Total Body Irradiation–Based Conditioning Regimen Improved the Survival of Adult Patients With T-Cell Lymphoblastic Lymphoma After Allogeneic Peripheral Blood Stem Cell Transplantation

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the consolidation modalities for adult patients with T-cell lymphoblastic lymphoma (T-LBL). However, the optimal conditioning regimen needs to be explored. In the present study, 40 patients with T-LBL undergoing allo-HSCT were retrospectively analyzed, including 23/40 (57.5%) with total body irradiation (TBI)–based conditioning regimen and 17/40 (42.5%) with busulfan (BU)-based regimen. TBI–based regimen significantly increased the cumulative incidence (CI) of grade II to IV acute graft-versus-host disease (aGvHD) as compared with BU-based regimen (13.0% vs 0%, $P = 0.000$). The relapse risk was significantly lowered in TBI-based group with a 2-year CI of relapse (CIR) of 9.1% as compared with that of 49.6% in BU-based group ($P = 0.008$). The 1-year and 2-year non-relapse mortalities (NRMs) for all patients were 5.0% and 10.3%, respectively. The 1-year and 2-year NRMs were 8.9% and 16.0% in TBI-based group, and 0.00% and 0.00% in BU-based group ($P = 0.140$). The 2-year probabilities of overall survival (OS) and relapse-free survival (RFS) were 83.0% [95% confidence interval, 63.4%–100%] and 74.0% (95% confidence interval, 54.4%–93.6%) in TBI-based group, which were higher than that of 35.0% (95% confidence interval, 0.0%–72.2%) and 50.0% (95% confidence interval, 24.5%–75.4%) in BU-based group, respectively ($P = 0.020$ for OS and $P = 0.081$ for RFS). In multivariate analysis, TBI-based regimen significantly reduced the risk of relapse [subdistribution hazard ratio (SHR) $= 0.030$, 95% CI, 0.002–0.040, $P = 0.000$] and improved the OS [hazard ratio (HR) 0.121, 95% CI, 0.021–0.683, $P = 0.017$] as an independent prognostic factor. These results suggested that TBI-based regimen might be an optimal choice for adult patients with T-LBL undergoing allo-HSCT.

Keywords

total body irradiation, T-cell lymphoblastic lymphoma, allogeneic hematopoietic stem cell transplantation

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Introduction

T-cell lymphoblastic lymphoma (T-LBL) is a relatively rare type of hematological malignancies originating from T-cell precursors, which accounts for about 90% of all lymphoblastic lymphoma and occurs mostly in children and adolescents[1]. Although the complete remission (CR) rates could be achieved for more than 90% of patients and the survival of adult T-LBL has been substantially improved by adopting pediatric-inspired chemotherapy regimens for B-cell acute lymphoblastic leukemia (ALL), the prognosis of adult T-LBL was inferior to pediatric patients with 40% to 50% of cumulative incidences of relapse (CIRs) and only 50% to 55% of long-term disease-free survival[2–4].

The optimal consolidation treatment modality for adult T-LBL has not been defined. Autologous hematopoietic stem cell transplantation (auto-HSCT) has been used as a consolidation modality to reduce the risk of disease recurrence, but the risk remains to be higher with 5-year relapse rates of 26.5% to 56.0%[5–8]. Liu et al[5] reported that tandem auto-HSCT could decrease the progression/relapse rate as compared with chemotherapy alone or single auto-HSCT, the 3-year progression/relapse rate remained to be higher of 26.5%. Allogeneic HSCT (allo-HSCT) as a consolidation modality for T-LBL could decrease the relapse rate, especially for high-risk patients, but might increase non-relapse mortality (NRM) as compared with auto-HSCT[8]. Levine et al[8] reported that the CIRs of T-LBL at 1 and 5 years after transplantation were significantly lower in allo-HSCT than that in auto-HSCT (32% vs 46%, $P = 0.05$; 34% vs 56%, $P = 0.004$, respectively), while the NRM in allo-HSCT was higher than that in auto-HSCT at 6 months after transplantation (18% vs 3%, $P = 0.002$). Along with the optimized prophylaxis regimens for graft-versus-host disease (GvHD)[9,10], the effective prevention and treatment modalities for infection, and so on, NRM was significantly decreased over the last decades[11,12]. The optimal conditioning regimen for allo-HSCT needs to be explored to decrease the relapse risk and improve the survival of adult patients with T-LBL.

In the present study, 40 patients with T-LBL undergoing allo-HSCT in our center were retrospectively analyzed and two types of conditioning regimens of total body irradiation (TBI)–based and busulfan (BU)-based were compared to determine the optimal conditioning regimen. The results suggested that TBI-based regimen could decrease the risk of relapse and improve the survival of adult patients with high-risk T-LBL. To our knowledge, this is the first report about evaluating the effects of different conditioning regimens for adult T-LBL.

Patients and Methods

Patients, Donors, and Grafts

Fifty patients were diagnosed with T-LBL in our center from May 1, 2017, to December 31, 2020. Forty of them underwent allogeneic peripheral blood stem cell transplantation (allo-PBSCT) and were enrolled in the retrospective study. T-cell lymphoblastic lymphoma was diagnosed according to World Health Organization (WHO) 2016 criteria[1]. Donors were from human leukocyte antigen (HLA)-matched related and unrelated donors and haploidentical family donors. HLA-matched was defined according to ≥8/10 matched loci at HLA A, B, C, DRB1, DQB1 loci between donor and recipient, while HLA haploidentical according to >3/10 mismatched loci between recipient and family donor. Grafts were from mobilized peripheral blood stem cells (PBSCs) with granulocyte–colony stimulating factor (G-CSF). This study had ethical approval from the local ethical committees and was conducted in accordance with the Declaration of Helsinki. All patient data originated from clinical trials with mandatory written informed consent.

Conditioning Regimens

Myeloablative conditioning (MAC) regimens including TBI-based or BU-based were prescribed to all patients. Total body irradiation–based regimen contained fractioned TBI (fTBI) 10 Gy at 2.0 Gy for five times, etoposide (VP-16) 15 mg/kg/d for 2 days, cyclophosphamide (CY) 50 to 60 mg/kg/d for 2 days. Busulfan-based regimen was composed of intravenous BU 3.2 mg/kg/d for 4 days, CY 50 to 60 mg/kg/d for 2 days, and VP-16 15 mg/kg/d for 2 days. Total body irradiation–based regimen was preferred to patients in partial remission (PR) status, while for patients in CR status, TBI- or BU-based regimen was chosen according to patient's choice and physician's decision.

