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Thiotepa, busulfan and fludarabine conditioning regimen in T-cell replete HLA-haploidentical hematopoietic stem cell transplantation

Rémy Duléry^{*1,2,3}, Juliana Bastos^{*1,4}, Annalisa Paviglianiti¹, Florent Malard^{1,2,3}, Eolia Brissot^{1,2,3}, Giorgia Battipaglia^{1,3}, Clémence Médiavilla^{1,3}, Federica Giannotti¹, Anne Banet¹, Zoé Van de Wyngaert¹, Tounes Ledraa¹, Ramdane Belhocine¹, Simona Sestili¹, Rosa Adaeva¹, Simona Lapusan¹, Françoise Isnard¹, Ollivier Legrand^{1,2,3}, Anne Vekhoff¹, Marie-Thérèse Rubio¹, Annalisa Ruggeri¹ and Mohamad Mohty^{1,2,3}

*equally contributed to this study

1. Department of Hematology and Cellular Therapy, Saint Antoine Hospital, AP-HP, Paris, France
2. INSERM, UMRs 938, Paris, France
3. Sorbonne Universités, Université Pierre et Marie Curie (UPMC) Paris 6, Paris, France
4. Department of Hematology, Sao Joao Hospital, Porto, Portugal

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Correspondence:

Prof. Mohamad Mohty, MD, PhD

Department of Clinical Hematology and Cellular Therapy

Saint-Antoine Hospital

75012 Paris, France

Tel: +33(0)1.49.28.26.20

Fax: +33(0)1.49.28.32.00

E-mail: mohamad.mohty@inserm.fr

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ABSTRACT

We report the outcome of 51 patients receiving an unmanipulated haploidentical hematopoietic stem cell transplantation with post-transplantation cyclophosphamide (PT-Cy) and anti-thymocyte globulin (ATG), from peripheral blood stem cells or bone marrow, after a TBF (thiotepa, busulfan, fludarabine) conditioning regimen. Their median age was 55 years (range, 16-72). Hematological diagnosis comprised acute leukemias (n=31), lymphoid neoplasm (n=12), myeloproliferative neoplasm (n=5) and myelodysplastic syndromes (n=3). Thirty-seven patients (73%) were in complete remission. GVHD prophylaxis consisted of cyclosporine and mycophenolate for all patients, associated with ATG in 39 cases (76.5%). Median time to neutrophil engraftment was 17 days (range, 12-34). The cumulative incidence (CI) of grade II-IV and grade III-IV acute GVHD were 27.5% and 14%, respectively. In patients receiving peripheral blood stem cells graft and ATG prophylaxis, grade II-IV aGVHD occurred in 16% cases. The use of ATG and a lower thiotepa dose (5 vs. 10 mg/kg) were associated with a reduced CI of grade II-IV acute GVHD ($p=0.03$ and $p=0.005$). The 2-year CI of chronic GVHD was 29% and was significantly reduced to 13% with lower thiotepa dose ($p=0.002$). After a median follow-up of 25 months (12-62), the CI of non-relapse mortality, relapse, overall survival, disease-free survival and GVHD-free, relapse-free survival were 20%, 22.5%, 67%, 58% and 51%, respectively. Pre-transplant disease status (complete remission vs. others) was the main factor associated with overall survival, disease-free survival and GVHD-free, relapse-free survival. In conclusion, the TBF conditioning regimen is an appealing platform in the haplo setting with PT-Cy, in terms of engraftment rate, toxicity and disease control. We found no benefit of a thiotepa dose at 10 mg/kg compared to 5 mg/kg. ATG reduced the risk of acute GVHD without comprising the outcomes.

INTRODUCTION

The widespread use of haploidentical (haplo) family donors allows the quick identification of an available donor for the majority of patients who need hematopoietic stem cell transplantation (HSCT). T-cell replete haplo transplants have now become feasible with the use of post-transplant cyclophosphamide (PT-Cy) (1). Recent retrospective studies suggest non-inferior survival outcomes when compared to matched-unrelated 10/10 (MUD), mismatched-unrelated 9/10 or umbilical cord blood donors (2–10). However, the optimal conditioning regimen in the setting of haplo-HSCT remains yet to be defined.

Thiotepa, an alkylating agent, has been used in HSCT with increasing frequency. Its antineoplastic, myelosuppressive and immunosuppressive activities, associated with its ability to penetrate the blood-brain barrier and a good safety profile, make it an attractive agent in the setting of HSCT for hematological malignancies (11–13). The preparative regimen associating the two alkylating agents, thiotepa and busulfan, with fludarabine (TBF), was initially reported in umbilical cord blood transplantation by *Sanz et al.*, as capable of improving engraftment and survival outcomes (14). TBF with myeloblastic (MAC) busulfan dose as conditioning regimen has been compared to busulfan-fludarabine (BF) MAC in acute myeloid leukemia (AML) patients in first remission who were transplanted with matched-sibling (MSD) or MUD donors. Patients who underwent TBF-MAC conditioning had lower relapse than BF-MAC. However, the non-relapse mortality (NRM) was increased with TBF-MAC, which counterbalanced the stronger anti-leukemic effect, thus resulting in similar survival (15).

