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Original Article

Total Body Irradiation, Busulfan, Fludarabine Conditioning for Pediatric Acute Myeloid Leukemia Patients Treated with Hematopoietic Stem Cell Transplantation in Second Complete Remission

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Purpose The optimum conditioning regimen for pediatric acute myeloid leukemia (AML) patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) in second complete remission (CR) remains unclear. In this study, we reviewed the outcome of AML patients treated with HSCT in second CR at our institution, focusing on the role of the conditioning regimen on post-transplant survival.

Materials and Methods We evaluated 43 AML patients who received myeloablative HSCT in second CR at our institution from 2009 to 2023. Thirteen of the patients (30.2%) received conditioning with busulfan and fludarabine (Bu/Flu), while 30 patients (69.8%) were treated with total body irradiation (TBI) 8 Gy combined with Bu and Flu (TBI/Bu/Flu).

Results Thirty-two of the patients received a haploidentical family donor (HFD) transplant (74.4%). Estimated 5-year event-free survival (EFS) was 57.5%±7.6% (24/43), with 5-year cumulative incidence of relapse and non-relapse mortality of 30.7%±7.2% and 11.8%±5.0%, respectively. Among risk factors for EFS, only the conditioning regimen was important with patients treated with TBI/Bu/Flu having significantly higher 5-year EFS than those who received Bu/Flu (73.0%±8.2% vs. 23.1%±11.7%, p=0.004). There was no significant difference in 5-year EFS between patients who received HFD transplant and those treated with transplant from other donors. Estimated 5-year overall survival was 66.8%±7.3% (28/43), with all 28 surviving patients remaining disease-free at last follow-up.

Conclusion A myeloablative TBI/Bu/Flu regimen resulted in 5-year EFS of 73.0%±8.2%, indicating a favorable long-term outcome for AML patients in second CR who receive HSCT with this conditioning regimen compared to previous studies.

Key words Acute myeloid leukemia, Child, Second complete remission, Hematopoietic stem cell transplantation, Conditioning

Introduction

Although a significant subset of pediatric acute myeloid leukemia (AML) patients are treated with a chemotherapy-only strategy, allogeneic hematopoietic stem cell transplantation (HSCT) is a key component of therapy for high-risk patients and for those who relapse [1,2]. Past studies have shown long-term leukemia-free survival (LFS) of 40%-50% for pediatric AML patients who received HSCT in second complete remission (CR) [3,4].

The pre-transplant conditioning of pediatric AML patients receiving HSCT is commonly myeloablative; however, the optimum conditioning regimen remains unclear. Data based mostly on adult HSCT patients showed better transplant outcomes with chemotherapy-only based conditioning with busulfan (Bu) and cyclophosphamide (Cy), compared to total body irradiation (TBI) and Cy [5]. Attempts at modifying the conditioning regimen to further improve post-HSCT survival include the addition of chemotherapy such as melphalan to minimize leukemic burden prior to HSCT [6], and replacement of Cy with agents such as fludarabine (Flu) and clofarabine to decrease transplant-related toxicity [6,7].

At our institution, AML patients who received HSCT in second CR previously received conditioning with myeloablative Bu/Flu. Since 2014, we amended the regimen to incorporate 8 Gy TBI and lower the cumulative Bu dose (TBI/Bu/Flu) with the aim of decreasing relapse with a relatively lower dose of TBI, while also decreasing non-relapse mortality (NRM) through an overall lower dose of Bu. In this study, we retrospectively analyzed the outcome and prognostic factors

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for AML patients who received HSCT in second CR, focusing on comparisons of the two different conditioning regimens as determinants of post-transplant survival.

