Acute Lymphoblastic Leukemia in Children: Better Transplant Outcomes After Total Body Irradiation-based Conditioning

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Abstract. *Background/Aim:* Comparison of transplant outcomes in long-term follow-up of children after total body irradiation (TBI)- or chemotherapy-based conditioning allogeneic hematopoietic cell transplantation (allo-HCT). *Patients and Methods:* Patients undergoing allo-HCT for Acute lymphoblastic leukemia (ALL) conditioned either with TBI (n=55) or chemotherapy (n=84) were compared. The following transplant outcomes were analyzed: overall survival (OS), event-free survival (EFS), relapse incidence (RI), and graft-versus-host-disease (GVHD)-free-relapse-free survival (GRFS). *Results:* All analyzed long-term transplant outcomes were significantly better for patients conditioned with TBI at 2 years after transplant. OS at 2 years was 84% after TBI and 60.5% after chemotherapy-conditioning ($p=0.005$). Risk factor analysis showed that two factors, TBI-based conditioning and transplant in first remission of ALL, significantly improved OS, EFS, GRFS, and decreased RI. *Conclusion:* TBI-based conditioning before allogeneic HCT in children with acute

lymphoblastic leukemia provides significantly better transplant outcomes, when compared to chemotherapy-based conditioning.

Acute lymphoblastic leukemia (ALL) is the most frequent type of malignancy in children. With international cooperation, outcomes have improved remarkably during the last decades and reached 90% of long-term survival (1, 2). ALL is also the most frequent indication for allogeneic hematopoietic cell transplantation (allo-HCT) in children, comprising both patients with high-risk disease in first complete remission (CR1) or in relapsed phase (rALL) (3). Two basic types of high-dose conditioning therapy before HCT for ALL are used both in children and adults, based on total body irradiation (TBI) or on chemotherapy (CHT), mainly with the use of busulfan or treosulfan (4, 5). Differences in the efficacy and short- and long-term safety between TBI and CHT-based transplantations is a matter of debate (4, 6, 7). A benefit in the outcome after the use of TBI has been observed in adults (6), but not univocally in children, as presented in a meta-analysis in 2011 (8). A recent large international prospective trial showed improved survival and lower relapse risk in patients following TBI+etoposide conditioning in comparison to CHT-based allo-HCT in children aged over 4 years (9). However, there are almost no real-world data on pediatric ALL-HCT (10).

Herein, we present our experience with allo-HCT in pediatric ALL with respect to the type of conditioning. The objective of this analysis was comparison of transplant outcomes: overall survival (OS), event-free survival (EFS), relapse incidence (RI), and graft-versus-host-disease (GVHD)-

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free-relapse-free survival (GRFS) in long-term follow-up of children after TBI- or CHT-based conditioning.

Patients and Methods

Design. Transplant outcomes were compared between groups of patients undergoing allo-HCT for ALL conditioned either with TBI or CHT. All consecutive children and adolescents aged between 1 and 18 years treated in the single center between 2003 and 2020 were qualified for the analysis, regardless of the type of donor (matched-related or unrelated donor), and stem cell source (bone marrow, peripheral blood, cord blood). The selection of conditioning was individualized in each case.

Patients. Pediatric patients in first (CR1) or subsequent complete remission ($\geq$ CR2), undergoing allo-HCT for ALL after myeloablative conditioning with the use of either TBI or chemotherapy were included in the study. A total number of 139 allo-HCT transplantations performed in a single center were analyzed: TBI-based conditioning in 55 patients, and chemotherapy-only in 84 patients (busulfan-based in 56 and treosulfan-based in 28 patients).

Transplant conditioning. TBI at a total dose of 12 Gy was delivered in six fractions over 3 days from a linear accelerator, with lung shielding at 10 Gy, followed by etoposide administration (60 mg/kg; upper total dose 3.6 g) on day -3 before HCT. In CHT-based conditioning, either busulfan over 4 days or treosulfan 14 g/m² once a day for 3 days was used together with cyclophosphamide (60 mg/kg for two days) or fludarabine 30 mg/m² once a day over 5 days and thiopeta 5 mg/kg twice a day for 1 day. Busulfan was administered four times a day with age and body weight dose adjustment. Other transplant procedures and supportive care were described elsewhere (11-14). Neutrophil engraftment was defined as the first of three consecutive days of absolute neutrophil counts exceeding $0.5 \times 10^9/l$. Platelet engraftment was defined as the first of three consecutive days with platelets of more than $20 \times 10^9/l$, with no platelet transfusions done during the preceding 7 days.