This regimen was also applied in the haploidentical setting by *Bacigalupo et al.* (thiotepa 10 mg/kg, busulfan 9.6 mg/kg, or 6.4 mg/kg for patients over 60 years or in poor clinical condition, and fludarabine 150 mg/m²), using unmanipulated bone marrow graft and PT-Cy (50 mg/Kg/day) at day +3 and +5 in association with cyclosporine (from day 0) and mycophenolate mofetil (MMF) (from day +6) as graft-versus-host disease (GvHD) prophylaxis (16,17). They reported lower rates of graft rejection (0.7%) than with the ~~reduced intensity (RIC)~~ non-myeloablative Baltimore conditioning regimen (13%) (1), acceptable NRM (18% at 1 year), low risk of acute (aGVHD) and chronic GVHD (cGVHD) and relapse rates comparable to MUD and MSD results.

In this study, peripheral blood was the preferred stem cell source in our center, and we used anti-thymocyte globulin (ATG) in the conditioning regimen. ATG can reduce the GVHD risk in conventional HSCT settings with MSD and MUD (18–20). However, data on the use of ATG are scarce in a haplo setting with PT-Cy. Thus, we aimed to evaluate the clinical outcomes of the patients receiving an unmanipulated haplo-HSCT in our center with TBF conditioning.

PATIENTS AND METHODS

Patient selection

We report a single-center retrospective analysis of all consecutive patients receiving a haplo-HSCT after a TBF conditioning regimen from August 2013 to December 2017 at Saint Antoine Hospital (Paris, France). Fifty-one patients ≥ 16 years old were included. All patients who proceeded to transplantation provided written informed consent for the use of their data for clinical research, in accordance with the modified Declaration of Helsinki and the local Ethical Committee. Patients were stratified according to the disease risk index (DRI) (21).

Conditioning regimens and GVHD prophylaxis

All patients received a TBF conditioning regimen (table 2). According to our center policy, all but 6 patients transplanted in 2013 and 2014 received a total dose of 10 mg/kg of thiotepa (5 mg/kg on days -7 and -6), that was reduced to 5 mg/kg (at day-6) in those transplanted between 2015 and 2017. A total dose of 150mg/m² of fludarabine was administered to all patients (30 mg/m² from day -5 to day -1) and the total dose of intravenous busulfan was 6.4 or 9.6 mg/kg (3.2 mg/kg/day on days -4, -3 or -4, -3, -2) according to the patient's age, comorbidities and clinical condition. The source of stem cells was peripheral blood stem cells (PBSC) or bone marrow (BM), with no ex-vivo T-cell depletion.

The dose of PT-Cy was adjusted according to the stem cell source. BM recipients were scheduled to receive 1 dose of PT-Cy (50 mg/kg/day) at day+3. PBSC recipients were given 2 doses of PT-Cy at days +3 and +5. GVHD prophylaxis consisted of cyclosporine A (starting from day-3 as a 3 mg/kg/day as continuous intravenous infusion and adjusting to blood levels) and MMF (starting from day +6 until day +35 at 15 mg/kg/12h intravenously) in all patients. In the absence of GVHD, cyclosporine A was tapered over 4 to 8 weeks from day +60 in high-risk diseases and day+90 in intermediate-risk. Patients could receive rabbit ATG (Thymoglobulin, Genzyme) at a total dose of 5 mg/kg (between 2013 and 2014) or 2.5 mg/kg (between 2015 and 2017). aGVHD and cGVHD were diagnosed and graded according to standard criteria (22,23).

Supportive care

Granulocyte colony-stimulating factor was given from day+6 until neutrophil engraftment. Mesna and hyperhydration were administered for prevention of the uroepithelial damage of Cy, and prophylactic clonazepam was given in association with busulfan. Prophylaxis of veno-occlusive hepatic disease

(VOD) was performed with orally applied ursodeoxycholic acid and low-dose unfractionated heparin. Patients at high-risk of VOD according to the EBMT criteria received defibrotide instead of heparin (24,25).

Antimicrobial prophylaxis consisted of valacyclovir or acyclovir at the start of the conditioning regimen. After engraftment, patients received amoxicilline and atovaquone or trimethoprim-sulfamethoxazole. Primary antifungal prophylaxis was not administered routinely. Patients were monitored weekly by real time polymerase chain reaction (PCR) for cytomegalovirus (CMV), human herpesvirus 6 (HHV6), Epstein Barr virus (EBV) and toxoplasma until day+100. Monitoring of BK virus in blood and urine was done according to clinical signs, as we previously reported (26).