Materials and Methods

1. Patient group

We evaluated AML patients who consecutively received allogeneic HSCT in second CR from April 1, 2009 to December 31, 2023 at our institution. We excluded one acute promyelocytic leukemia (APL) patient who received allogeneic HSCT in second CR to focus on the outcome of non-APL AML patients. We further excluded one patient treated with HSCT for relapse and clonal evolution to acute bilineage leukemia after initial treatment for AML, and one patient treated with a conditioning regimen other than Bu/Flu or TBI/Bu/Flu in second CR. The final study group consisted of 43 patients (Table 1). Nineteen of the patients had previously been reported as part of different studies [2,8,9].

2. Conditioning regimen and graft-versus-host disease prophylaxis

Donor-patient human leukocyte antigen (HLA) typing was done for HLA-A, -B, -C and -DR at the allele level. Patients who received HSCT from 2009 to 2013 were treated with a conditioning regimen consisting of intravenous Bu 130 mg/m^2/day (day –6 to day –3), and Flu 40 mg/m^2/day (day –6 to day –3). In contrast, the conditioning regimen for the majority of patients who received HSCT from 2014 onwards was the following: fractionated TBI 8 Gy total (day –8 to day –7), Bu 130 mg/m^2/day (day –6 to day –5), and Flu 40 mg/m^2/day (day –6 to day –3). Bu was given intravenously as a single dose each day, and Bu drug levels were not assessed.

Patients treated with unrelated donor (UD) or haploidentical family donor (HFD) HSCT received *in vivo* T-cell depletion. HSCT recipients from 2009 to 2018 were treated with rabbit anti-thymocyte globulin (ATG) (thymoglobulin) at total doses ranging from 3.75 mg/kg to 7.5 mg/kg for UD HSCT, and 5 mg/kg to 10 mg/kg for HFD HSCT. ATG was combined with cyclosporine and low-dose methotrexate for overall graft-versus-host disease (GVHD) prophylaxis. The majority of UD or HFD HSCT patients from 2019 onwards received post-transplantation cyclophosphamide (PTCy) at standard doses of 50 mg/kg/day for 2 days on days 3 and 4. For these patients, overall GVHD prophylaxis consisted of PTCy combined with cyclosporine starting on day 5.

3. Study outcomes and definitions

The main study outcomes were the event-free survival (EFS) and overall survival (OS) of the study group of patients who received HSCT in second CR. We analyzed the following variables with regard to prognostic impact on EFS in univariate analysis: sex, age at diagnosis, genetic risk group, overall AML risk group, history of previous HSCT, time to relapse, number of pre-transplant chemotherapy courses after relapse, period of HSCT, donor type, conditioning regimen, GVHD prophylaxis, diagnosis of acute or chronic GVHD. Prognostic variables with $p < 0.1$ regarding EFS were evaluated in the multivariate setting.

We also determined the incidence of relapse, NRM, acute GVHD (both grades 2-4 and grades 3-4), and chronic GVHD (overall, as well as moderate/severe). Acute and chronic GVHD were graded according to established criteria [10,11].

The date of neutrophil engraftment was defined as the first of three consecutive days with absolute neutrophil count $> 0.5\times10^9$/L and the date of platelet engraftment was defined as the first of three consecutive days with platelet count $> 20\times10^9$/L without platelet transfusions in the preceding week.

4. Statistics

Comparison of categorical and continuous variables between Bu/Flu and TBI/Bu/Flu subgroups was done with Fisher's exact test and Mann-Whitney U test, respectively. The EFS of the patients was determined from the time of HSCT to relapse, death in CR, diagnosis of secondary malignancy, or last follow-up, while OS was calculated from the time of HSCT to death or last follow-up. EFS and OS were estimated with the Kaplan-Meier method. Univariate and multivariate analysis of risk factors for EFS were done with the log-rank test and Cox proportional hazards regression, respectively. Both acute GVHD and chronic GVHD were considered time-dependent covariates when analyzing their impact on EFS.

