ARTICLE

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Thiotepa, busulfan and fludarabine conditioning-regimen is a promising approach for older adult patients with acute lymphoblastic leukemia treated with allogeneic stem cell transplantation

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For acute lymphoblastic leukemia (ALL) patients, total body irradiation (TBI)- based conditioning regimens are the first choice specially in young population. However, several studies have shown an equivalence in clinical outcomes with thiotepa-based conditioning regimen. We performed a retrospective study to evaluate the outcome of adult ALL patients who received allogeneic hematopoietic stem cell transplantation (allo-HCT) with a thiotepa-busulfan-fludarabine (TBF) myeloablative conditioning regimen with reduced toxicity. Fifty-five patients received a TBF regimen. The median age of the patients was 51 years (range, 17 to 72.4). Most patients had a diagnosis of B-ALL (93%) with 7% having T-ALL. Two - and 5-year overall survival was 73.2% and 64%, respectively. At 2 years, leukemia-free survival and GVHD-free, relapse-free survival were 59.5% and 57.6%, and at 5 years, 53.4% and 51.8%, respectively. The 5-year non-relapse mortality was 15%. The day 180 cumulative incidence (CI) of grade II–IV acute GVHD and grade III–IV acute GVHD were 38.2% and 5.5%, respectively. At 2 years, the CI of chronic GVHD and extensive chronic GVHD was 16.9% and 1.9%, respectively. Our study results do suggest that using TBF as the conditioning regimen in adult ALL patients is a promising option with acceptable toxicity.

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INTRODUCTION

Allogeneic stem cell transplantation (allo-HCT) is an effective treatment for patients with high risk or refractory acute lymphoblastic leukemia (ALL). Indeed, several studies have shown a significant increase in the survival of patients after allo-HCT compared to consolidation treatments by chemotherapy or autograft [1–3]. Currently, a total body irradiation (TBI)-based conditioning regimen is the gold standard for pediatric patients allowing an anti-leukemic effect and a prevention of relapse on sanctuary sites [4–8]. Recently, Peters et al. published the results of the FORUM study, a randomized phase III study that compared the outcomes of myeloablative conditioning (MAC) with fractionated TBI 12 Gy and etoposide versus fludarabine (Flu), thiotepa and either busulfan or treosulfan [9]. The study was prematurely stopped because chemotherapy-based conditioning was significantly inferior to TBI. In adult patients, no prospective data on this issue is available. Eders et al., in a retrospective analysis of the European Society for Blood and Marrow Transplantation (EBMT), compared thiotepa-based conditioning versus TBI conditioning for ALL patients transplanted from a matched sibling donor (MSD) or matched unrelated donor (MUD) [10]. Thiotepa conditioned patients have a trend towards inferior leukemia-free survival (LFS) with a significantly higher relapse incidence (RI). Overall survival (OS), non-relapse mortality (NRM), acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD) were not significantly different between either group [10]. More recently, Swoboda et al. compared TBI-Flu versus thiotepa-busulfan-fludarabine (TBF) conditioning for adults with ALL treated with haploidentical (Haplo) allo-HCT [11]. In patients in 1st or 2nd complete remission (CR1/CR2), TBI-Flu compared to TBF was associated with a reduced risk of NRM at 2 years and a significantly increased RI. No difference between conditioning regimens was found with respect to LFS and OS. However, high dose TBI is still associated with the disadvantage of frequent and late complications such as cataracts, pituitary dysfunction, gonadal failure, hypothyroidism, cardiac dysfunction, cognitive dysfunction, osteopenia, xerostomia, chronic kidney disease and secondary malignancies [12–14]. Moreover, in clinical practice, TBI is hampered by challenging logistics of administration, and coordination between hematology and radiation oncology departments [15].

However, this MAC regimen is toxic and so few adult patients are eligible [16–18]. Over several years, with the use of alternative

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donors and the consideration of patients' age and comorbidities, reduced-intensity conditioning (RIC) regimens have been developed. They are based on the combination of chemotherapies, and several studies have shown their feasibility and effectiveness [19–21]. Such RIC regimens are an attractive alternative to TBI in adults with ALL, including the use of the validated combination of thiotepa, busulfan and fludarabine (TBF). Each of these drugs showed comparable results to TBI in terms of outcomes [10, 22–24].

Thus, we analyzed the outcomes of adult patients with ALL who received allo-HCT after conditioning with TBF, a MAC regimen with reduced toxicity.