Statistical analysis

Continuous variables were recorded as median and range and were compared using the Mann-Whitney *U* test. Qualitative variables were recorded as frequency and percent, and were compared using the chi-square test. Overall survival (OS), defined as the time from transplant to death from any cause, disease-free survival (DFS), defined as the time from transplant to relapse or progression or death from any cause, whichever came first, and GVHD-free, relapse-free survival (GRFS) (27), defined as being alive with neither grade III-IV aGVHD, severe cGVHD nor disease relapse were calculated by the Kaplan-Meier method, and the differences between groups were compared using the log-rank test. Neutrophil engraftment was defined as an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9/L$ for 3 consecutive days, and platelet engraftment was defined as achieving platelet count $\geq 20 \times 10^9/L$ unsupported by platelet transfusions for 7 days. Full donor chimerism was measured by PCR and defined as $\geq 95\%$ leucocytes of donor origin in the peripheral blood. Engraftment, GVHD, relapse, and NRM were calculated using the cumulative incidence (CI) method and analyzed in a time-dependent fashion. For acute and chronic GVHD or relapse, death was considered a competing risk of the event. For NRM, the competing event was relapse. All variables having a significance level of $p < 0.10$ in univariate analysis were introduced in a multivariable Cox regression model, with backward selection (28). Interactions between main effect and adjusting were tested, and variables with significant interaction were excluded from the final model. Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were computed and $p < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS 22 (SPSS Inc./IBM, Armonk, NY) and R 3.2 (R Development Core Team, Vienna, Austria) software packages.

RESULTS

Patients, disease and transplant characteristics

Patients and disease characteristics are summarized in table 1. Median age at HSCT was 55 years (range, 16-72). Patients had AML (n=23), acute lymphoblastic leukemia (ALL; n=8), lymphoid neoplasm (n=12), myeloproliferative neoplasm (n=5) and myelodysplastic syndrome (n=3). Thirty-seven patients were in complete remission (CR) at transplant (27 in first CR, CR1), 6 in partial remission and 8 had progressive disease. DRI stratified patients in intermediate (n=35), high (n=14) and very-high (n=2). Nine patients had failed a previous allogeneic (n=3) or autologous (n=6) transplantation. Twenty-seven patients received a dose of 6.4 mg/kg of busulfan (table 2). Thirty-nine patients received ATG associated to the conditioning regimen, at a dose of 2.5 mg/kg (n=29) or 5mg/kg (n=10). BM recipients (n=9) received mainly (n=8) 1 dose of PT-Cy (50 mg/kg/day) at day+3. PBSC recipients (n=42) were given 2 doses of PT-Cy at days +3 and +5, except for 2 patients (one with pre-transplant left ventricular ejection fraction of 40% and another who received a graft with a low CD34+ cells count) (table 2). Nine patients received defibrotide prophylaxis for VOD.

Engraftment

Of the 51 evaluable patients, all achieved neutrophil engraftment, within a median time of 17 days (range, 12-34 days). Platelet counts $> 20 \times 10^9/L$ were reached in 48 patients within a median time of 18 days (range, 7-130), with 7 non-evaluable patients (due to transfusion support at superior platelet number cutoffs) (table 3). Forty-five patients (88%) had a platelet count recovery to $>50 \times 10^9/L$ within a median time of 28 days (range, 9-406). All patients had full donor chimerism at day+30, +60 and +90, except for one patient presenting a 94% donor chimerism at day+30, and a full donor chimerism at day+60 and +90. No graft rejection was observed. Four patients received a successfully CD34+cell boost from the same donor for poor graft function, after initial engraftment, and achieved neutrophil recovery with in a period of 4, 5, 7 and 11 months post-HSCT, respectively.

Transplant-related complications and infections

Transplant-related complications and infections are outlined in table 4. VOD developed in two patients (4%) and was fatal in one. Signs of transplant-associated microangiopathy were observed in 8 patients (16%), requiring plasma exchanges in one patient and responding to cyclosporine withdrawal alone in the other patients. Grade 3-4 mucositis occurred in 16 patients (31%) and hepatic, cardiac, or neurological toxicities of grade ≥ 3 after the conditioning chemotherapy were observed in 5, 4 and 1

patients, respectively. At last follow-up, hemorrhagic cystitis associated with BK virus reactivation occurred in 24 patients (47%) and required bladder irrigation in 13 (26%). Four patients received cidofovir and 9 polyvalent intravenous immunoglobulins. CMV reactivation occurred in 34 patients (67%). All patients received preemptive therapy with foscarnet or ganciclovir (according to hematopoietic recovery and renal function). One patient developed CMV retinitis 9 months after HSCT, which resolved with intraocular injections of ganciclovir. EBV reactivation (viral load > 5000 UI/mL) occurred in 30 patients (59%) and was preemptively treated by rituximab. Two patients (4%) had an EBV-related post-transplant lymphoproliferative disease (PTLD), treated successfully by rituximab alone in one case and chemotherapy in the second. HHV6 reactivation occurred in 31/46 evaluable patients (67%). Two patients developed symptomatic adenovirus infection and 5 had varicella-zoster virus reactivation. Bacteremia occurred in 33 patients (64%), including 16 (31%) *Staphylococcus* positive blood culture and 19 (37%) catheter-related bloodstream infections. Invasive fungal infection was documented in 5 patients (10%), including possible or probable invasive aspergillosis in 2 patients (4%).