GvHD Prophylaxis

Rabbit anti-human thymocyte globulin (ATG, 10 mg/kg, Thymoglobin®, Genzyme Polyclonals S.A.S., LYON, AUVERGNE RHONE ALPES, France)–based regimen or low-dose ATG (2.5 mg/kg/d on days –2 to –1) plus low-dose post-transplant cyclophosphamide (50 mg/kg/d on day 3) (low-dose ATG/PTCy)–based regimen were used for prevention of GvHD after haploidentical transplantation, while cyclosporine (CsA) combined with mycophenolate mofetil (MMF) and short-course methotrexate (MTX) were provided for prophylaxis of GvHD after HLA-matched sibling donor transplantation and unrelated donor transplantation with additional ATG 5 mg/kg[9,10,13]. Cyclosporine was prescribed at 2 mg/kg/d as a continuous infusion, and its dose was modified to obtain nadir serum levels between 200 and 300 ng/ml. Mycophenolate mofetil was administered for 30 days at 15 mg/kg oral three times per day (maximum dose 3 g per day) and then stopped if no GvHD.

Infection Prophylaxis

All patients received prophylactic posaconazole and acyclovir from the beginning of conditioning to at least 6 months

after transplantation. Compound sulfamethoxazole tablets were prescribed to all patients from the engraftment to at least 1 year for preventing *Pneumocystis jiroveci* pneumonia. Quantitative real-time polymerase chain reaction (PCR) assays for cytomegalovirus (CMV) DNA in serum and Epstein–Barr (EBV) DNA in whole blood were performed once or twice per week. Preemptive therapies with ganciclovir for CMV and Rituximab for EBV reactivation were described in reference[10].

Definition

Evaluation of treatment response included computed tomography (CT) scanning and/or PET-CT scan and bone marrow examination. Complete remission was defined as the complete disappearance of all clinical, radiological, and histological/immunophenotypic evidence of the disease. Partial remission was defined as a 50% or greater reduction in the area of tumor based on bidimensional measurements[14]. Neutrophil engraftment was defined as achieving an absolute neutrophil count greater than 0.5×10^9/l on the first day of 3 consecutive days without G-CSF, while platelet engraftment was defined as a platelet count greater than 20×10^9/l on the first day of 7 consecutive days without platelet infusion[15]. Chimerism analysis was performed on bone marrow aspiration using short tandem repeat (STR)–PCR in patients with a sex-matched donor, and fluorescence *in situ* hybridization (FISH) analysis of X and Y chromosome in sex-mismatched patients. Complete chimerism was defined by the detection of ≥95% of donor cells using STR-PCR and FISH[16–18]. Acute GvHD (aGvHD) was graded according to the modified Glucksberg criteria[19] and chronic GvHD (cGvHD) according to the revised Seattle criteria[20].

Statistical Analysis

All statistics and Kaplan–Meier estimates were performed using IBM SPSS version 23.0. The characteristics of patients in the two different conditioning regimen groups were compared using the χ^2 test. The probabilities of overall survival (OS), relapse-free survival (RFS), and GvHD-free relapse-free survival (GRFS) were estimated using the Kaplan–Meier method with log-rank test. Cumulative incidence of relapse, NRM, relapse-related mortality (RRM), and grade II to IV aGvHD were estimated using the Gray method. Cumulative incidence functions were used to estimate RRM and NRM in a competing risk setting[21], because NRM and relapse are competing events. To estimate the cumulative incidence of aGvHD, we considered relapse and NRM as competing events. Multivariate analysis was performed using the Cox regression hazard model for OS, RFS, and GRFS. Factors with a P value < 0.20 and those that may affect survival were included in the multivariate analysis. The incidences

of opportunistic infections were compared using the χ^2 test. All the P values were two-sided, and statistical significance was set at $P < 0.05$.

Overall survival was defined as the time from HSCT to death, regardless of the cause. Relapse-free survival was defined as the time from HSCT to disease relapse/progression, or death from any cause. The GRFS was defined as being alive with neither grade III to IV aGvHD nor severe cGvHD nor disease relapse at any time point[22]. Relapse was defined as the reappearance of the underlying disease. Death without evidence of relapse or progression was defined as NRM.

Results

Patient Characteristics

Ten out of 50 patients diagnosed as T-LBL in our center did not receive allogeneic transplantation. Four of 10 patients achieved CR with first-line chemotherapy and subsequently relapsed. Four developed disease progression and two achieved PR after first-line therapy. The two patients with PR refused allogeneic transplantation. All the 10 patients did not respond to salvage chemotherapy and died from disease progression with a median OS of 8 (range, 6–14) months. Forty adult patients with T-LBL undergoing allo-PBSCT were enrolled into the retrospective study. All patients were in stage III/IV at diagnosis. The majority of patients (31/40, 77.5%) were male with a median age of 28 years old (range, 18–50) at transplantation. A total of five patients received local irradiation therapy for mediastinum residual mass, of which three (two in BU-based group and one in TBI-based group) at 1 month pre-transplant, and two in BU-based group at 3 months post-transplant. Most patients (26/40, 65.0%) received transplantation from haploidentical family donors, while 14 (14/60, 35.0%) from HLA-matched donors (related or unrelated). In total, 23 patients (57.5%) received TBI-based conditioning regimen (TBI-based group) and 17 (42.5%) received BU-based regimen (BU-based group). The other characteristics including B symptoms, mediastinal mass, lactate dehydrogenase (LDH) level at diagnosis, and so on between two groups were similar as shown in Table 1.

Engraftment

All patients engrafted successfully and achieved full donor chimerism at 30 days after transplantation. One patient in TBI-based group suffered from secondary graft failure at 46 days post-transplant. For all patients in the cohort, the median time for neutrophil engraftment was 11 (range, 9–21) days, while for platelet engraftment was 12 (range, 10–40) days. The median time for neutrophil engraftment was 12 (range, 9–21) days in TBI-based group and 11 (range, 10–18) days in BU-based group, respectively ($P = 0.283$), while for platelet

Table 1. Patient and Donor Characteristics.