Incidence of relapse, NRM, acute and chronic GVHD were calculated with the cumulative incidence (CI) function, and comparison according to groups was done with Gray's test. Competing risks were death in CR for relapse, AML relapse for NRM, relapse or NRM without acute GVHD within 100 days post-HSCT for acute GVHD, and relapse or NRM without chronic GVHD within 1 year post-HSCT for chronic GVHD.

p-values < 0.05 were considered significant. Patient follow-up was done up to December 31, 2025.

Results

1. Salvage therapy after first relapse

The median time to relapse was 14.3 months from diagnosis (range, 7.8 to 82.2 months). All patients received flu-

Table 1. Key characteristics of AML patients who received HSCT in second CR, according to conditioning regimen

	Bu/Flu (n=13)	TBI/Bu/Flu (n=30)	p-value
Sex			0.742
Male	8 (61.5)	20 (66.7)	
Female	5 (38.5)	10 (33.3)	
Age at diagnosis (yr)	10.7 (1.4-14.3)	10.4 (1.9-15.2)	0.764
Genetics			
RUNX1::*RUNX1T1*	4 (30.8)	6 (20.0)	
CBFB::*MYH11*	1 (7.7)	2 (6.7)	
Biallelic *CEBPA*	0	5 (16.7)	
NPM1	1 (7.7)	2 (6.7)	
KMT2A rearrangement	1 (7.7)	4 (13.3)	
FLT3-ITD	2 (15.4)	0	
-7	1 (7.7)	0	
Complex karyotype[a]	3 (23.1)	1 (3.3)	
del(5q)	0	1 (3.3)	
FUS::*ERG*	0	1 (3.3)	
Normal karyotype	0	3 (10.0)	
Non-complex karyotype	0	5 (16.7)	
Overall risk group[b]			0.645
Low	5 (38.5)	9 (30.0)	
Intermediate	4 (30.8)	14 (46.7)	
High	4 (30.8)	7 (23.3)	
Previous HSCT in first CR			0.699
No	11 (84.6)	23 (76.7)	
Yes	2 (15.4)	7 (23.3)	
No. of pre-transplant chemotherapy courses after relapse			
One	3 (23.1)	0	
Two	9 (69.2)	27 (90.0)	
Three	1 (7.7)	2 (6.7)	
Four	0	1 (3.3)	

Values are presented as number (%) or median (range). AML, acute myeloid leukemia; Bu, busulfan; CR, complete remission; Flu, fludarabine; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation. [a]Defined as 3 or more unrelated chromosomal abnormalities in the absence of World Health Organization–designated recurrent genetic abnormalities, [b]Based on genetic risk and response to induction chemotherapy.

darabine, cytarabine, granulocyte colony-stimulating factor (FLAG)±idarubicin-based reinduction chemotherapy. Patients received a median of 2 cycles of chemotherapy (range, 1 to 4) after relapse and prior to HSCT. Median time to achievement of second CR after relapse was 38 days (range, 24 to 104 days).

2. Hematopoietic stem cell transplantation

Median age at HSCT was 12.4 years (range, 2.6 to 18.0 years) (Table 2). Thirty-two of the patients received an HFD transplant (74.4%), and all but 4 patients received peripheral blood stem cell transplantation (90.7%). Overall, 13 patients (30.2%) were treated with Bu/Flu conditioning, while 30 patients (69.8%) received TBI/Bu/Flu conditioning.

3. Engraftment

All but one patient who experienced primary graft failure showed neutrophil engraftment at a median of 12 days post-HSCT (range, 9 to 20 days). Forty of 43 patients showed platelet engraftment at a median of 20 days post-HSCT (range, 14 to 61 days). The three patients who did not show platelet engraftment experienced the following: primary graft failure at day 23, death from lung hemorrhage at day 92, and relapse at day 108.