The use of ATG and ATG doses were not significantly associated with an increased incidence of infection. In patients receiving ATG, CMV, EBV and HHV6 reactivations occurred in 67%, 59% and 62% cases, respectively. BK virus hemorrhagic cystitis developed in 38% patients and required irrigations in 23%. Bacteremia and invasive fungal infections occurred in 64% and 8% patients respectively.

Graft-versus-host disease

Acute GVHD

At day 100, the CI of grade II-IV aGVHD was 27.5%. Grade III-IV aGVHD occurred in 7 (14%) patients (table 3). Using PBSC graft and ATG prophylaxis, grade II-IV aGVHD and grade III-IV aGVHD occurred in 5/31 (16%) and 3/31 (10%) patients, respectively. All patients with aGVHD grade ≥ 2 were treated with methylprednisolone 1-2 mg/kg/day as standard first line therapy. Eight patients (16%) were steroid-refractory and received second-line treatment consisting of weekly low dose methotrexate (n=6) and/or extracorporeal photopheresis (n=3) according to the GVHD organ involvement. A third line of treatment with anti-CD25 monoclonal antibody (inolimomab) was administered to 2 patients with refractory GVHD.

In univariate analysis (table 5), the CI of grade II-IV aGVHD was significantly lower in patients receiving ATG (21% versus 50%, p=0.03). There was with no significant difference according to the dose of ATG (p=0.09). The CI of grade II-IV aGVHD was significantly reduced with 5 mg thiotepa as

compared to 10 mg (16% vs. 57%, $p=0.005$). Patients who underwent transplant after 2015 had also a lower CI of aGVHD ($p=0.02$). No factor significantly influenced aGVHD in multivariate analysis (table 6).

Chronic GVHD

The overall CI of cGVHD was 29% at 2 years. Six patients (12%) had moderate to severe cGVHD forms (table 3). The organs affected were: skin ($n=12$), mucosa ($n=11$), genitals ($n=3$), gastrointestinal tract ($n=2$), eyes ($n=6$), liver ($n=1$) or lungs ($n=4$). Four patients died during the follow-up period, 2 from relapse and 2 from infection. No significant benefit of ATG in reducing the CI of cGVHD was observed. The CI of cGVHD was significantly reduced in intermediate-DRI patients compared to high- and very high-risk patients (18% vs. 47%, $p=0.02$) and in patients who received 5 mg/kg thiotepa as compared to 10 mg/kg (13% vs. 57%, $p=0.002$). However, these factors were not significant in multivariate analysis (table 6).

Relapse and NRM

The relapse incidence (RI) was 4% at day+100 and 23% at 2 years. Relapse or disease progression occurred in 11 patients, within a median time of 171 days (range, 20-559): 5 AML patients with high risk features, 2 ALL, 1 HTLV1+ acute T-cell lymphoma, 1 Hodgkin lymphoma in 3rd partial remission, 1 Sezary syndrome with progressive disease at transplantation and 1 refractory double hit diffuse large B-cell lymphoma.

At last follow-up, 4 out of the 11 patients experiencing relapse were in remission and 7 died. Ten patients received prophylactic therapy to prevent relapse: azacytidine in 2 patients with AML, sorafenib in 4 AML patients with internal tandem duplications of the Fms-like tyrosine kinase 3, dasatinib in one patient with AML secondary to myeloid chronic leukemia, nilotinib in one patient with Philadelphia positive ALL and DLI in two other patients (refractory Hodgkin's lymphoma and biclonal ALL). One out of these 10 patients has experienced further relapse during the follow-up period after sorafenib withdrawal.

The CI of NRM was 6% at day+100 and 20% at 2 years. At last-follow-up, 17 patients died. The main causes of death were disease relapse ($n=7$), GVHD ($n=7$), infection ($n=2$) and VOD ($n=1$). ATG was not significantly associated with the RI or the NRM, both in univariate and multivariate analyses. Patients in CR had a lower NRM (HR 5.67, 95% CI 1.52-21.16, $p=0.01$) in multivariate analysis (table 6).

Survival, DFS and GRFS

With a median follow-up of 25 months (range, 12 – 62 months), the GRFS, DFS and OS were 51%, 58% and 67%, respectively (figure 1). In univariate analysis, the DFS and OS were 63% and 74% in patients with acute leukemia as compared to 47% and 53% in the patients with other diseases, respectively ($p=0.09$ and $p=0.06$). Overall survival and DFS were significantly higher in patients in CR at transplant compared to those who were not (76% vs. 43%, $p=0.003$ and 63% vs. 43%, $p=0.04$, respectively) (figure 2). In multivariate analysis (table 6), CR disease status was independently associated with a better GRFS (HR 3.04, 95%CI 1.27-7.26, $p=0.01$), DFS (HR 3.32, 95%CI 1.31-8.42, $p=0.01$) and OS (HR 5.19, 95%CI 1.90-14.17, $p=0.001$). Patients who underwent transplant after 2015 had also a higher DFS (HR 3.64 95%CI 1.14-11.63, $p=0.003$).