Statistical analysis. Non-categorical variables were compared with the Mann-Whitney test, and categorical variables with the chi-squared test, with odds ratio (OR) and 95% confidence interval (95%CI). The mean survival was calculated with the Kaplan-Meier method. The primary endpoint of the study was OS, and secondary endpoints included: event-free survival (EFS), relapse incidence (RI), and severe GVHD-free relapse-free survival (GRFS). Severe GVHD was defined as grade III-IV acute (aGVHD) and chronic (cGVHD). Kaplan-Meier curves and cumulative incidence functions were used to summarize survival and time-dependent incidence and compared with the log-rank test. Additionally, we compared frequencies of veno-occlusive disease (VOD), acute and chronic GVHD (aGVHD/cGVHD), idiopathic pneumonia syndrome (IPS), cytomegalovirus (CMV) reactivation, and invasive fungal disease (IFD). In order to correlate each potential prognostic factor with a primary or secondary endpoint, risk factor analysis was performed using a univariate Cox proportional-hazards regression model. The following risk factors were analyzed: conditioning (TBI-based vs. chemotherapy-based), age (as continuous variable; and ≥ 10 vs. < 10 years), donor type (matched family donor, MFD vs. matched unrelated donor, MUD), Karnofsky/Lansky performance score (≥ 80 vs. < 80), disease status (CR=1 vs. CR>1), stem cell source (PB vs.

BM), pre-transplant patient CMV serostatus (IgG negative vs. IgG positive), CMV reactivation, dose of mononuclear cells (MNC), dose of CD34-positive cells, and year of transplantation (≤ 2012 vs. > 2012). The factors that appeared to be important were then fitted together in multivariate Cox models and then backward selection was used to remove any non-significant variables using the likelihood ratio test at a 0.05 level. A final check was made to ensure that no excluded factors would improve the fit. The results of the uni- and multi-variate analysis are presented as hazard ratios (HR) with their 95%CI. The analysis was performed using the statistical package SPSS 27.0 (IBM, Armonk, NY, USA).

Ethical considerations. All investigations and treatments analyzed in this study were established clinical practices carried out according to accepted clinical practices and in compliance with the medical principles of the Declaration of Helsinki. Informed consent was obtained from all parents and patients (if applicable) prior to treatment. In this retrospective analysis of common clinical practice, formal ethical approval was not required.

Results

Demographics. Overall, 55 patients were conditioned with TBI, and 84 with chemotherapy-only. Detailed patient characteristics are presented in Table I. There were no differences between groups, except for the older age of patients undergoing TBI, since only one child was at the age of < 4 years (TBI was performed under conditions of general anesthesia), and most of them were over 7 years of age.

Engraftment and early complications. Patients after TBI had higher rate of neutrophil and platelet engraftment (Table II). There were no differences in frequency of VOD, CMV reactivation, idiopathic pneumonia syndrome, invasive fungal disease, and acute and chronic GVHD in the first year after allo-HCT. Additionally, no differences were found in both early and long-term transplant outcomes in patients treated with chemotherapy only: busulfan- vs. treosulfan-based conditioning (data not shown).

Transplant outcomes and risk factor analysis. All analyzed long-term transplant outcomes (OS, EFS, RI and GRFS) were significantly better in patients conditioned with TBI at 2 years after transplant (Table III). Overall survival at 2 years was 84% after TBI and 60.5% after chemotherapy-conditioning ($p=0.005$). Risk factor analysis for primary and secondary study endpoints with factors listed in the “statistical methods” section, showed that two factors, TBI conditioning and transplant in first remission of ALL, improved OS, EFS, GRFS and decreased RI (Table IV, Figure 1).

Discussion

In this real-world single center study, we showed that TBI-based conditioning before allogeneic HCT in children with

Table I. Patient pre-transplant characteristics.