	Total	TBI-based	BU-based	
	(*n* = 40)	(*n* = 23)	(*n* = 17)	*P* value
Age, median (range) years	28 (18–50)	28 (18–46)	28.5 (18–50)	0.32
<20	9 (22.5)	4 (17.4)	5 (29.4)	0.368
20–30	19 (47.5)	12 (52.2)	7 (41.2)	0.538
>30	12 (30.0)	7 (30.4)	5 (29.4)	0.944
Gender, *n* (%)				
Male/female	32/8 (80.0/20.0)	19/4 (82.6/17.4)	13/4 (76.5/23.5)	0.702
Mediastinal bulky (>10 cm), *n* (%)				
With/without	17/23 (42.5/57.5)	11/12 (47.8/52.2)	6/11 (35.3/64.7)	0.525
B symptoms, *n* (%)				
Present/absent	22/18 (55.0/45.0)	10/13 (43.4/56.6)	12/5 (70.6/29.4)	0.116
LDH at diagnosis				
Normal/elevated	28/12 (70.0/30.0)	15/8 (65.2/34.8)	13/4 (76.5/23.5)	0.505
ECOG				
0–1/2	38/2	22/1	16/1	0.826
Disease status (%)				
CR/PR	34/6 (85.0/15.0)	19/4 (82.6/17.4)	15/2 (88.2/11.8)	0.622
Pre-transplant chemotherapy cycles (range)	6 (2–10)	6 (2–10)	5 (3–8)	0.623
Donor type, *n* (%)				
HLA-matched/haploidentical	14/26 (35.0/65.0)	8/15 (34.8/65.2)	6/11 (35.3/64.7)	0.973
GVHD prophylaxis, *n* (%)				
ATG-based/low-dose ATG + PTCy/ CSA + MMF + MTX	26/10/4 (65.0/25.0/10.0)	15/5/3 (65.2/21.7/13.1)	11/5/1 (64.7/29.4/5.89)	0.973
HCT-CI median (range)	0 (0–1)	0 (0–1)	0 (0–1)	0.952
Donor age, median (range) years	34 (14–56)	34 (14–55)	31 (14–56)	0.821
Donor–recipient sex, *n* (%)				
Female–male/others	24/16 (60/40.0)	14/9 (60.9/39.1)	10/7 (58.8/41.2)	0.896
ABO blood types, *n* (%)				
Matched/mismatched	22/18 (55.0/45.0)	10/13 (43.5/56.5)	12/5 (70.6/29.4)	0.088
PBSC graft, median (range)				
MNCs × 10^8/kg	12.98 (3.12–49.1)	11.06 (4.60–49.1)	13.75 (3.12–27.5)	0.169
CD34+ cells × 10^6/kg	9.38 (1.45–28.0)	9.09 (1.45–28.0)	9.32 (5.8–16.1)	0.291
CD3+ cells × 10^8/kg	2.86 (1.08–6.21)	2.87 (1.08–6.01)	2.49 (1.08–6.21)	0.737

Additional ATG (5 mg/kg) for matched related family donor GvHD prophylaxis. ATG: anti-thymocyte globin; BU: busulfan; CR: complete remission; CSA: cyclosporine A; GvHD: Graft-versus-host disease; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; LDH: lactate dehydrogenase; MMF: mycophenolate mofetil; MNC: mononucleated cells; MTX: methotrexate; PBSC: peripheral blood stem cell; PR: partial remission; TBI: total body irradiation; ECOG: Eastern Cooperative Oncology Group; ABO: blood types A, B, O, and AB; HLA: human leukocyte antigen.

engraftment was 12 (range, 10–40) days and 11.5 (range, 10–13) days, respectively (*P* = 0.368).

GvHD and Infectious Complications

Among all the patients, nine developed any grade of aGvHD with a CI of 22.8% within 180 days after transplantation and three developed grade II to IV aGvHD with a CI of 7.7%. No patient developed grade IV aGvHD. The CIs of any grade aGvHD within 180 days after transplantation had no significant difference between TBI-based and BU-based groups (21.7% vs 5.9%, *P* = 0.222), while the CI of grade II to IV aGvHD was significantly higher in TBI-based group than

that in BU-based group (13.0% vs 0%, *P* = 0.000). Only one patient in BU-based group developed mild cGvHD at 7 months after transplantation.

Among all 40 patients, 6 patients developed CMV reactivation (2 in BU-based and 4 in TBI-based group, *P* = 0.622) and 2 suffered from CMV pneumonia (both in TBI-based group, *P* = 0.499) within 180 days after transplantation. Both the patients recovered from CMV pneumonia with antiviral therapy. Seven patients experienced EBV reactivation (three in BU-based and four in TBI-based group, *P* = 0.983) and two developed EBV-associated post-transplant lymphoproliferative disorder (PTLD, both in TBI-based group, *P* = 0.499). One patient developed PTLD of high-grade
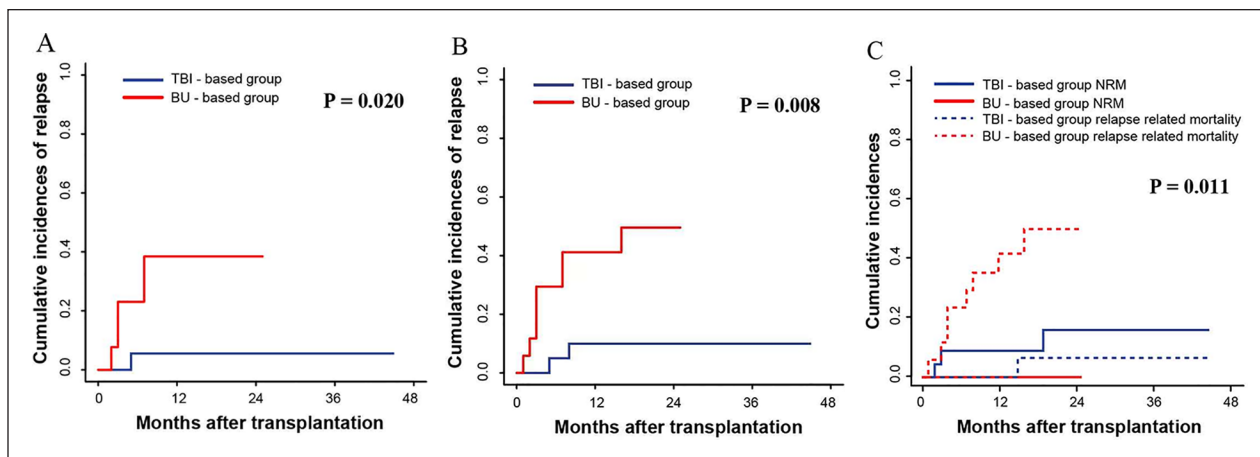
Figure 1. (A) The cumulative incidences of relapse (CIRs) for CR patients at transplantation. (B) The CIRs for all patients by conditioning regimens. (C) Non-relapse mortalities (NRMs, $P = 0.140$) and relapse-related mortalities ($P = 0.011$) for all patients by conditioning regimens. BU: busulfan; TBI: total body irradiation.

B-cell lymphoma at 1.5 months after transplantation and recovered from Rituximab 375 mg/m^2 once a week for four times, while the other developed peripheral T-cell lymphoma (non-specific subtype) at 3 months post-transplant and recovered from four cycles of chemotherapy with hyper-CVAD regimen (fractionated CY, vincristine, doxorubicin, and dexamethasone).

Relapse, RRM, and NRM

All the six patients in PR status at transplantation achieved CR after allo-PBSCT. In the whole cohort, 10 patients (2 in TBI-based group and 8 in BU-based group) relapsed with a median relapse time of 5 months (range, 2–16). In the TBI-based group, one patient relapsed at 5 months post-transplant and was still alive till the end of follow-up after second allo-HSCT, while the other patient relapsed at 8 months and lost follow-up at 14 months post-transplant. Compared with patients in TBI-based group, all eight relapsed patients died of disease progression in BU-based group. One out of two relapsed patients in TBI-based group and four of eight in BU-based group were in non-remission status at transplantation. For CR patients at transplantation, the 1-year and 2-year CIRs were 5.0% and 5.0% in TBI-based group, while 38.46% and 38.46% in BU-based group ($P = 0.020$) (Fig. 1A). For total patients, the 1-year and 2-year CIRs were 9.1% and 9.1% in TBI-based group, which were significantly lower than that of 41.2% and 49.6% in BU-based group ($P = 0.008$) (Fig. 1B). The 1-year and 2-year RRMs were 0% and 7.0% in TBI-based group, which were significantly lower than that of 41.8% and 50.1% in BU-based group ($P = 0.011$) (Fig. 1C).