DISCUSSION

Findings from this study confirm that the TBF conditioning regimen is feasible in a haplo setting with PT-Cy and allows for sustained engraftment, manageable toxicity and efficient disease control. The use of ATG reduced the CI of aGVHD and did not seem to increase the incidences of infectious complications or relapse. Disease status before HSCT remained the most important factor associated with GRFS, DFS and OS.

Neutrophil engraftment occurred in all patients, which compares favorably to the reported 13% graft failure rate with the Baltimore RIC-regimen (1). The median time to neutrophil recovery was similar to Bacigalupo et al.'s study on TBF conditioning regimen in haplo using BM graft (median 17 days, range 13-32) (16), and shorter than with the Baltimore RIC regimen using PBSC graft (median 20 days, range 14-27) (29).

Our results on bacterial and fungal infections are in line with previous reports in a haplo setting with PT-Cy (1,16,17,30–34). However, viral reactivations seemed to have occurred more frequently in our cohort, with CMV and EBV reactivations receiving preemptive therapy in 67% and 59% of patients, respectively. The incidence of PTLD was 4%. Previous reports described incidences of CMV reactivation of 38% to 81%, EBV reactivation of 0% to 34% and PTLD of 0% to 3% (1,16,17,30–34). The incidence of BK virus hemorrhagic cystitis (47%), which required bladder irrigation in half of these patients, was in line with the incidence of 11% to 75% reported in other studies (26,30,31,34). The use of ATG in our study may explain the higher incidence of viral reactivations found in this population. Indeed, ATG is known to increase the risk of infection after HSCT, especially EBV reactivations (18–20). Nevertheless, no significant difference was observed in our study between patients receiving ATG and those who did not in terms of incidence of viral reactivations.

The CI of cGVHD in our study was in line with previous studies, which reported a CI ranging from 7% to 56% (1,2,9,16,17,31–33,35,35–37). However, the CI of grade II-IV aGVHD was higher in our patients than in the study by Bacigalupo et al. on MAC in a haplo setting with PT-Cy (27.5% vs. 18%). There may be two explanations: (1) we used PBSC in the majority of our patients and (2) we used only TBF conditioning regimen, whereas fludarabine-TBI was used in 38% of patients in Genova (16). Indeed, our results are in line with the reported CI of grade II-IV aGVHD in MAC haplo with PBSC, which ranges from 15% to 43% (2,32,34,35). Three retrospective studies have confirmed that the use of PBSC increases the risk of aGVHD in haplo HSCT with PT-Cy (36–38), and the CI was higher with PBSC, but not significantly different than with BM in another study (31). Interestingly, a low thiotepa dose at 5 mg/kg reduced significantly the risk of aGVHD and cGVHD without compromising the outcomes. Based on these data, we found no benefit of a thiotepa dose at 10 mg/kg compared to 5 mg/kg. Our results are in line with previous reports with melphan-based conditioning regimen, which used thiotepa dose at 5 mg/kg and showed that thiotepa dose at 10mg/kg is not needed to allow for disease control (39,40).

Our data show for the first time the benefit of ATG on aGVHD in a haplo setting with PT-Cy. Patients receiving both ATG and PT-Cy in our study had a similar CI of aGVHD with PBSC than in studies reporting BM haplo without ATG. In contrast with our study, ATG had no impact on GVHD and a detrimental role on NRM, leukemia-free survival and OS in a trial including patients with secondary AML undergoing unmanipulated haplo HSCT, compared to patients receiving PT-Cy without ATG. However, patients receiving both ATG and PT-Cy were excluded from that study (41). We recently published a series of patients undergoing HSCT for the treatment of refractory hematologic malignancies after sequential conditioning with thiotepa and ATG (10). There was no significant difference in terms of toxicity and outcomes between haplo with PT-Cy and MRD patients. Compared with MUD, the outcomes were improved in haplo in terms of incidence of aGVHD and GVHD-free, relapse-free survival. Despite the use of ATG in patients with progressive disease, the 2-year RI was 36% in haplo patients. This is comparable to the reported RIs of 33% in patients with active disease who received MAC Haplo without ATG and 37% in those treated with the FLAMSA regimen (17,42). Overall, ATG in haplo with PT-Cy seems to reduce the risk of aGVHD without compromising outcomes. Due to the limited number of patients who did not receive ATG in our study, these results need to be validated in larger cohorts and in well-designed prospective randomized trials.

The NRM in our study is in the higher range of the reported NRM in previous studies on haplo with PT-Cy, in which 1-year NRM ranged from 10% to 22% (1–3,9,9,16,17,31–33,38,43). However, our study included only 53% patients in CR1. The NRM was significantly reduced to 14% in patients in CR. Our results are in line with the 26% incidence NRM at 6-months reported with TBF haplo in patients who were not in CR (17). For the whole patient group, the outcomes compare favorably to the

results of haplo with PT-Cy using the Baltimore RIC regimen (1). The TBF conditioning regimen allowed for favorable outcomes in patients in CR, in line with previous studies on MAC haplo. However, our data in patients in partial response or progressive disease, and the results of recent studies, suggest that those patients would benefit more from a sequential approach including early post-transplantation immune-intervention combining prophylactic DLI with preventive targeted therapies (10,44,45).