MATERIAL AND METHODS

Study design and selection criteria

We performed a retrospective multicenter study in patients treated at the Saint-Antoine and Mount Liban Hospital between May 2013 and June 2020. The inclusion criteria were as follow: adult patients, with B- and T-lineage ALL, undergoing bone marrow (BM) or peripheral blood stem cell (PBSC) transplant from an allogeneic human leukocyte antigen (HLA)-MSD, 10/10 MUD, 9/10 MMUD, or Haplo-HCT with TBF conditioning. TBF regimens contained 5 or 10 mg/kg of thiotepa, intravenous (IV) busulfan 130 mg/m2/d (2 or 3 days), and Flu 30 mg/m2/d for 5 days.

For Ph+ ALL, all patients received a tyrosine kinase inhibitor (TKI) prior to allo-HCT, and also in the post-allo-HCT maintenance setting (between day 60 and day 90), if hematological recovery allowed it.

Statistical analysis

The primary end point was OS. Secondary end points included LFS, cumulative incidence (CI) of relapse (RI), NRM, aGVHD, cGVHD, and GVHD-free, relapse-free survival (GRFS) [25, 26]. LFS was defined as survival without evidence of relapse or progression. LFS and OS probabilities were calculated using the Kaplan–Meier estimates. RI, NRM, and the probabilities of aGVHD and cGVHD were calculated using CI in a competing risk setting, with death in remission treated as a competing event for relapse.

Minimal residual disease (MRD) response was assessed by PCR amplification-based methods that use either leukemia-specific (fusion gene transcripts) or patient specific (IG/TCR gene rearrangements) molecular markers or by flow cytometry of leukemia-associated immunophenotypes.

RESULTS

Patient characteristics

Fifty-five patients were included in the study. The demographics of the population and disease characteristics are described in Table 1. The median age was 51 years (range 17 to 72.4). The gender distribution was almost equivalent, with 28 men (50.9%) and 27 women (49.7%). A large majority of patients ($n = 51$, 92.7%) had a diagnosis of B-ALL. Patients were fit at the time of transplantation with a Karnofsky Performance Score of 90 in 53 (96.4%) of them. Most patients had poor-risk cytogenetics: seven (13.2%) patients had a complex karyotype, 25 (47.2%) had a t(9;22), two (3.8%) had a t(4;11) and one patient had near-triploidy. Nine (17%) patients had a normal karyotype. Molecular markers showed the presence of Ph+ in 25 (45.4%) patients and a mixed-lineage leukemia (MLL) rearrangement in four (5.6%) patients.

Thirty-four (61.9%) patients received an allograft as first line treatment (CR1), 13 (23.6%) as second line (CR2) and eight (14.5%) as 3rd line treatment (CR3). Fifty-three (96.4%) patients underwent an allograft for the first time. At the time of transplantation, one patient was in partial response, 39 patients (70.9%) were in CR and 15 (27.3%) patients were in cytological remission but had a positive MRD.

Allograft characteristics

Allo-HCT characteristics are summarized in Table 2. The main stem cell source (90%) was PBSCs. The median CD34+ cell dose was 6.7×10^6/kg (range, 0.8–10.5). Donor specific antibodies (DSA) were identified in 3 (5.5%) patients but with a non-significant rate (<2000 mean fluorescence intensity). Thirty-four (61.8%) donors were male. Only nine (16.4%) male patients received a graft from a female donor. Twenty-seven (49.1%) patients were transplanted from an MSD, ten (18.2%) from a MUD, two (3.6%) patients from an MMUD (9/10), and 16 (29.1%) from a Haplo donor. GVHD prophylaxis was based on a combination of cyclosporine A (CsA) and mycophenolate mofetil (MMF) in 36 (65.5%) patients, CsA and methotrexate (MTX) in one patient, and the administration of CsA alone in 18 (32.7%). In addition, patients received a median dose of 2 days of antithymocyte globulin (ATG). Post-transplant cyclophosphamide (PTCy) at a dose of 35 to 50 mg/Kg/day over 2 days was administered to Haplo allo-HCT recipients, and to one patient with an MMUD.

Table 1. Baseline characteristics of study population.