	TBI-based	Chemotherapy-based	<i>p</i> -Value
Number of patients	55	84	
Gender	41 M (74.5%); 14 F	49 M (58.3%); 35 F	0.076
Age at HCT	12.4 (2.4-17.9)	6.2 (1.0-17.9)	<0.001
Age >10 years	39 (70.9%)	23 (27.4%)	<0.001
MFD	20 (36.4%)	21 (25%)	0.152
MD-HCT	55 (100%)	80 (95.2%)	0.102
MFD-vs.-MUD	20 (36.4%)	21 (25%)	0.211
First HCT	52 (94.5%)	73 (83.9%)	0.145
Karnofsky/Lansky >80	54 (98.2%)	80 (95.2%)	0.364
CR>1 at HCT	28 (50.9%)	46 (54.8%)	0.657
Stem cell source	PBSC 41 (74.5%); BM 14 (25.5%)	PBSC 57 (67.9%); BM 25 (29.8%); CB 2 (2.4%)	0.360
Patient CMV serostatus	41 (74.5%)	70 (83.3%)	0.189
ATG	25 (45.5%)	44 (52.4%)	0.532
Dose of MNC	8.6 (1.7-53)	10.1 (0.3-52.1)	0.426
MNC >10×10 ⁸ cells/kg	22 (40%)	44 (52.4%)	0.154
Dose of CD34	6.6 (0.4-17.0)	7.3 (0.1-23.4)	0.382
CD34 >5×10 ⁶ cells/kg	30 (54.5%)	50 (59.5%)	0.563

HCT: Hematopoietic cell transplantation; TBI: total body irradiation; M: male; F: female; MFD: matched family donor; MD: matched donor; MUD: matched unrelated donor; CR: complete remission; ATG: anti-thymocyte globulin; CMV: cytomegalovirus; PBSC: peripheral blood stem cells; BM: bone marrow; CB: cord blood; MNC: mononuclear cells.

Table II. Immediate transplant outcomes: engraftment and early complications.

	TBI-based	Chemotherapy-based	<i>p</i> -Value
Neutrophil engraftment	55 (100%)	78 (92.9%)	0.043
Time to neutrophil engraftment [days] (median, range)	19 (12-25)	17 (11-33)	0.253
Platelet engraftment	54 (98.2%)	72 (85.7%)	0.014
Time to platelet engraftment [days] (median, range)	15 (7-65)	15 (9-62)	0.893
Veno-occlusive disease (VOD)	8 (14.5%)	8 (9.5%)	0.525
aGVHD grade 3/4	7 (12.7%)	9 (10.7%)	0.926
cGVHD	7 (12.7%)	9 (10.7%)	0.926
severe GVHD	8 (14.5%)	10 (11.9%)	0.651
CMV reactivation	16 (29.1%)	25 (29.8%)	0.699
Idiopathic pneumonia syndrome (IPS)	8 (14.5%)	9 (10.7%)	0.682
Invasive fungal disease (IFD)	15 (27.3%)	24 (28.5%)	0.999

TBI: Total body irradiation; GVHD: graft-versus-host disease.

Table III. Transplant outcomes: 2-year probabilities.

Parameter	TBI-based	Chemotherapy-based	<i>p</i> -Value
Number of patients	55	84	
Mean survival [years]	10.3 (95%CI=8.9-11.7)	8.6 (95%CI=7.2-10.1)	
Overall survival	84.0±5.2%	60.5±5.5%	0.005
Event free survival	80.4±5.6%	54.5±5.5%	0.002
Relapse incidence	10.2±4.3%	29.3±5.4%	0.016
GRFS	69.6±6.5%	45.2±5.6%	0.007

TBI: Total body irradiation; GRFS: GVHD-free-relapse-free survival; GVHD: graft-versus-host disease.

Table IV. Risk factor analysis.