In conclusion, our study confirms that the TBF conditioning regimen is an appealing platform in a haplo setting with PT-Cy. Engraftment was sustained in all patients, toxicities were manageable and similar to those reported with other MAC in haplo. A thiotepa dose of 10 mg/kg was more toxic than 5 mg/kg, mainly because of the induction of acute GVHD, with no apparent benefit in terms of disease control. Although the use of PBSC may have increased the CI of aGVHD, the CI of cGVHD and the outcomes were similar to those with BM. Most notably, the addition of ATG seems effective for reducing the CI of aGVHD without increasing the RI or the risk of infectious complications.

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Author contributions

M Mohty: designed the study, supervised research, analyzed data, and wrote the manuscript;

J Bastos and R Dulery: designed the study, collected, assembled and analyzed data, performed statistical analysis, and wrote the manuscript;

A Ruggeri and A Paviglianiti: analyzed data, performed statistical analysis and commented on the manuscript;

F Malard, E Brissot, C Médiavilla, F Giannotti, G Battipaglia, A Banet, Z Van de Wyngaert, T Ledraa, R Belhocine, S Sestili, A Vekhoff, R Adaeva, F Isnard, O Legrand, MT Rubio: recruited patients and helped writing and commenting on the manuscript;

All authors approved submission of the manuscript for publication purposes.

REFERENCES

1. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. juin 2008;14(6):641-50.
2. Bashey A, Zhang X, Jackson K, Brown S, Ridgeway M, Solh M, et al. Comparison of Outcomes of Hematopoietic Cell Transplants from T-Replete Haploidentical Donors Using Post-Transplantation Cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 Allele-Matched Unrelated Donors and HLA-Identical Sibling Donors: A Multivariable Analysis Including Disease Risk Index. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. janv 2016;22(1):125-33.
3. Raiola AM, Dominietto A, di Grazia C, Lamparelli T, Gualandi F, Ibatci A, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. oct 2014;20(10):1573-9.
4. Burroughs LM, O'Donnell PV, Sandmaier BM, Storer BE, Luznik L, Symons HJ, et al. Comparison of outcomes of HLA-matched related, unrelated, or HLA-haploidentical related hematopoietic cell transplantation following nonmyeloablative conditioning for relapsed or refractory Hodgkin lymphoma. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. nov 2008;14(11):1279-87.
5. Ringdén O, Labopin M, Ciceri F, Velardi A, Bacigalupo A, Arcese W, et al. Is there a stronger graft-versus-leukemia effect using HLA-haploidentical donors compared with HLA-identical siblings? *Leukemia*. févr 2016;30(2):447-55.
6. Ruggeri A, Labopin M, Sanz G, Piemontese S, Arcese W, Bacigalupo A, et al. Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia. *Leukemia*. sept 2015;29(9):1891-900.
7. Martínez C, Gayoso J, Canals C, Finel H, Peggs K, Dominietto A, et al. Post-Transplantation Cyclophosphamide-Based Haploidentical Transplantation as Alternative to Matched Sibling or Unrelated Donor Transplantation for Hodgkin Lymphoma: A Registry Study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. *J Clin Oncol Off J Am Soc Clin Oncol*. 20 oct 2017;35(30):3425-32.
8. Gauthier J, Poiré X, Gac A-C, Leclerc M, Guillaume T, Chalandon Y, et al. Better outcome with haploidentical over HLA-matched related donors in patients with Hodgkin's lymphoma undergoing allogeneic haematopoietic cell transplantation-a study by the Francophone Society of Bone Marrow Transplantation and Cellular Therapy. *Bone Marrow Transplant*. 12 janv 2018;
9. Ciurea SO, Zhang M-J, Bacigalupo AA, Bashey A, Appelbaum FR, Aljitan OS, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood*. 20 août 2015;126(8):1033-40.
10. Duléry R, Ménard A-L, Chantepie S, Cheikh JE, François S, Delage J, et al. Sequential

Conditioning with Thiotepa in T Cell- Replete Hematopoietic Stem Cell Transplantation for the Treatment of Refractory Hematologic Malignancies: Comparison with Matched Related, Haplo-Mismatched, and Unrelated Donors. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. 11 janv 2018;

11. Bacigalupo A, Raiola AM, Lamparelli T, Gualandi F, Occhini D, Bregante S, et al. Thiotepa-based reduced intensity conditioning regimen: a 10 year follow up. *Bone Marrow Transplant*. déc 2007;40(11):1091-3.

12. Eder S, Beohou E, Labopin M, Sanz J, Finke J, Arcese W, et al. Thiotepa-based conditioning for allogeneic stem cell transplantation in acute lymphoblastic leukemia-A survey from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Am J Hematol*. janv 2017;92(1):18-22.