	***n* = 55**
Age patient	
Median (range)	51 (17–72.4)
Patient sex	
Male	28 (50.9%)
Female	27 (49.1%)
Karnofsky performance score	
90	53 (96.4%)
80	2 (3.6%)
Diagnosis	
B-ALL	51 (92.7%)
T-ALL	4 (7.3%)
Cytogenetics	
Normal	9 (17%)
Complex	7 (13.2%)
t(9;22)	25 (47.2%)
t(4;11)	2 (3.8%)
Near triploid	1 (1.8%)
Other	9 (17%)
Missing	2
Minimal residual disease monitoring	
Ig-TCR PCR	9 (16.7%)
Ph positive	25 (46.3%)
MLL	4 (7.4%)
FCM	16 (29.6%)
Missing	1
Allograft	
First	53 (96.4%)
Second	2 (3.6%)
Previous treatments	
1	34 (61.9%)
2	13 (23.6%)
3	8 (14.5%)
Status at transplant	
Complete remission MRD negative	39 (70.9%)
Minimal residual disease positive	15 (27.3%)
Partial response	1 (1.8%)

Data are presented as *n* (%) or median (range).
FCM flow cytometry, *MLL* mixed-lineage leukemia, *TCR* T cell receptor.

Table 2. Allograft characteristics.

	***N* = 55**
Type of donor	
MSD	27 (49.1%)
MUD	10 (18.2%)
MMUD (9/10)	2 (3.6%)
Haploidentical	16 (29.1%)
Donor sex	
Male	34 (61.8%)
Female	21 (38.2%)
Female to male combination	
No	46 (83.6%)
Yes	9 (16.4%)
Stem cell source	
Bone Marrow	5 (9.1%)
PBSC	50 (90.9%)
Total infused CD34 positive cells (10e6/kg)	
Median (range)	6.7 (0.8–10.5)
Regimen	
T1B2F	17 (30.9%)
T1B3F	18 (32.7%)
T2B2F	1 (1.8%)
T2B3F	19 (34.5%)
ATG days	
Median (min-max)	2 (0–3)
ATG dose mg/kg	
Median (min-max)	5 (0–6)
GvHD prevention	
CsA	18 (32.7%)
CsA_MMF	36 (65.5%)
CsA_MTX	1 (1.8%)

Data are presented as *n* (%) or median (range).
MSD matched sibling donor, *MUD* matched unrelated donor, *MMUD* mismatched unrelated donor, *PBSC* peripheral blood stem cells, *ATG* antithymocyte globulin, *GvHD* graft-versus-host disease, *Csa* cyclosporine A, *MMF* mycophenolate mofetil, *MTX* methotrexate.

Table 3. Follow-up post-allograft.

Engraftment	
Engrafted	55 (100%)
Time to ANC > 500 median (range)	15 (5–27)
Infection	
BKV hemorrhagic cystitis	
No	41 (74.5%)
Yes	14 (25.5%)
CMV	
No	23 (41.8%)
Yes	32 (58.2%)
EBV	
No	29 (52.7%)
Yes	26 (47.3%)
HHV6	
No	45 (81.8%)
Yes	10 (18.2%)
Fungal infection	
No	51 (92.7%)
Yes	4 (7.3%)
Type of fungal infection	*n* (%)
Aspergillus	3 (5.5%)
Candida	1 (1.8%)
ICU	
missing	1
No	45 (83.3%)
Yes	9 (16.7%)

Data are presented as *n* (%) or median (range).
ANC absolute neutrophil count, *BKV* BK virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr Virus, *HHV6* human herpesvirus 6, *ICU* intensive care unit.

Engraftment and infections

All patients engrafted at a median time of 15 days (range, 5–27) (Table 3).

Several patients developed viral infections: 14 (25.5%) patients had BK virus (BKV) reactivation with clinical cystitis (seven patients received immunoglobulin therapy, and two patients a combination of immunoglobulin and cidofovir). Among these 14 patients who developed a clinical hemorrhagic cystitis: half received a allo-HCT form a haploidentical donor, 3 from a MSD and 4 from a MUD. Cytomegalovirus (CMV) reactivation occurred in 32 (58.2%) patients, and 26 (47.3%) had Epstein-Barr Virus (EBV) viremia but no post-transplant lymphoproliferative disease (PTLD). Of the ten (18.2%) patients who reactivated HHV6, two required treatment, one with cidofovir for fever and rash, and one with immunoglobulin for fever.

Four (5.5%) patients had a fungal infection, including three with *Aspergillus* and one with *Candida*. It was probable pulmonary aspergillosis with radiological signs and positivity of blood fungal markers. Only one patient had clinical expression (cough).

During follow-up, nine patients were transferred to the intensive care unit (ICU), one of whom died from a relapse of his disease. The others were admitted because of neurological impairment (2), respiratory failure (3), sepsis (1), cardiogenic shock (1) and one patient because of aGVHD.