Three patients died of non-relapse causes, and all were from TBI-based group. One died from secondary graft failure at 2 months, one from poor graft function at 1 month, and another from veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) at 3 months after transplantation. No patients died of GvHD and infection. The 1-year and 2-year NRMs for all patients were 5.0% and 10.3%, respectively. The 1-year and 2-year NRMs were 8.9% and 16.0% in TBI-based group, which had no significant differences with that of 0.00% and 0.00% in BU-based group ($P = 0.140$) (Fig. 1C).

Survival

For all patients, the median follow-up time was 15.5 (range, 1.0–45.0) months. The 1-year and 2-year probabilities of OS (Fig. 2A), RFS (Fig. 2B), and GRFS (Fig. 2C) were 76.0% [95% confidence interval, 62.2%–89.7%] and 65.0% (95% confidence interval, 45.4%–84.6%), 72.0% (95% confidence interval, 58.2%–85.7%) and 64.0% (95% confidence interval, 46.3%–81.6%), and 70.0% (95% confidence interval, 56.2%–83.7%) and 62.0% (95% confidence interval, 46.3%–77.2%), respectively. The 1-year and 2-year probabilities of OS of 91.0% (95% confidence interval, 79.2%–100%) and 83.0% (95% confidence interval, 63.4%–100%) in TBI-based group were significantly higher than that of 58.0% (95% confidence interval, 34.4%–81.5%) and 35.0% (95% confidence interval, 0.0%–72.2%) in BU-based group ($P = 0.020$) (Fig. 3A). The 1-year and 2-year probabilities of RFS in TBI-based group were 82.0% (95% confidence interval, 66.3%–97.6%) and 74.0% (95% confidence interval, 54.4%–93.6%), which were higher than that of 59.0% (95% confidence interval, 35.4%–82.5%) and 50.0% (95% confidence interval, 24.5%–75.4%) in BU-based group, respectively ($P = 0.081$) (Fig. 3B). The 1-year and 2-year probabilities of GRFS were similar between TBI- and BU-based groups [78.0% (95% confidence interval, 60.3%–95.6%) and 71.0% (95% confidence interval, 51.4%–90.6%) vs 59.0% (95% confidence interval, 35.4%–82.5%) and
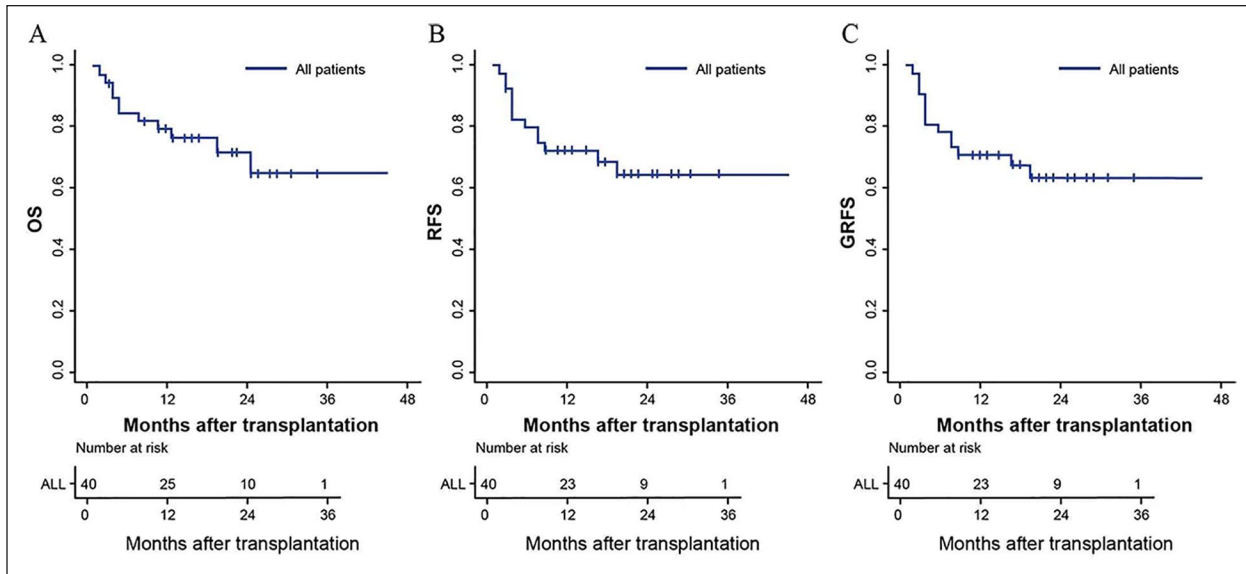
Figure 2. (A) Overall survival (OS). (B) Relapse-free survival (RFS). (C) Graft-versus-host disease/relapse-free survival (GRFS).
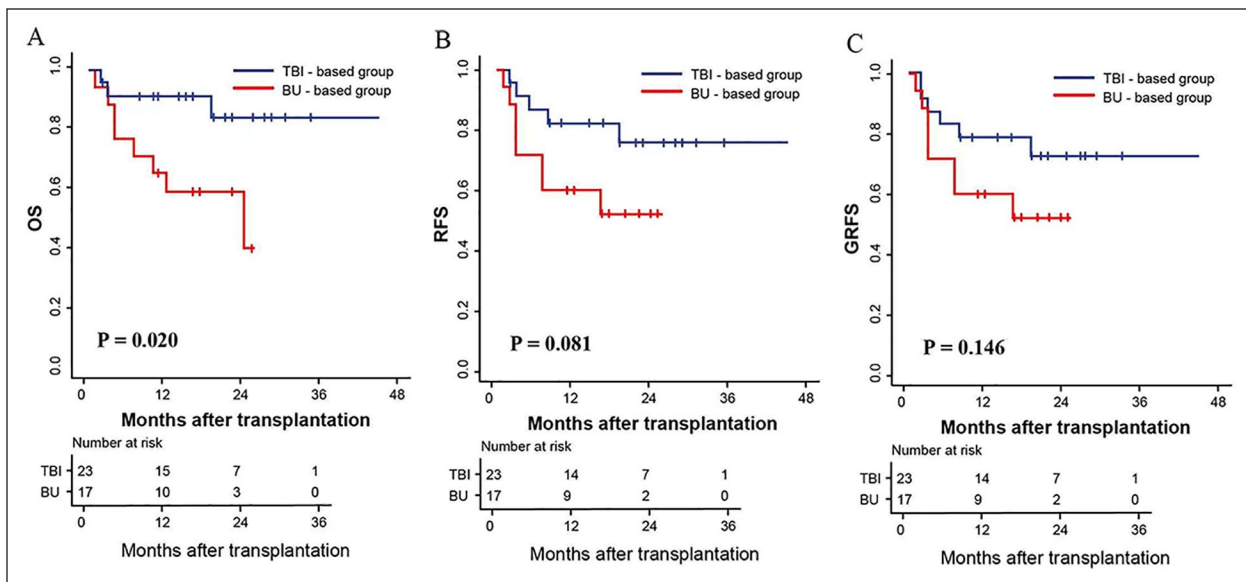

Figure 3. (A) Overall survival (OS) by conditioning regimens. (B) Relapse-free survival (RFS) by conditioning regimens. (C) Graft-versus-host disease/relapse-free survival (GRFS) by conditioning regimens. BU: busulfan; TBI: total body irradiation.