13. Heideman RL, Cole DE, Balis F, Sato J, Reaman GH, Packer RJ, et al. Phase I and pharmacokinetic evaluation of thiotepa in the cerebrospinal fluid and plasma of pediatric patients: evidence for dose-dependent plasma clearance of thiotepa. *Cancer Res*. 1 févr 1989;49(3):736-41.

14. Sanz J, Boluda JCH, Martín C, González M, Ferrá C, Serrano D, et al. Single-unit umbilical cord blood transplantation from unrelated donors in patients with hematological malignancy using busulfan, thiotepa, fludarabine and ATG as myeloablative conditioning regimen. *Bone Marrow Transplant*. oct 2012;47(10):1287-93.

15. Saraceni F, Labopin M, Hamladji R-M, Mufti G, Socié G, Shimoni A, et al. Thiotepa-busulfan-fludarabine compared to busulfan-fludarabine for sibling and unrelated donor transplant in acute myeloid leukemia in first remission. *Oncotarget*. 9 janv 2018;9(3):3379-93.

16. Bacigalupo A, Dominietto A, Ghiso A, Di Grazia C, Lamparelli T, Gualandi F, et al. Unmanipulated haploidentical bone marrow transplantation and post-transplant cyclophosphamide for hematologic malignancies following a myeloablative conditioning: an update. *Bone Marrow Transplant*. juin 2015;50 Suppl 2:S37-39.

17. Raiola AM, Dominietto A, Ghiso A, Di Grazia C, Lamparelli T, Gualandi F, et al. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. janv 2013;19(1):117-22.

18. Baron F, Mohty M, Blaise D, Socié G, Labopin M, Esteve J, et al. Anti-thymocyte globulin as graft-versus-host disease prevention in the setting of allogeneic peripheral blood stem cell transplantation: a review from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica*. 2017;102(2):224-34.

19. Devillier R, Labopin M, Chevallier P, Ledoux M-P, Socié G, Huynh A, et al. Impact of antithymocyte globulin doses in reduced intensity conditioning before allogeneic transplantation from matched sibling donor for patients with acute myeloid leukemia: a report from the acute leukemia working party of European group of Bone Marrow Transplantation. *Bone Marrow Transplant*. 12 janv 2018;

20. Storek J, Mohty M, Boelens JJ. Rabbit anti-T cell globulin in allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. juin 2015;21(6):959-70.
21. Armand P, Gibson CJ, Cutler C, Ho VT, Koreth J, Alyea EP, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. *Blood*. 26 juill 2012;120(4):905-13.
22. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. juin 1995;15(6):825-8.
23. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. mars 2015;21(3):389-401.e1.
24. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant*. juill 2016;51(7):906-12.
25. Picod A, Bonnin A, Battipaglia G, Giannotti F, Ruggeri A, Brissot E, et al. Defibrotide for Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease Prophylaxis in High-Risk Adult Patients: A Single-Center Experience Study. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. 1 mars 2018;
26. Ruggeri A, Roth-Guepin G, Battipaglia G, Mamez A-C, Malard F, Gomez A, et al. Incidence and risk factors for hemorrhagic cystitis in unmanipulated haploidentical transplant recipients. *Transpl Infect Dis Off J Transplant Soc*. déc 2015;17(6):822-30.
27. 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*. avr 2016;51(4):610-1.
28. Fine J, Gray RJ. A Proportional Hazards Model for the Subdistribution of A Competing Risk. *J Am Stat Assoc*. 1999;94:496-509.
29. Castagna L, Crocchiolo R, Furst S, Bramanti S, El Cheikh J, Sarina B, et al. Bone marrow compared with peripheral blood stem cells for haploidentical transplantation with a nonmyeloablative conditioning regimen and post-transplantation cyclophosphamide. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. mai 2014;20(5):724-9.
30. Crocchiolo R, Bramanti S, Vai A, Sarina B, Miner R, Casari E, et al. Infections after T-replete haploidentical transplantation and high-dose cyclophosphamide as graft-versus-host disease prophylaxis. *Transpl Infect Dis Off J Transplant Soc*. avr 2015;17(2):242-9.
31. Castagna L, Crocchiolo R, Furst S, Bramanti S, El Cheikh J, Sarina B, et al. Bone marrow compared with peripheral blood stem cells for haploidentical transplantation with a nonmyeloablative conditioning regimen and post-transplantation cyclophosphamide. *Biol Blood*

Marrow Transplant J Am Soc Blood Marrow Transplant. mai 2014;20(5):724-9.

32. Cieri N, Greco R, Crucitti L, Morelli M, Giglio F, Levati G, et al. Post-transplantation Cyclophosphamide and Sirolimus after Haploidentical Hematopoietic Stem Cell Transplantation Using a Treosulfan-based Myeloablative Conditioning and Peripheral Blood Stem Cells. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. août 2015;21(8):1506-14.