Prophylaxis treatment was administered in 30 patients: 9 patients received prophylactic intrathecal chemotherapy alone, 9 patients received a TKI (5 alone, 3 with an association of prophylactic cranial radiotherapy and one with association of prophylactic intrathecal chemotherapy). Four received DLI: 3 for ALL relapse and one for MRD positivity.

Outcomes

Median follow-up was 42.8 months. At 2 years, OS was 73.2% (95% CI, 58.9–83.2), LFS 59.5% (95% CI, 45.2–71.2), RI 27.7% (95% CI, 16.5–40.1) and NRM 12.8% (95% CI, 5.6–23.2) (Fig. 1 and Table 1-supplementary data). At 5 years, OS was 64% (95% CI, 48.8–75.7), LFS 53.4 % (95% CI, 38.2–66.5), RI 31.5% (95% CI, 18.6–45.3) and NRM 15% (95% CI, 6.9–26.1) (Table 1-supplementary data). The day 180 cumulative incidences of grade II–IV aGVHD and grade III–IV aGVHD were 38.2% (95% CI, 25.4–50.9) and 5.5% (95% CI, 1.4–13.7), respectively (Fig. 2 and Table 2-supplementary data). The cGVHD rate at 2 years was 16.9% (95% CI, 8.2–28.2), and the extensive cGVHD rate was 1.9% (95% CI, 0.1–8.9) (Fig. 2 and Table 2-supplementary data). The GRFS at 2 years was 57.6% (95% CI, 43.4–69.5), and at 5 years was 51.8% (95% CI, 36.7–64.9) (Fig. 2 and Table 1-supplementary data). No statistically significant difference on outcomes were observed considering the types of donors (Table 3-supplementary data).

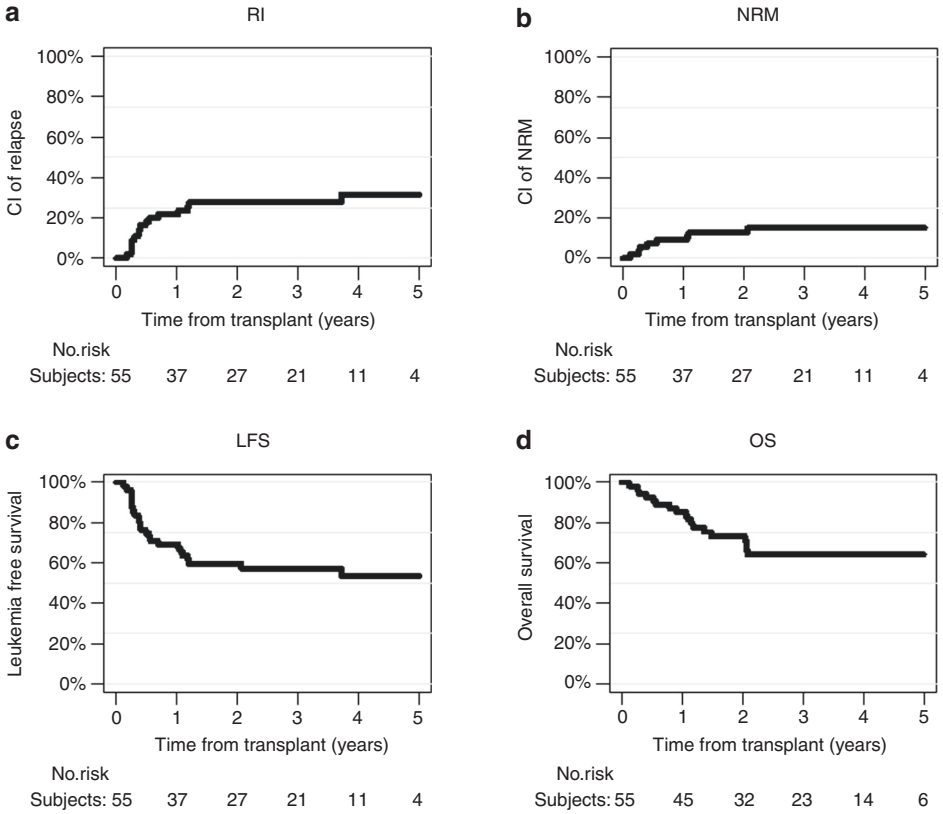

Fig. 1 Long term outcomes after alloHSCT with conditioning regimen by TBF for ALL patients. a Relapse incidence (RI), **b** non-relaspse morality (NRM), **c** leukemia-free survival (LFS) and **d** overall survival (OS).