4. Acute and chronic GVHD

The 100-day CI of grades 2-4 and grades 3-4 acute GVHD were 62.8%±7.5% (27/43) and 18.6%±6.0% (8/43), respectively. In addition, the 3-year CI of overall chronic GVHD and

Table 2. Transplantation procedure, according to conditioning regimen

	Bu/Flu (n=13)	TBI/Bu/Flu (n=30)	p-value
Age at HSCT (yr)	13.4 (2.6-16.1)	12.1 (3.0-18.0)	0.907
Donor type			
MSD	0	4 (13.3)	
UD	3 (23.1)	4 (13.3)	
HFD	10 (76.9)	22 (73.3)	
HLA compatibility			0.696
Match	2 (15.4)	8 (26.7)	
Mismatch	11 (84.6)	22 (73.3)	
Cell source			
BM	1 (7.7)	2 (6.7)	
CB	1 (7.7)	0	
PBSC	11 (84.6)	28 (93.3)	
GVHD prophylaxis[a]			0.001
ATG-based	13 (100)	12 (46.2)	
PTCy-based	0	14 (53.8)	
Infused cell dose[b]			
TNC ($\times 10^8$/kg)	19.61 (0.75-41.61)	20.12 (1.07-42.10)	0.573
MNC ($\times 10^8$/kg)	15.16 (0.26-27.72)	13.84 (0.51-37.58)	0.984
CD34+ ($\times 10^6$/kg)	6.61 (1.29-11.37)	6.75 (1.66-20.52)	0.752
CD3+ ($\times 10^7$/kg)	70.47 (1.12-153.76)	46.08 (1.17-225.73)	0.518

Values are presented as median (range) or number (%). ATG, anti-thymocyte globulin; BM, bone marrow; BMT, BM transplantation; Bu, busulfan; CB, cord blood; CBT, CB transplantation; Flu, fludarabine; GVHD, graft-versus-host disease; HFD, haploidentical family donor; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MNC, mononuclear cells; MSD, matched sibling donor; PBSC, peripheral blood stem cells; PBSCT, PBSC transplantation; PTCy, post-transplantation cyclophosphamide; TBI, total body irradiation; TNC, total nucleated cells; UD, unrelated donor. [a]For the 39 patients who received unrelated donor or haploidentical family donor HSCT, [b]For the 42 patients who received BMT or PBSCT. The cell dose for the 1 CBT patient was as follows: TNC 3.2×10^7/kg, MNC 2.0×10^7/kg, CD34+ 7.6×10^5/kg, CD3+ 3.6×10^6/kg.

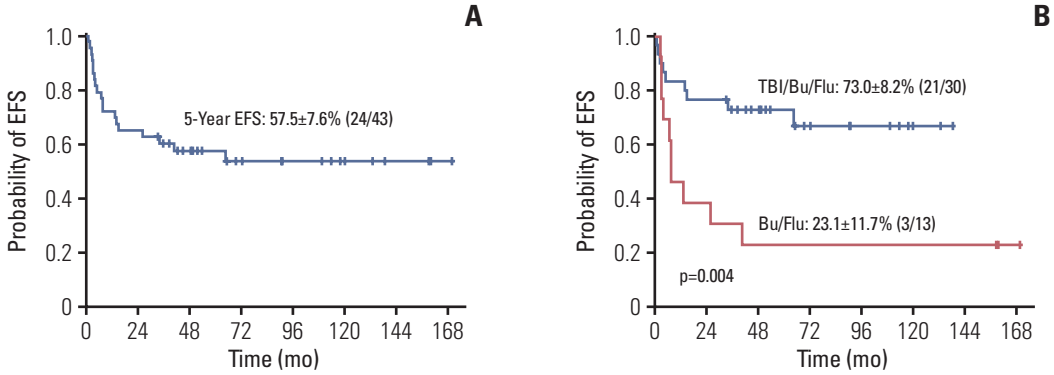


Fig. 1. (A) Estimated 5-year event-free survival (EFS) of the overall study group. (B) Estimated 5-year EFS of the overall study group according to the conditioning regimen. Bu, busulfan; Flu, fludarabine; TBI, total body irradiation.

moderate/severe chronic GVHD were 30.2%±7.1% (13/43) and 25.7%±6.8% (11/43), respectively.