50.0% (95% confidence interval, 24.5%–75.4%), $P = 0.146$] (Fig. 3C).

Univariate and Multivariate Analysis

The results of univariate and multivariate analysis are shown in Table S1 in the Supplemental Material and Table 2, respectively. In multivariate analysis, conditioning regimen as an independent prognostic factor significantly affected the OS, RFS, and the risk of relapse. Total body irradiation–based conditioning regimen increased the OS [hazard ratio (HR),

0.121, 95% CI, 0.021–0.683, $P = 0.017$] and RFS with a strong trend (HR, 0.302, 95% CI, 0.078–1.165, $P = 0.082$), while BU-based regimen increased the risk of relapse (HR, 33.32, 95% CI, 6.62–166.679, $P = 0.000$). Elevated LDH level negatively affected the OS (HR, 9.145, 95% CI, 2.062–40.565, $P = 0.004$), RFS (HR, 6.375, 95% CI, 1.829–22.217, $P = 0.004$) and GRFS (HR, 4.567, 95% CI, 1.447–14.418, $P = 0.010$). Partial remission status at transplantation significantly decreased the RFS and GRFS as an independent risk factor. The presence of B symptoms at diagnosis significantly increased the risk of relapse [subdistribution hazard

Table 2. Multivariate Analysis for OS, RFS, GRFS, and Relapse.

Outcome	Variable	HR/SHR	95% CI	*P* value
OS				
	Elevated LDH vs normal	9.145	2.062–40.565	0.004
	TBI-based vs BU-based	0.121	0.021–0.683	0.017
RFS				
	PR vs CR	3.555	1.020–12.394	0.046
	Elevated LDH vs normal	6.375	1.829–22.217	0.004
	TBI-based vs BU-based	0.302	0.078–1.165	0.082
GRFS				
	PR vs CR	3.325	1.003–11.026	0.049
	Elevated LDH vs normal	4.567	1.447–14.418	0.010
	TBI-based vs BU-based	0.415	0.122–1.407	0.158
Relapse				
	TBI-based vs BU-based	0.030	0.002–0.040	0.000
	B symptoms presence vs absence	7.662	1.056–55.593	0.040
	HLA haploidentical vs matched	0.241	0.503–1.158	0.076
	PR vs CR	5.178	0.923–29.055	0.062

The risk factors for OS, RFS, and GRFS were estimated using Cox regression and were described as HR. Relapse were estimated using the competing regression and were described as SHR. BU: busulfan; CI: cumulative incidence; CR: complete remission; GRFS: graft-versus-host disease/relapse-free survival; HR: hazard ratio; LDH: lactate dehydrogenase; OS: over survival; PR: partial remission; RFS: relapse-free survival; SHR: subdistribution hazard ratio; TBI: total body irradiation; HLA: human leukocyte antigen.

ratio (SHR), 7.662, 95% CI, 1.056–55.593, $P = 0.040$], while TBI-based regimen reduced the relapse risk (SHR, 0.030, 95% CI, 0.002–0.040, $P = 0.000$). Partial remission status at transplant had a strong trend toward relapse (SHR, 5.178, 95% CI, 0.923–29.055, $P = 0.062$).

Discussion

In the present study, the results showed that TBI-based conditioning regimen could significantly reduce the CIR and improve the OS and RFS, which suggested that TBI-based MAC regimen might be an optimal conditioning regimen for adult T-LBL patients receiving allo-HSCT.

Total body irradiation as a conditioning regimen was first reported in the 1970s[23] and then widely used for its efficiency. The optimal TBI dosage and fractionation remain to be undefined[24,25]. Initial experience using TBI was based on a single dose of 10 Gy[26]. Dose-fractionated strategy could increase the total dose of TBI to 12 Gy or above and lower the risks of early acute toxicities, but the late effects of TBI remain to be notable, which include growth and endocrine dysfunction[27], organ-specific damages like as cardiovascular and pulmonary[28,29], ocular complications and second malignancies[30], and so on. Vitale's study compared the safety and efficacy of a 10 Gy single-dose TBI (sTBI) with a 10 Gy fTBI (3.3 Gy on 3 consecutive days) and suggested that fTBI was the only significant factor associated with a lower incidence of interstitial pneumonia (IP) ($P = 0.002$), a lower mortality from GvHD and IP ($P = 0.03$ and $P = 0.001$, respectively), and a better 100-day survival ($P = 0.03$)[31]. A 12 Gy dose fTBI still resulted in a higher risk of developing cataract that eventually required surgery[32] and central nervous system (CNS) complications[33]. As patients enrolled in our study were mostly adolescent and young adult patients, a 10 Gy fTBI was chosen to maintain efficacy and lower acute and late toxicities.

As an alternative to TBI, non-TBI regimens such as BU substituting for TBI have been investigated[34,35]. Total body irradiation–based and BU-based regimens were the most common used MAC regimens for patients with ALL[36–39]. For pediatric patients, TBI-based regimen was superior to chemotherapy-based regimen with a lower CIR and a better OS[40]. While for adult patients, the benefit of lowering the relapse frequencies from TBI-based conditioning regimen was offset by its higher NRM as compared with BU-based regimen, resulting in a similar RFS and OS[41–43]. Kalaycio et al[44] comparatively analyzed the data of adult ALL patients with BU- and TBI-based regimens, which showed the incidence of initial relapse in extramedullary sites following BU was 50%, but only 9% following TBI ($P = 0.005$), but no survival advantage in either event-free survival (EFS) ($P = 0.11$) or OS ($P = 0.20$) for TBI-based regimen. An European Society for Blood and Marrow Transplantation (EBMT) study suggested that TBI-based regimen could not bring any survival benefit for T-cell ALL patients of ≥35 years old, owing to a higher risk of NRM as compared with BU-based regimen (38% vs 9%, $P = 0.01$)[45]. On the contrary, a study by Shigematsu et al[46] showed the results of a medium-dose VP-16 combined with CY and fTBI (12 Gy) conditioning regimen for adult ALL patients and found this regimen resulted in a good disease control without an increase of NRM (1-year NRM 14.0%). In our study, NRMs had no significant difference between the two conditioning regimens ($P = 0.140$),

although the NRM was higher in TBI-based group than that in BU-based group (15.95% vs 0%). The NRMs were relatively lower not only for all patients in the study, but also for patients with TBI-based regimen compared with that in previous studies[4,7,8,11,38]. The risk of NRM after transplantation mainly correlated with GvHD and infection. The incidence of grade II to IV aGvHD was only 13.04% in TBI-based group, while no patient in BU-based group in our study, which was relatively lower compared with that of 40% to 47%[43,47,48] in previous studies. The lower incidences of aGvHD might come from the effective prevention of GvHD[9,10,13]. A lower incidence of cGvHD was present in the whole cohort, which might be related to the lower incidence of aGvHD, the early death of some relapsed patients in the BU-based group, the shorter period of the follow-up, and the small size of sample. All the patients suffering from CMV and EBV infection recovered, and no patient died from infection. Older age is an important risk factor for NRM, especially in patients receiving MAC regimens[49]. In a study by Marks et al[50] evaluating the effects of different fTBI-based MAC regimens (12 Gy < TBI <14.5 Gy) for ALL patients, over 60% of patients were younger than 30 years old in each group and the treatment-related mortalities (TRMs) at 3 year were 9% to 27%. In our study, the majority (70%) of patients were younger than 30 years old, which might be one of the causes for a lower NRM.