Of the 15 patients who were MRD positive before allograft, six relapsed. Nineteen patients died: 11 from relapse, four from infections, two from aGVHD of the gastrointestinal tract, and one from secondary myelodysplastic syndrome.

DISCUSSION

In this retrospective study, we assessed the feasibility and toxicity of TBF conditioning in ALL patients with indication for transplantation, regardless of their status at the time of transplantation (CR1 or not) or their age. Post-transplant outcomes were relatively good with 5-year OS of 64% and 5-year NRM of 15%. These results are similar to published data on MAC and other RIC regimens. Indeed, Giebel et al. analyzed data from 4859 patients with ALL in CR1 who received an allograft between 1993 and 2012 after MAC including TBI [4]. The 2-year NRM was 11–29% in those younger than 55 years, and the 3-year NRM was 23–24% in those older than 60 years [4]. Overall survival was 60–76% at 2 years in patients under 55 years of age and only 39–46% at 3 years in patients aged over 60 years [4]. Another retrospective study, conducted on allografts for ALL between 1993 and 2006, found a 2-year NRM of 20% for standard-risk ALL and a NRM of 36% for high-risk ALL, with an OS at 5 years of 63% [3]. These two important studies were performed before 2012, and since then, improved preventive and curative treatment of infections (especially fungal), and the use of ATG or PTCy for transplants from unrelated donors to reduce the risk of acute or cGVHD, have significantly reduced patients' NRM and improved their quality of life. [27]. Several studies using a RIC regimen have found equivalent NRM rates of between 14 and 23% [28–30].

In a retrospective study comparing TBI-based versus chemotherapy-based conditioning regimens, Greil et al. reported a 5-year NRM of 20.6% with TBI versus 34.8% in the chemotherapy group [31]. In a study by Swoboda et al. that compared TBI-Flu versus TBF conditioning for adults with ALL in CR1/CR2 treated with Haplo allo-HCT, TBI-Flu was associated with a reduced risk of NRM at 2 years (19.5%) compared to TBF (30.9%) [11]. In our study we did not find such a high CI of NRM. We obviously did not only study Haplo allo-HCT as in Swoboda's study. However, it should be emphasized that our cohort median age (51 years) was higher than those of the Eders and Swoboda cohorts, which were 30 and 36 years, respectively [10, 11]. NRM is a real issue in the management and in the decision-making of allo-HCT. The acceptable rate of NRM in our study may be related to the fact that most patients were transplanted in CR1, which influences the NRM by decreasing the risk of cumulative toxicity. In addition, these results could be attributed both to age and to the few comorbidities of the patients. Indeed, 96% of the patients had a Karnosky score of 90 at the time of transplantation.

Several factors, such as better patient selection and improved care surrounding transplantation [4, 32], have led, in addition to the use of RIC, to NRM improvement over the past 10 years.

A further important parameter is the reduction of the risk of GVHD. In our study, we found a low incidence of GVHD III–IV (5.5%) and only 1.9% of extensive cGVHD, which clearly impacts the NRM. TBI has been shown (in large cohorts) to be a risk factor for GVHD, like patient age, HLA mismatch, and the use of alternative donors [33, 34]. In our study, the use of ATG, validated GVHD prophylaxis, and the use of PTCy for alternative donor transplants enabled achievement of an acceptable incidence of GVHD.

Of note, there was no veno-occlusive disease (VOD) in our cohort, whereas one study showed an incidence of VOD of 5.3% in patients who received RIC with busulfan [35].

MAC has long been preferred because it allows better clearance of the disease, decreases the risk of relapse due to the graft-versus-leukemia (GVL) effect, and thus improves long-term patient survival [4, 7, 22, 31, 36]. A TBI-based regimen is the conditioning