5. EFS and risk factors for EFS

The estimated 5-year EFS was 57.5%±7.6% (24/43) (Fig. 1A). Events included relapse (n=13), NRM (n=5), and secondary malignancy (n=1). Causes of NRM included chronic GVHD (n=2), acute GVHD (n=1), cytomegalovirus pneumonia (n=1), and lung hemorrhage (n=1).

Among univariate risk factors for EFS, only the conditioning

Table 3. Univariate study of risk factors for EFS

	Patients (Events)	5-Year EFS±SE (%)	p-value
Sex			0.439
Male	28 (11)	63.3±9.3	
Female	15 (8)	46.7±12.9	
Age at diagnosis (yr)[a]			0.561
≤ 11	23 (9)	59.8±10.5	
> 11	20 (10)	54.5±11.2	
Genetic risk			0.903
Low	17 (7)	64.2±11.8	
Intermediate	18 (8)	55.0±11.9	
High	8 (4)	50.0±17.7	
Overall risk group[b]			0.353
Low	14 (4)	70.7±12.4	
Intermediate	18 (9)	55.0±11.9	
High	11 (6)	45.5±15.0	
Previous HSCT			0.401
No	34 (14)	60.8±8.5	
Yes	9 (5)	44.4±16.6	
Time to relapse (mo)[a]			0.152
≤ 14	21 (11)	45.8±11.3	
> 14	22 (8)	67.9±10.0	
Pre-transplant chemo courses			0.930
≤ 2 courses	39 (17)	58.7±7.9	
> 2 courses	4 (2)	37.5±28.6	
Period of HSCT			0.064
2009-2016	19 (12)	42.1±11.3	
2016-2023	24 (7)	70.8±9.3	
Donor type			0.237
Haploidentical	32 (16)	52.3±9.0	
Others	11 (3)	72.7±13.4	
Conditioning regimen			0.004
Bu/Flu	13 (10)	23.1±11.7	
TBI/Bu/Flu	30 (9)	73.0±8.2	
GVHD prophylaxis			0.304
Cyclosporine+MTX	29 (15)	51.3±9.4	
PTCy+cyclosporine	14 (4)	71.4±12.1	
Acute GVHD (≥ grade 2)			0.164
No	16 (9)	43.8±12.4	
Yes	27 (10)	65.8±9.3	
Chronic GVHD			0.386
No	30 (14)	52.9±9.2	
Yes	13 (5)	68.4±13.1	

Bu, busulfan; EFS, event-free survival; Flu, fludarabine; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; PTCy, post-transplantation cyclophosphamide; SE, standard error; TBI, total body irradiation. [a]Cutoff based on median value, [b]Based on genetic risk and response to induction chemotherapy.

regimen was an important factor, with patients treated with TBI/Bu/Flu having significantly higher EFS than those who received Bu/Flu (5-year EFS, 73.0%±8.2% vs. 23.1%±11.7%; p=0.004) (Table 3, Fig. 1B). Also, patients treated with HSCT in the later period (2016-2023) had higher 5-year EFS than those treated in the earlier period (2009-2016), with borderline significance (70.8%±9.3% vs. 42.1%±11.3%, p=0.064). A multivariate study of the impact of the conditioning regimen

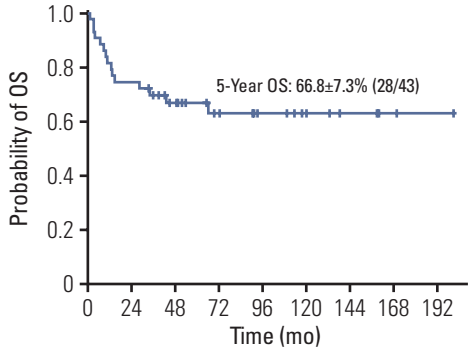


Fig. 2. Estimated 5-year overall survival (OS) of the overall study group.