	OS	EFS	RI	GRFS
Univariate analysis				
Chemotherapy vs. TBI	HR=2.7 (1.3-5.7) $p=0.007$	HR=2.7 (1.4-5.1) $p=0.003$	HR=2.8 (1.3-6.8) $p=0.020$	HR=2.1 (1.2-3.6) $p=0.008$
MUD vs. MFD	HR=1.1 (0.5-2.2) $p=0.732$	HR=1.0 (0.5-1.8) $p=0.972$	HR=1.8 (0.8-3.6) $p=0.133$	HR=1.0 (0.6-1.7) $p=0.917$
CR>1 vs. CR=1	HR=2.1 (1.2-4.5) $p=0.021$	HR=1.8 (1.0-3.1) $p=0.057$	HR=2.4 (1.1-5.3) $p=0.028$	HR=2.0 (1.2-3.4) $p=0.007$
Karnofsky/Lansky score <80 vs. ≥80	HR=2.8 (0.8-9.0) $p=0.090$	HR=2.2 (0.8-7.2) $p=0.134$	HR=1.5 (0.2-9.9) $p=0.748$	HR=1.6 (0.5-4.8) $p=0.402$
Multivariate analysis				
Chemotherapy vs. TBI	HR=2.8 (1.3-5.9) $p=0.007$	HR=2.7 (1.4-5.3) $p=0.002$	HR=2.9 (1.3-7.1) $p=0.014$	HR=2.1 (1.3-3.8) $p=0.006$
CR>1 vs. CR=1	HR=2.1 (1.2-4.6) $p=0.019$	HR=1.9 (1.1-3.4) $p=0.039$	HR=2.6 (1.2-5.6) $p=0.019$	HR=2.1 (1.2-3.5) $p=0.005$
Karnofsky/Lansky score <80 vs. ≥80	HR=1.9 (0.6-6.3) $p=0.297$	NA	NA	NA

TBI: Total body irradiation; MFD: matched family donor; MUD: matched unrelated donor; CR: complete remission; HR: hazard ratio; NA: not applicable; OS: overall survival; EFS: event-free survival; RI: relapse incidence; GRFS: GVHD-free-relapse-free survival; GVHD: graft-versus-host disease.

Figure 1. Major transplant outcomes in pediatric Acute lymphoblastic leukemia with respect to type of conditioning [total body irradiation (TBI)-based vs. chemotherapy-based]: (A) overall survival; (B) event-free survival; (C) relapse incidence; (D) GVHD-free-relapse-free survival.

ALL provides significantly better OS, EFS, and GRFS and a lower RI, when compared to chemotherapy-based conditioning. The second factor contributing to better long-term transplant outcomes was CR1 in comparison to relapsed phases of disease.

All other analyzed factors had no impact on transplant outcomes. This is especially important in the context of the type of donor and the source of hematopoietic cells. Both findings are already well-known in the pediatric setting. It was shown in the prospective multinational Berlin-Frankfurt-Muenster (BFM) study group trial (ALL-SCT-BFM 2003) that the outcome among high-risk children with ALL after allo-HCT was not affected by donor type, and was the same for the matched family and matched unrelated donors. Moreover, among recipients of HCT from unrelated donors, there were no significant differences in transplant outcomes (OS, EFS, RFS) between patients with HLA 9/10 and those with HLA 10/10 matched antigens grafts. Additionally, no differences in transplant outcomes between patients grafted from peripheral blood stem cells and those transplanted from the bone marrow were noted (15).

In ALL not only diagnosis and treatment of the disease, but also complications and supportive therapy (16, 17), monitoring of residual disease (18), and treatment of relapse including HCT (9, 15, 18) are subjects of detailed scientific analysis.

The positive impact of TBI conditioning on children with ALL is in line with the results of the prospective FORUM trial (9), and a retrospective single-center analysis of early transplant outcomes (10). In our study, we additionally analyzed a new composite endpoint, GRFS, which indicates not only remission of leukemia, but also the quality of life expressed by the absence of severe GVHD (19). We found a positive effect of TBI conditioning on GRFS in children with ALL.

In addition, TBI has a high risk of long-term complications, such as infertility, cataract, thyroid and other endocrine insufficiency, short stature, and other sequelae. Nevertheless, with an improved overall survival by 10-20%, an interdisciplinary approach may lead to the prevention and treatment of any possible TBI complications.

This study has several limitations. It is underpowered with respect to the analysis of outcome of the busulfan- vs. treosulfan-based conditioning. Also, the period of inclusion was relatively long, however, our results were not influenced by its duration.

In conclusion, this single-center real-world study showed that TBI-based conditioning before allo-HCT in pediatric ALL provides better survival than chemotherapy-based conditioning before transplantation.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

Study design: JS. Data analysis: JS, RD, KC and MRP. Article writing: JS. Provision of important clinical data and interpretation: All Authors. Data check: All Authors. Statistical analysis: JS and KC. Administrative support: JS. Final approval: All Authors.

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