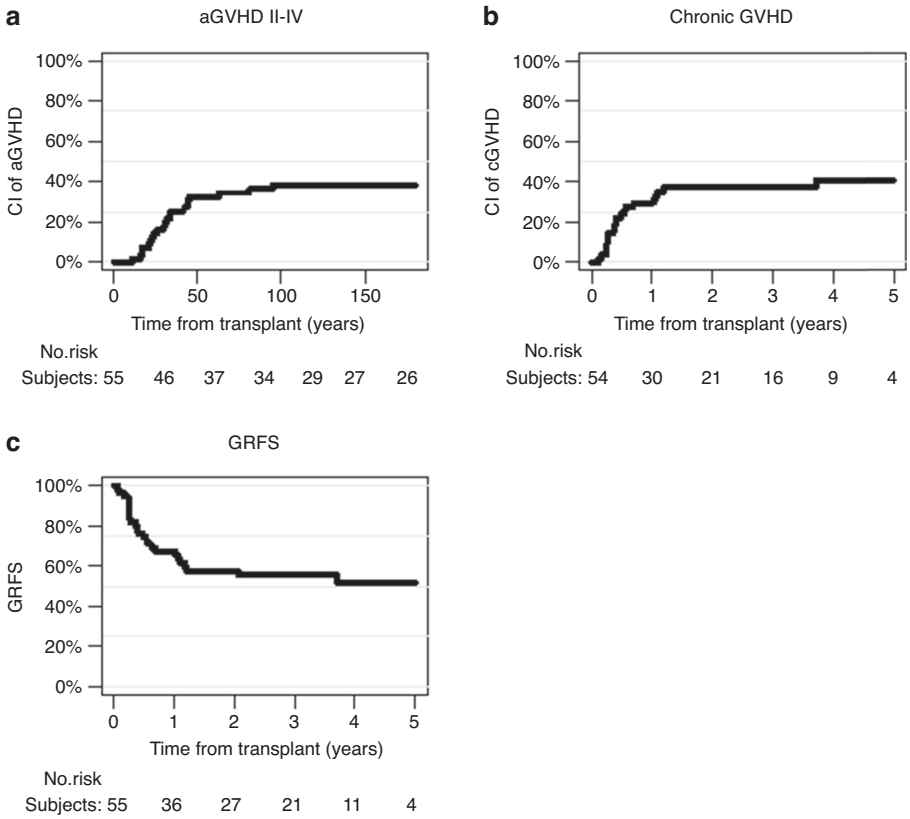

Fig. 2 Incidence and impact of GVHD in the cohort of patients with conditioning by TBF. a Cumulative incidence of grade II-IV acute GVHD, **b** cumulative incidence of chronic GVHD and **c** GVHD/relapse free survival (GRFS).

of choice in ALL because several retrospective studies have demonstrated its superiority over other MAC regimens by providing a more durable immunosuppression together with avoiding variations in the distribution and interactions of drugs [4, 31, 37–39]. With an OS at 2 years of 73.2% and at 5 years of 64%, and an IR of 31.5% at 5 years in patients with a median age of 55 years, TBF conditioning seems to be a good option. These results are equivalent to the survival with TBI and are even increased compared to the OS in patients over 60 years old which is less than 46% [4]. Only one patient in our cohort of allograft patients was refractory at the time of transplantation, a factor known to be significantly associated with poorer OS [40].

Slightly more than half of our patients received relapse prevention therapy, which may have impacted patient survival. In the last few years, the importance of implementing a post-transplant maintenance treatment has been clearly demonstrated. The first results were obtained with the use of TKIs in Ph positive ALL for at least 2 years post-transplant, which significantly decreased the risk of relapse, and thus increased the overall patient survival [41–43].

However, despite its long follow-up, our study has limitations related to its retrospective nature, and to the cohort size which did not permit analysis of subgroup data, especially with respect to the different TBF dosing regimens, or patient age.

In summary, the TBF regimen is an attractive conditioning regimen in adult ALL with good OS, good safety profiles and acceptable toxicity. To validate these promising results, prospective study cohorts of adult patients are needed.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, AB, upon reasonable request.

REFERENCES

1. Thomas X, Boiron JM, Huguet F, Dombret H, Bradstock K, Vey N, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol J Am Soc Clin Oncol. 2004;22:4075–86.
2. Hunault M, Harousseau JL, Delain M, Truchan-Graczyk M, Cahn JY, Witz F, et al. Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. Blood. 2004;104:3028–37.
3. Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, 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;111:1827–33.
4. Giebel S, Labopin M, Socié G, Beelen D, Browne P, Volin L, et al. Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica. 2017;102:139–49.
5. Marks DI, Forman SJ, Blume KG, Pérez WS, Weisdorf DJ, Keating A, 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 J Am Soc Blood Marrow Transpl. 2006;12:438–53.
6. Davies SM, Ramsay NK, Klein JP, Weisdorf DJ, Bolwell B, Cahn JY, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol J Am Soc Clin Oncol. 2000;18:340–7.
7. Eroglu C, Pala C, Kaynar L, Yaray K, Aksozen MT, Bankir M, et al. Comparison of total body irradiation plus cyclophosphamide with busulfan plus cyclophosphamide as conditioning regimens in patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplant. Leuk Lymphoma. 2013;54:2474–9.
8. Cahu X, Labopin M, Giebel S, Aljurf M, Kyrcz-Krzemien S, Socié G, 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;51:351–7.