and transplant period on EFS showed that neither was a significant factor. To further clarify the role of transplant period on outcome, we evaluated the impact of transplant period on EFS in the subgroup of TBI/Bu/Flu patients; patients treated in the earlier (2014-2018) and later (2018-2023) periods had similar outcomes (69.2%±12.8% vs. 76.5%±10.3%, p=0.637). In the overall group of patients, there was no significant difference in 5-year EFS between patients who received HFD transplant, and those treated with transplant from other donors (52.3%±9.0% vs. 72.7%±13.4%, p=0.237).

The 5-year CI of relapse and NRM were 30.7%±7.2% (13/43) and 11.8%±5.0% (5/43), respectively. Patients treated with TBI/Bu/Flu had significantly lower 5-year CI of relapse compared with those who received Bu/Flu (20.0%±7.4% vs. 53.8%±15.1%, p=0.043). TBI/Bu/Flu regimen also resulted in a lower 5-year CI of NRM compared to Bu/Flu, although without statistical significance (7.0%±4.9% vs. 23.1%±12.4%, p=0.135).

6. Overall survival

The estimated 5-year OS was 66.8%±7.3% (28/43), with all 28 surviving patients remaining disease-free at last follow-up (Fig. 2). Of the 19 patients who experienced an event, 3 patients who relapsed post-HSCT achieved CR once more and remain disease-free (chemotherapy only, chemotherapy and donor lymphocyte infusion, chemotherapy and second HSCT, respectively), and one patient diagnosed with thyroid cancer as a second malignancy underwent curative surgery.

Discussion

Recent studies have shown long-term OS of 30%-40% for relapsed pediatric AML patients [12,13]. In contrast, patients who receive allogeneic HSCT in second CR have shown 5-year LFS of 40%-50% [3,4], indicating improved outcome for relapsed patients who are able to achieve second CR and proceed to HSCT. The 5-year EFS of 57.5% for our study group was comparable to the survival rates reported in these past studies.

The conditioning regimen may have a significant impact on the outcome of pediatric AML patients who receive HSCT. One key comparison is Bu-based chemotherapy only conditioning versus the incorporation of TBI as part of the conditioning regimen. Past studies in pediatric AML patients have either shown no difference in major transplant outcomes between the two conditioning types [14,15], or improved survival with Bu-based chemotherapy conditioning in first CR [16]. Modification of the standard Bu/Cy has also been attempted, with one study reporting higher 5-year LFS with the addition of melphalan (BuCyMel), or the replacement of Cy with clofarabine and fludarabine (CloFluBu), compared to BuCy [6].

In our study, we found that the conditioning regimen was the only significant factor for EFS, with patients who received a TBI/Bu/Flu regimen having higher EFS than those treated with Bu/Flu. The significantly lower relapse rate in the patients who received TBI/Bu/Flu compared with those treated with Bu/Flu contributed to the higher EFS in these patients. An early study added 4 Gy TBI to myeloablative Bu/Flu to limit potential increase in relapse rate resulting from concurrent use of ATG in the study protocol [17]. The study found similarly high disease-free survival for both matched related donor and alternative donor HSCTs in adult acute leukemia patients. Subsequent studies of 4 Gy TBI/Bu/Flu conditioning focused on adult AML patients showed conflicting results on whether the addition of TBI improved OS compared to Bu/Flu alone [18,19]. In addition, a study of adult AML patients showed that HFD transplant based on a higher dose of 8 Gy TBI combined with Bu/Flu and ATG resulted in outcome comparable to matched UD (MUD) transplant [20]. While previous studies of TBI/Bu/Flu were mostly based on patients who received HSCT in first CR [17-20], our study showed a high 5-year EFS of 73.0% in patients treated with TBI/Bu/Flu in second CR, emphasizing the efficacy of this conditioning regimen in relapsed pediatric AML patients.