As a result of the lower risk of disease recurrence and NRM, patients in the TBI-based group had a better OS than the BU-based group. The 1-year OS and RFS of 91.0% and 82% in the TBI-based group were higher than that of 58.0% and 59% in the BU-based group ($P = 0.020$ and $P = 0.081$, respectively). The lower number of patients developed severe aGvHD (only one patient with grade III aGvHD in TBI group), and no patient experienced severe cGvHD might be related with the similar incidences of GRFS between two groups.

The prognostic factors for adult T-LBL with chemotherapy have been largely studied[51–53], but fewer studies concerned the prognostic factors for patients with allo-HSCT. In GRAALL-LYSALL03 study, multivariate analysis showed that LDH level (normal or elevated) was an independent prognostic indicator for EFS (HR, 2.8, 95% CI, 1.3–5.9; $P = 0.010$) and OS (HR, 3.4, 95% CI, 1.3–8.7; $P = 0.012$)[54], while other prognostic factors like as CNS involvement[55], bone marrow involvement[56], and disease status at transplantation[8] were also reported. Hu et al[47] analyzed the prognostic factors for T-LBL patients, of which 22 patients (45.8%) received allogeneic transplantation and found that a higher Ki-67 score, evaluated LDH, and pleural effusion at diagnosis significantly affect the prognosis of patients. Our study found that elevated LDH level at diagnosis as an independent prognostic factor negatively affected the OS, RFS, and GRFS. Partial remission status at transplantation leaded to a higher risk of relapse, a poorer RFS, and GRFS. Total body irradiation–based conditioning regimen as an independent prognostic factor significantly reduced the risk of disease recurrence, increased the OS and RFS. Interestingly, a trend toward haploidentical transplantation decreased the incidence of relapse as a prognostic factor, which indicated that a haploidentical donor should be preferred to a HLA-matched donor for higher risk T-LBL patients.

In conclusion, our data showed that adult T-LBL patients achieving CR at transplantation might have an excellent prognosis with TBI-based conditioning regimen. For patients in PR status, allo-HSCT might not be an optimal choice due to the high risk of relapse, but it could be operated after achieving CR with alternative strategies like as CD7 chimeric antigen T-cell therapy[57], new drugs like venetoclax combined with chemotherapy[58]. The results suggested that TBI-based conditioning regimen might be an optimal regimen for adult T-LBL patients receiving allo-HSCT.

Our study also had some limitations for a retrospective study with a relative small number of sample, different donor sources and GvHD prophylaxis strategies, and a relative shorter follow-up. Thus, a well-designed prospective study with a larger sample size and a longer follow-up is required.

Author Contributions

Conception and design: Xianmin Song and Jun Yang
Provision of study materials or patients: All authors
Collection and assembly of data: Jiahua Niu, Zhixiao Chen
Analysis and interpretation: Jiahua Niu, Zhixiao Chen and Jie Gao
Manuscript writing: Jiahua Niu
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

Ethical Approval

This study was approved by the Ethics Committee of the coordinating institution of Shanghai General Hospital (Code: 2022KY023).

Statement of Human and Animal Rights

This study was approved by the Ethics Committee of the coordinating institution of Shanghai General hospital (Code: 2022KY023).

Statement of Informed Consent

Informed consent was waived because we used datasets provided by Shanghai General Hospital.

Declaration of Conflicting Interests

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Supplemental Material

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References

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.

2. Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M, Pierce S, Huh Y, Andreeff M, Koller C, Ha CS, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol. 2000;18(3):547–61.

3. Kantarjian H, Thomas D, O'Brien S, Cortes J, Giles F, Jeha S, Bueso-Ramos CE, Pierce S, Shan J, Koller C, Beran M, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer. 2004;101(12):2788–801.

4. Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, Burnett AK, Chopra R, Wiernik PH, Foroni L, Paietta E, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008;111(4):1827–33.

5. Liu Y, Rao J, Li J, Wen Q, Wang S, Lou S, Yang T, Li B, Gao L, Zhang C, Kong P, et al. Tandem autologous hematopoietic stem cell transplantation for treatment of adult T-cell lymphoblastic lymphoma: a multiple center prospective study in China. Haematologica. 2021;106(1):163–72.

6. Cortelazzo S, Ferreri A, Hoelzer D, Ponzoni M. Lymphoblastic lymphoma. Crit Rev Oncol Hematol. 2017;113:304–17.

7. Morita-Fujita M, Arai Y, Yoshioka S, Ishikawa T, Kanda J, Kondo T, Akasaka T, Ueda Y, Imada K, Moriguchi T, Yago K, et al. Indication and benefit of upfront hematopoietic stem cell transplantation for T-cell lymphoblastic lymphoma in the era of ALL-type induction therapies. Sci Rep. 2020;10(1):21418.

8. Levine JE, Harris RE, Loberiza FR Jr, Armitage JO, Vose JM, Van Besien K, Lazarus HM, Horowitz MM, Bashey A, Bolwell BJ, Burns LJ, et al. A comparison of allogeneic and autologous bone marrow transplantation for lymphoblastic lymphoma. Blood. 2003;101(7):2476–82.

9. Xu X, Yang J, Cai Y, Li S, Niu J, Zhou K, Jiang Y, Xu X, Shen C, Huang C, Qiu H, et al. Low dose anti-thymocyte globulin with low dose posttransplant cyclophosphamide (low dose ATG/PTCy) can reduce the risk of graft-versus-host disease as compared with standard-dose anti-thymocyte globulin in haploidentical peripheral hematopoietic stem cell transplantation combined with unrelated cord blood. Bone Marrow Transplant. 2021;56(3):705–708.

10. Yang J, Jiang J, Cai Y, Li S, Wan L, Zhu J, Liu H, Shao S, Bai H, Wang C, Song X. Low-dose anti-thymocyte globulin plus low-dose posttransplant cyclophosphamide as graft-versus-host disease prophylaxis in haploidentical peripheral blood stem cell transplantation combined with unrelated cord blood for patients with hematologic malignancies: a prospective, phase II study. Bone Marrow Transplant. 2019;54(7):1049–57.

11. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, Martin PJ, Sandmaier BM, Marr KA, Appelbaum FR, Storb R, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010;363(22):2091–101.

12. Malard F, Chevallier P, Guillaume T, Delaunay J, Rialland F, Harousseau JL, Moreau P, Mechinaud F, Milpied N, Mohty M. Continuous reduced nonrelapse mortality after allogeneic hematopoietic stem cell transplantation: a single-institution's three decade experience. Biol Blood Marrow Transplant. 2014;20(8):1217–23.

13. Sun X, Yang J, Cai Y, Wan L, Huang C, Qiu H, Tong Y, Xu X, Zhou K, Ding X, Song X. Low-dose antithymocyte globulin plus low-dose posttransplant cyclophosphamide combined with cyclosporine and mycophenolate mofetil for prevention of graft-versus-host disease after HLA-matched unrelated donor peripheral blood stem cell transplantation. Bone Marrow Transplant. 2021;56(10):2423–31.

14. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA, Alliance AL, Australasian Leukaemia and Lymphoma Group, Eastern Cooperative Oncology Group, European Mantle Cell Lymphoma Consortium, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–68.

15. Hutt D. Engraftment, graft failure, and rejection. In: Kenyon M, Babic A, editors. The European blood and marrow transplantation textbook for nurses: under the auspices of EBMT. Cham (Switzerland): Springer; 2018. p 259–70.

16. Delie A, Verlinden A, Beel K, Deeren D, Mazure D, Baron F, Breems D, De Becker A, Graux C, Lewalle P, Maertens J, et al. Use of chimerism analysis after allogeneic stem cell transplantation: Belgian guidelines and review of the current literature. Acta Clin Belg. 2021;76(6):500–508.

17. Turkiewicz D, Gorczynska E, Toporski J, Kalwak K, Rybka B, Noworolska D, Boguslawska-Jaworska J, Chybicka A. Monitoring of hematopoietic chimerism after sex-mismatched allogeneic stem cell transplantation (alloSCT) by dual-color FISH analysis of X and Y chromosomes. Leuk Res. 2003;27(11):993–98.

18. Clark JR, Scott SD, Jack AL, Lee H, Mason J, Carter GI, Pearce L, Jackson T, Clouston H, Sproul A, Keen L, et al. Monitoring of chimerism following allogeneic haematopoietic stem cell

transplantation (HSCT): technical recommendations for the use of short tandem repeat (STR) based techniques, on behalf of the United Kingdom National External Quality Assessment Service for Leucocyte Immunophenotyping Chimerism Working Group. Br J Haematol. 2015;168(1):26–37.

19. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED. 1994 consensus conference on acute GVHD grading. Bone Marrow Transplant. 1995;15(6):825–28.

20. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2003;9(4):215–33.

21. Fine JP, Gray RJ. A proportional hazards model for the sub-distribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509.

22. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in remission. Bone Marrow Transplant. 2016;51(4):610–11.

23. Thomas E, Storb R, Clift RA, Fefer A, Johnson FL, Neiman PE, Lerner KG, Glucksberg H, Buckner CD. Bone-marrow transplantation (first of two parts). N Engl J Med. 1975;292(16):832–43.

24. Giebel S, Miszczyk L, Slosarek K, Moukhtari L, Ciceri F, Esteve J, Gorin NC, Labopin M, Nagler A, Schmid C, Mohty M. Extreme heterogeneity of myeloablative total body irradiation techniques in clinical practice: a survey of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Cancer. 2014;120(17):2760–65.

25. Studinski RCN, Fraser DJ, Samant RS, MacPherson MS. Current practice in total-body irradiation: results of a Canada-wide survey. Curr Oncol. 2017;24(3):181–86.

26. Thomas ED, Buckner CD, Banaji M, Clift RA, Fefer A, Flournoy N, Goodell BW, Hickman RO, Lerner KG, Neiman PE, Sale GE, et al. One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation. Blood. 1977;49(4):511–33.

27. Ishibashi N, Maebayashi T, Aizawa T, Sakaguchi M, Abe O, Sakanishi K, Endoh Y, Saito T, Kawamori J, Tanaka Y. Various regimens of total body irradiation for hematopoietic stem cell transplant. Exp Clin Transplant. 2016;14(6):670–75.

28. Hartman AR, Williams SF, Dillon JJ. Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophospha-mide vs total body irradiation: a meta-analysis. Bone Marrow Transplant. 1998;22(5):439–43.

29. Esiashvili N, Lu X, Ulin K, Laurie F, Kessel S, Kalapurakal JA, Merchant TE, Followill DS, Sathiaseelan V, Schmitter MK, Devidas M, et al. Higher reported lung dose received during total body irradiation for allogeneic hematopoietic stem cell transplantation in children with acute lymphoblastic leukemia is associated with inferior survival: a report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys. 2019;104(3):513–21.

30. McDonald AM, Chen Y, Wu J, Hageman L, Francisco L, Kung M, Wong FL, Ness E, Landier W, Battles K, Salzman D, et al. Total body irradiation and risk of breast cancer after blood or marrow transplantation: a blood or marrow transplantation survivor study report. J Clin Oncol. 2020;38(25):2872–82.

31. Vitale V, Bacigalupo A, Van Lint MT, Frassoni F, Ricci G, Siracusa G, Marziano G, Vitali ML, Scielzo G, Tomassini A, Bistolfi F, et al. Fractionated total body irradiation in marrow

32. Fahnehjelm KT, Tornquist AL, Olsson M, Winiarski J. Visual outcome and cataract development after allogeneic stem-cell transplantation in children. Acta Ophthalmol Scand. 2007;85(7):724–33.

33. Siegal D, Keller A, Xu W, Bhuta S, Kim DH, Kuruvilla J, Lipton JH, Messner H, Gupta V. Central nervous system complications after allogeneic hematopoietic stem cell transplantation: incidence, manifestations, and clinical significance. Biol Blood Marrow Transplant. 2007;13(11):1369–79.

34. Tutschka PJ, Copelan EA, Klein JP. Bone marrow transplantation for leukemia following a new busulfan and cyclophosphamide regimen. Blood. 1987;70(5):1382–88.

35. Santos GW, Tutschka PJ, Brookmeyer R, Saral R, Beschorner WE, Bias WB, Braine HG, Burns WH, Elfenbein GJ, Kaizer H, Mellits D, et al. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclophosphamide. N Engl J Med. 1983;309(22):1347–53.

36. Bunin N, Aplenc R, Kamani N, Shaw K, Cnaan A, Simms S. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study. Bone Marrow Transplant. 2003;32(6):543–48.

37. Giebel S, Boumendil A, Labopin M, Seesaghur A, Baron F, Ciceri F, Esteve J, Gorin NC, Savani B, Schmid C, Wetten S, et al. Trends in the use of hematopoietic stem cell transplantation for adults with acute lymphoblastic leukemia in Europe: a report from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Ann Hematol. 2019;98(10):2389–98.