9. Peters C, Dalle JH, Locatelli F, Poetschger U, Sedlacek P, Buechner J, et al. Total body irradiation or chemotherapy conditioning in childhood ALL: a multinational, randomized, noninferiority phase III study. J Clin Oncol J Am Soc Clin Oncol. 2021;39:295–307.
10. Eder S, Canaani J, Beohou E, Labopin M, Sanz J, Arcese W, et al. Thiotepa-based conditioning versus total body irradiation as myeloablative conditioning prior to allogeneic stem cell transplantation for acute lymphoblastic leukemia: A matched-pair analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Am J Hematol. 2017;92:997–1003.
11. Swoboda R, Labopin M, Giebel S, Angelucci E, Arat M, Aljurf M, et al. Total body irradiation plus fludarabine versus thiotepa, busulfan plus fludarabine as a myeloablative conditioning for adults with acute lymphoblastic leukemia treated with haploidentical hematopoietic cell transplantation. A study by the Acute Leukemia Working Party of the EBMT. Bone Marrow Transplant. 2022;57:399–406.
12. Baker KS, Leisenring WM, Goodman PJ, Ermoian RP, Flowers ME, Schoch G, et al. Total body irradiation dose and risk of subsequent neoplasms following allogeneic hematopoietic cell transplantation. Blood. 2019;133:2790–9.
13. Aristei C, Alessandro M, Santucci A, Aversa F, Tabillo A, Carotti A, et al. Cataracts in patients receiving stem cell transplantation after conditioning with total body irradiation. Bone Marrow Transplant. 2002;29:503–7.
14. Savani BN, Montero A, Wu C, Nlonda N, Read E, Dunbar C, et al. Prediction and prevention of transplant-related mortality from pulmonary causes after total body irradiation and allogeneic stem cell transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transpl. 2005;11:223–30.
15. Borras JM, Lievens Y, Barton M, Corral J, Ferlay J, Bray F, et al. How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis. Radiother Oncol. 2016;119:5–11.
16. Paix A, Antoni D, Waissi W, Ledoux MP, Bilger K, Fornecker L, et al. Total body irradiation in allogeneic bone marrow transplantation conditioning regimens: a review. Crit Rev Oncol Hematol. 2018;123:138–48.
17. Wong JYC, Filippi AR, Scorsetti M, Hui S, Muren LP, Mancosu P. Total marrow and total lymphoid irradiation in bone marrow transplantation for acute leukaemia. Lancet Oncol. 2020;21:e477–87.
18. Friedman DL, Rovo A, Leisenring W, Locasciulli A, Flowers MED, Tichelli A, et al. Increased risk of breast cancer among survivors of allogeneic hematopoietic cell transplantation: a report from the FHCRC and the EBMT-Late Effect Working Party. Blood. 2008;111:939–44.
19. Marks DI, Wang T, Pérez WS, Antin JH, Copelan E, Gale RP, et al. The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. Blood. 2010;116:366–74.
20. Tanaka J, Kanamori H, Nishiwaki S, Ohashi K, Taniguchi S, Eto T, et al. Reduced-intensity vs myeloablative conditioning allogeneic hematopoietic SCT for patients aged over 45 years with ALL in remission: a study from the Adult ALL Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). Bone Marrow Transplant. 2013;48:1389–94.
21. Mohty M, Labopin M, Volin L, Gratwohl A, Socié G, Esteve J, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Blood. 2010;116:4439–43.
22. Mitsuhashi K, Kako S, Shigematsu A, Atsuta Y, Doki N, Fukuda T, et al. Comparison of cyclophosphamide combined with total body irradiation, oral Busulfan, or intravenous Busulfan for allogeneic hematopoietic cell transplantation in adults with acute lymphoblastic leukemia. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transpl. 2016;22:2194–200.
23. Kebriaei P, Anasetti C, Zhang MJ, Wang HL, Aldoss I, de Lima M, et al. Intravenous Busulfan compared with total body irradiation pretransplant conditioning for adults with acute lymphoblastic leukemia. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transpl. 2018;24:726–33.
24. Patel B, Kirkwood AA, Dey A, Marks DI, McMillan AK, Menne TF, et al. Pegylated-asparaginase during induction therapy for adult acute lymphoblastic leukaemia: toxicity data from the UKALL14 trial. Leukemia. 2017;31:58–64.
25. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus conference on acute GVHD grading. Bone Marrow Transplant. 1995;15:825–8.
26. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med. 1980;69:204–17.
27. Socié G, Schmoor C, Bethge WA, Ottinger HD, Stelljes M, Zander AR, et al. Chronic graft-versus-host disease: long-term results from a randomized trial on graft-versus-host disease prophylaxis with or without anti-T-cell globulin ATG-Fresenius. Blood. 2011;117:6375–82.
28. Speziali C, Daly A, Abuhaleeqa M, Nitta J, Abou Mourad Y, Seftel MD, et al. Fludarabine, busulfan, and low-dose TBI conditioning versus cyclophosphamide and TBI in allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia. Leuk Lymphoma. 2019;60:639–48.
29. Peric Z, Labopin M, Peczynski C, Polge E, Cornelissen J, Carpenter B, et al. Comparison of reduced-intensity conditioning regimens in patients with acute lymphoblastic leukemia >45 years undergoing allogeneic stem cell transplantation-a retrospective study by the Acute Leukemia Working Party of EBMT. Bone Marrow Transplant. 2020;55:1560–9.
30. Czyz A, Labopin M, Giebel S, Socié G, Apperley J, Volin L, et al. Cyclophosphamide versus etoposide in combination with total body irradiation as conditioning regimen for adult patients with Ph-negative acute lymphoblastic leukemia undergoing allogeneic stem cell transplant: On behalf of the ALWP of the European Society for Blood and Marrow Transplantation. Am J Hematol. 2018;93:778–85.
31. Greil C, Engelhardt M, Ihorst G, Duque-Afonso J, Shoumariyeh K, Bertz H, et al. Prognostic factors for survival after allogeneic transplantation in acute lymphoblastic leukemia. Bone Marrow Transplant. 2021;56:841–52.
32. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N. Engl J Med. 2010;363:2091–101.
33. Flowers MED, Inamoto Y, Carpenter PA, Lee SJ, Kiem HP, Petersdorf EW, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood. 2011;117:3214–9.
34. Jagasia M, Arora M, Flowers MED, Chao NJ, McCarthy PL, Cutler CS, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood. 2012;119:296–307.
35. Tsirigotis PD, Resnick IB, Avni B, Grisariu S, Stepensky P, Or R, et al. Incidence and risk factors for moderate-to-severe veno-occlusive disease of the liver after allogeneic stem cell transplantation using a reduced intensity conditioning regimen. Bone Marrow Transplant. 2014;49:1389–92.
36. Pavlů J, Labopin M, Zoellner AK, Sakellari I, Stelljes M, Finke J, et al. Allogeneic hematopoietic cell transplantation for primary refractory acute lymphoblastic leukemia: a report from the Acute Leukemia Working Party of the EBMT. Cancer. 2017;123:1965–70.
37. Campana D. Minimal residual disease in acute lymphoblastic leukemia. Semin Hematol. 2009;46:100–6.
38. Gökbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012;120:1868–76.
39. Bourlon C, Lacayo-Leñero D, Inclán-Alarcón SI, Demichelis-Gómez R. Hematopoietic stem cell transplantation for adult philadelphia-negative acute lymphoblastic leukemia in the first complete remission in the era of minimal residual disease. Curr Oncol Rep. 2018;20:36.
40. Bazarbachi AH, Al Hamed R, Labopin M, Afanasyev B, Hamladji RM, Beelen D, et al. Allogeneic stem-cell transplantation with sequential conditioning in adult patients with refractory or relapsed acute lymphoblastic leukemia: a report from the EBMT Acute Leukemia Working Party. Bone Marrow Transplant. 2020;55:595–602.
41. de Labarthe A, Rousselot P, Huguet-Rigal F, Delabesse E, Witz F, Maury S, et al. Imatinib combined with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: results of the GRAAPH-2003 study. Blood. 2007;109:1408–13.
42. Brissot E, Labopin M, Beckers MM, Socié G, Rambaldi A, Volin L, et al. Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. Haematologica. 2015;100:392–9.
43. Pfeifer H, Wassmann B, Bethge W, Dengler J, Bornhäuser M, Stadler M, et al. Randomized comparison of prophylactic and minimal residual disease-triggered imatinib after allogeneic stem cell transplantation for BCR-ABL1-positive acute lymphoblastic leukemia. Leukemia. 2013;27:1254–62.

AUTHOR CONTRIBUTIONS

AB and EB designed the study; ML performed the statistical analyses; AB wrote the manuscript; EB, AA and MM revised the manuscript, and all authors reviewed the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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