Important prognostic factors in relapsed AML, such as time to relapse and overall AML risk group [12,13], were not significant predictors of outcome in our second CR HSCT patient group. Achievement of second CR after relapse may contribute towards a diminished effect of established prognostic factors in relapsed AML. The majority of our patients also received HSCT from an HFD (n=32, 74.4%), indicating a strategy to consolidate second CR with allogeneic HSCT, regardless of the presence of a well-matched donor. We found no significant difference in 5-year EFS between patients who

received HFD HSCT and those who received transplant from other donors. A previous study of 516 children with AML compared MUD HSCT with ATG and HFD HSCT utilizing PTCy, and found no difference in LFS and OS [21]. The 100-day CI of grades 2-4 acute GVHD was significant at 62.8%, possibly reflecting the high number of HFD transplants, and the use of varying methods of *in vivo* T-cell depletion, including both ATG and PTCy in our patients. However, the 100-day CI of grades 3-4 acute GVHD was 18.6%, similar to the 14.4% incidence found in HFD HSCT recipients of a previous report [21].

We emphasize the major limitations of our study. Patients in the earlier part of our study period received Bu/Flu conditioning, while most of the patients in the later period were treated with TBI/Bu/Flu. Although supportive measures remained largely unchanged throughout this period, changes in GVHD prophylaxis methods and improvements in overall transplant procedures may have contributed to the better outcome of TBI/Bu/Flu recipients, as manifest in the lower NRM for these patients. Multivariate analysis of the impact of both conditioning regimen and transplant period on EFS did not show a significant factor for outcome, underscoring the limitation of concluding upon conditioning regimen as a key prognostic factor, independent of transplant period.

Although the univariate study showed significantly higher EFS for TBI/Bu/Flu compared to Bu/Flu, our small patient group data derive from a single institution, and further study is necessary to conclude upon the relative advantages of TBI/Bu/Flu over Bu-based regimens which are commonly used in the transplant of pediatric AML patients. Our main aim in this paper is to emphasize the favorable outcomes of our patients treated with TBI/Bu/Flu, rather than to conclude upon its relative efficacy compared to other conditioning regimens.

Utilization of TBI as part of the conditioning regimen allowed for a decrease in the overall Bu dose, and may have contributed to lower alkylating agent-related toxicities. However, TBI incorporation in the transplant of pediatric AML patients may result in a higher incidence of late effects. One registry study of 624 children with AML found a decreased relapse incidence, but higher NRM in patients treated with TBI as part of the conditioning regimen, resulting in similar LFS and OS between the TBI and non-TBI groups. However, patients who received TBI showed a significantly higher 3-year incidence of endocrine problems such as gonadal and growth hormone deficiency [22]. In contrast, another large-scale study focused specifically on adolescent and young adult AML patients reported that the incidence of late effects depended more on the development of chronic GVHD rather than the use of TBI in conditioning [23].

In summary, we found that pediatric AML patients in second CR treated with a myeloablative TBI/Bu/Flu conditioning regimen achieved a high 5-year EFS of 73.0%. HSCT with TBI/Bu/Flu conditioning may result in favorable long-term outcome for relapsed AML patients who are able to achieve second CR.

Ethical Statement

The study received approval from the institutional data review board and ethics review board of Seoul St. Mary's Hospital (KC25RISI0400). Informed consent was waived with IRB approval.

Author Contributions

Conceived and designed the analysis: Lee JW, Chung NG, Cho B.
Collected the data: Lee JW, Jo S, Yoo JW, Kim S.
Contributed data or analysis tools: Lee JW, Jo S, Yoo JW, Kim S, Chung NG, Cho B.
Performed the analysis: Lee JW, Jo S, Yoo JW, Kim S.
Wrote the paper: Lee JW.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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