38. Davies SM, Ramsay NK, Klein JP, Weisdorf DJ, Bolwell B, Cahn JY, Camitta BM, Gale RP, Giralt S, Heilmann C, Henslee-Downey PJ, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol. 2000;18(2):340–47.

39. Willasch AM, Peters C, Sedlacek P, Dalle JH, Kitra-Roussou V, Yesilipek A, Wachowiak J, Lankester A, Prete A, Hamidieh AA, Ifversen M, et al. Myeloablative conditioning for allo-HSCT in pediatric ALL: FTBI or chemotherapy? A multicenter EBMT-PDWP study. Bone Marrow Transplant. 2020;55(8):1540–51.

40. Peters C, Dalle JH, Locatelli F, Poetschger U, Sedlacek P, Buechner J, Shaw PJ, Staciuk R, Ifversen M, Pichler H, Vettenranta K, et al. Total body irradiation or chemotherapy conditioning in childhood ALL: a multinational, randomized, noninferiority phase III study. J Clin Oncol. 2021;39(4):295–307.

41. Abdelaty MM, Gawaly A, Fathy GM, Kabbash I, Taha A. Irradiation free conditioning regimen is associated with high relapse rate in Egyptian patients with acute lymphoblastic leukemia following allogeneic hematopoietic stem cell transplantation. J Egypt Natl Canc Inst. 2020;32(1):28.

42. Storb R, Georges GE, Gooley TA. Total body irradiation-based versus chemotherapy-based myeloablative conditioning for allogeneic hematopoietic cell transplant. Biol Blood Marrow Transplant. 2019;25(12):e356–62.

43. Kebriaei P, Anasetti C, Zhang MJ, Wang HL, Aldoss I, de Lima M, Khoury HJ, Sandmaier BM, Horowitz MM, Artz A, Bejanyan N, et al. Intravenous busulfan compared with total

body irradiation pretransplant conditioning for adults with acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2018;24(4):726–33.

44. Kalaycio M, Bolwell B, Rybicki L, Absi A, Andresen S, Pohlman B, Dean R, Sobecks R, Copelan E. BU- vs TBI-based conditioning for adult patients with ALL. Bone Marrow Transplant. 2011;46(11):1413–17.

45. Cahu X, Labopin M, Giebel S, Aljurf M, Kyrcz-Krzemien S, Socie G, Eder M, Bonifazi F, Bunjes D, Vigouroux S, Michallet M, et al. Impact of conditioning with TBI in adult patients with T-cell ALL who receive a myeloablative allogeneic stem cell transplantation: a report from the acute leukemia working party of EBMT. Bone Marrow Transplant. 2016;51(3):351–57.

46. Shigematsu A, Ozawa Y, Onizuka M, Fujisawa S, Suzuki R, Atsuta Y, Hatanaka K, Masuko M, Ito T, Kobayashi N, Kato J, et al. A safety and efficacy study of medium-dose etoposide, cyclophosphamide and total body irradiation conditioning before allogeneic stem cell transplantation for acute lymphoblastic leukemia. Transplant Direct. 2015;1(2):e8.

47. Hu M, Wang H, Wang L, Yang M, Lou Y, Jin J. Outcome of adult T-lymphoblastic lymphoma depends on ALL-type chemotherapy, prognostic factors, and performance of allogeneic hematopoietic stem cell transplantation. Medicine (Baltimore). 2018;97(28):e11374.

48. Friend BD, Bailey-Olson M, Melton A, Shimano KA, Kharbanda S, Higham C, Winestone LE, Huang J, Stieglitz E, Dvorak CC. The impact of total body irradiation-based regimens on outcomes in children and young adults with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation. Pediatr Blood Cancer. 2020;67(2):e28079.

49. Nagler A, Labopin M, Houhou M, Aljurf M, Mousavi A, Hamladji RM, Al Zahrani M, Bondarenko S, Arat M, Angelucci E, Koc Y, et al. Outcome of haploidentical versus matched sibling donors in hematopoietic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. J Hematol Oncol. 2021;14(1):53.

50. Marks DI, Forman SJ, Blume KG, Perez WS, Weisdorf DJ, Keating A, Gale RP, Cairo MS, Copelan EA, Horan JT, Lazarus HM, et al. A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. Biol Blood Marrow Transplant. 2006;12(4):438–53.

51. Morel P, Lepage E, Brice P, Dupriez B, D'Agay MF, Fenaux P, Gosselin B, Bauters F, Gisselbrecht C. Prognosis and treatment of lymphoblastic lymphoma in adults: a report on 80 patients. J Clin Oncol. 1992;10(7):1078–85.

52. Zinzani PL, Bendandi M, Visani G, Gherlinzoni F, Frezza G, Merla E, Manfroi S, Gozzetti A, Tura S. Adult lymphoblastic lymphoma: clinical features and prognostic factors in 53 patients. Leuk Lymphoma. 1996;23(5–6):577–82.

53. Li C, Wuxiao ZJ, Chen X, Chen G, Lu Y, Xia Z, Liang Y, Wang H. A modified NHL-BFM-95 regimen produces better outcome than HyperCVAD in adult patients with T-lymphoblastic lymphoma, a two-institution experience. Cancer Res Treat. 2020;52(2):573–85.

54. Lepretre S, Touzart A, Vermeulin T, Picquenot JM, Tanguy-Schmidt A, Salles G, Lamy T, Bene MC, Raffoux E, Huguet F, Chevallier P, et al. Pediatric-like acute lymphoblastic leukemia therapy in adults with lymphoblastic lymphoma: the GRAALL-LYSA LL03 study. J Clin Oncol. 2016;34(6):572–80.

55. Ellin F, Jerkeman M, Hagberg H, Relander T. Treatment outcome in T-cell lymphoblastic lymphoma in adults—a population-based study from the Swedish Lymphoma Registry. Acta Oncol. 2014;53(7):927–34.

56. Song KW, Barnett MJ, Gascoyne RD, Chhanabhai M, Forrest DL, Hogge DE, Lavoie JC, Nantel SH, Nevill TJ, Shepherd JD, Smith CA, et al. Primary therapy for adults with T-cell lymphoblastic lymphoma with hematopoietic stem-cell transplantation results in favorable outcomes. Ann Oncol. 2007;18(3):535–40.

57. Pan J, Tan Y, Wang G, Deng B, Ling Z, Song W, Seery S, Zhang Y, Peng S, Xu J, Duan J, et al. Donor-derived CD7 chimeric antigen receptor T cells for T-cell acute lymphoblastic leukemia: first-in-human, phase I trial. J Clin Oncol. 2021;39(30):3340–51.

58. Richard-Carpentier G, Jabbour E, Short NJ, Rausch CR, Savoy JM, Bose P, Yilmaz M, Jain N, Borthakur G, Ohanian M, Alvarado Y, et al. Clinical experience with venetoclax combined with chemotherapy for relapsed or refractory T-cell acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk. 2020;20(4):212–18.