group (76%) was significantly higher than that in the busulfan group (62%). The transplantation-related mortality rate in the busulfan group (62%) was significantly higher than that in the TBI group (12%). The results of this study established TBI as the treatment of choice. However, this study included pediatric as well as adult patients, and patients with acute and chronic myeloid leukemia in addition to patients with acute lymphoblastic leukemia. In a study by Granados et al., 156 patients with ALL were divided into TBI-based and non-TBI-based conditioning groups for comparison of EFS, transplant-related mortality, and probability of relapse between groups [23]. The 6-year EFS rate after transplantation in the TBI group (43%) was significantly higher than that in the non-TBI group (22%). Transplant-related mortality did not differ between the groups. However, the probability of relapse at 3 years after transplantation in the non-TBI group (71%) was significantly higher than that in the TBI group (47%). These results established the TBI-based conditioning regimen as the standard preparative regimen for patients with ALL. Although this study included only patients with ALL, it included both pediatric and adult patients. Kim et al. compared HSCT outcomes in 77 patients with various pediatric leukemias divided into a TBI group and a non-TBI group, and reported no difference in the overall 5-year EFS between the two groups [24]. However, when data from only patients with ALL were compared between groups, the 5-year EFS rate in the TBI group (65%) was significantly higher than that in the non-TBI group (17%). Davies et al. compared outcomes between 451 ALL patients treated with TBI+cyclophosphamide and 176 patients treated with busulfan+cyclophosphamide; all patients were aged <20 years, [11] The 3-year OS rate in the TBI group (55%) was significantly higher than that in the non-TBI group (40%). The 3-year EFS rate in the TBI group was also significantly higher than that in the non-TBI group. In a randomized prospective study conducted by Bunin et al., outcomes were compared among 43 patients with ALL aged <21 years who were randomized into a TBI group and a non-TBI group [25]. The 3-year EFS rate in the TBI group (58%) was significantly higher than that in the non-TBI group (29%).

Taken together, the results of all these aforementioned
studies indicate that a TBI-based conditioning regimen is superior to a non-TBI-based conditioning regimen in terms of survival rate, despite the potential for development of late sequelae. The poor outcomes of busulfan-based conditioning regimens might be because the plasma clearance rate of busulfan in pediatric patients is higher than that in adults, resulting in lower therapeutic drug levels of busulfan in pediatric patients. However, this higher clearance rate might also result in lower toxicity in pediatric patients, despite the disadvantage of poor survival and a high relapse rate [21].

In the present study, the 5-year EFS rate in the TBI group was not significantly different from that in the non-TBI group. Thus, in contrast to the aforementioned studies, the present study revealed that outcomes in the non-TBI group were not inferior to those in the TBI group, suggesting that a non-TBI-based conditioning regimen can be developed and used as a viable alternative to a TBI-based conditioning regimen. In addition, no endocrine complications were observed in the non-TBI group, suggesting that a non-TBI-based conditioning regimen might result in a better quality of life in pediatric patients with ALL who are long-term survivors after transplantation. The discrepancy in results between the present study and previous studies might be a result of the differences in populations between these studies i.e., adult vs. pediatric populations and patients with ALL vs. patients with other leukemias.

This study has some limitations. First, it was a single-centered, retrospective study with a relatively small number of subjects. Second, combined chemotherapy with TBI and busulfan in the TBI group and non-TBI group was not the same for each patient. Third, the different donor sources and high number of CR1 patients in the non-TBI group could affect survival outcomes. In addition, a trend of decreased EFS was observed in the non-TBI group. This observation should be interpreted with caution considering the small sample size of the study. Furthermore, T-cell lymphoblastic leukemia and infant ALL, which are not relevant to transplant indication, were subjects for transplantation at CR1. This might also have an effect on the result and it will be the limits of retrospective study.

In summary, the TBI-based regimen is still a standard preparative regimen for HSCT of pediatric acute lymphoblastic leukemia. However, considering that long-term complications of pediatric patients and the adverse effects of the TBI-based regimen affect the quality of life, the non-TBI-based conditioning regimen will be an alternative treatment option of the treatment of pediatric acute lymphoblastic leukemia, avoiding the adverse effects of the TBI-based regimens.

**Acknowledgments**

This work was supported by the 2015 Yeungnam University Research Grant.

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