33. Di Stasi A, Milton DR, Poon LM, Hamdi A, Rondon G, Chen J, et al. Similar transplantation outcomes for acute myeloid leukemia and myelodysplastic syndrome patients with haploidentical versus 10/10 human leukocyte antigen-matched unrelated and related donors. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. déc 2014;20(12):1975-81.

34. Solomon SR, Sizemore CA, Sanacore M, Zhang X, Brown S, Holland HK, et al. Haploidentical Transplantation Using T Cell Replete Peripheral Blood Stem Cells and Myeloablative Conditioning in Patients with High-Risk Hematologic Malignancies Who Lack Conventional Donors is Well Tolerated and Produces Excellent Relapse-Free Survival: Results of a Prospective Phase II Trial. Biol Blood Marrow Transplant. déc 2012;18(12):1859-66.

35. Solomon SR, Sizemore CA, Sanacore M, Zhang X, Brown S, Holland HK, et al. Total Body Irradiation-Based Myeloablative Haploidentical Stem Cell Transplantation Is a Safe and Effective Alternative to Unrelated Donor Transplantation in Patients Without Matched Sibling Donors. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. juill 2015;21(7):1299-307.

36. Ruggeri A, Labopin M, Bacigalupo A, Gülbas Z, Koc Y, Blaise D, et al. Bone marrow versus mobilized peripheral blood stem cells in haploidentical transplants using posttransplantation cyclophosphamide. Cancer. 1 avr 2018;124(7):1428-37.

37. O'Donnell PV, Eapen M, Horowitz MM, Logan BR, DiGilio A, Brunstein C, et al. Comparable outcomes with marrow or peripheral blood as stem cell sources for hematopoietic cell transplantation from haploidentical donors after non-ablative conditioning: a matched-pair analysis. Bone Marrow Transplant. 2016;51(12):1599-601.

38. Bashey A, Zhang M-J, McCurdy SR, St Martin A, Argall T, Anasetti C, et al. Mobilized Peripheral Blood Stem Cells Versus Unstimulated Bone Marrow As a Graft Source for T-Cell-Replete Haploidentical Donor Transplantation Using Post-Transplant Cyclophosphamide. J Clin Oncol Off J Am Soc Clin Oncol. 10 sept 2017;35(26):3002-9.

39. Majolino I, Davoli M, Carnevalli E, Locasciulli A, Di Bartolomeo P, Scimè R, et al. Reduced intensity conditioning with thiotepa, fludarabine, and melphalan is effective in advanced multiple myeloma. Leuk Lymphoma. avr 2007;48(4):759-66.

40. Brammer JE, Khouri I, Gaballa S, Anderlini P, Tomuleasa C, Ahmed S, et al. Outcomes of Haploidentical Stem Cell Transplantation for Lymphoma with Melphalan-Based Conditioning. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 20 oct 2015;

41. Li Z, Labopin M, Ciceri F, Blaise D, Tischer J, Ehninger G, et al. Haploidentical transplantation outcomes for secondary acute myeloid leukemia: ALWP of the EBMT study. Am J Hematol [Internet].

[cité 30 mars 2018]; Disponible sur: <https://onlinelibrary-wiley-com.gate2.inist.fr/doi/abs/10.1002/ajh.25087>

42. Schmid C, Schleuning M, Schwerdtfeger R, Hertenstein B, Mischak-Weissinger E, Bunjes D, et al. Long-term survival in refractory acute myeloid leukemia after sequential treatment with chemotherapy and reduced-intensity conditioning for allogeneic stem cell transplantation. *Blood*. 1 août 2006;108(3):1092-9.
43. Kasamon YL, Bolaños-Meade J, Prince GT, Tsai H-L, McCurdy SR, Kanakry JA, et al. Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults. *J Clin Oncol Off J Am Soc Clin Oncol*. 1 oct 2015;33(28):3152-61.
44. Battipaglia G, Ruggeri A, Massoud R, El Cheikh J, Jestin M, Antar A, et al. Efficacy and feasibility of sorafenib as a maintenance agent after allogeneic hematopoietic stem cell transplantation for Fms-like tyrosine kinase 3-mutated acute myeloid leukemia. *Cancer*. 1 août 2017;123(15):2867-74.
45. Goodyear OC, Dennis M, Jilani NY, Loke J, Siddique S, Ryan G, et al. Azacitidine augments expansion of regulatory T cells after allogeneic stem cell transplantation in patients with acute myeloid leukemia (AML). *Blood*. 5 avr 2012;119(14):3361-9.

Table 1. Patient and donor characteristics at transplant

	Total (n=51)
Recipient age , median (range)	55 (16-72)
Gender (male/female), n (%)	32 (63%)/ 19 (38%)
Diagnosis , n (%)	
Acute Leukemia	31 (61%)
AML	23 (45%)
ALL	8 (16%)
Lymphoid neoplasm	12 (24%)
NHL (DLBCL, MCL, T NOS, ATL)	7 (14%)
HL	3 (6%)
Pro-lymphocytic leukemia	2 (4%)
Myeloproliferative neoplasm	5 (10%)
Myelodysplastic syndromes	3 (6%)
Disease status at transplant , n (%)	
Complete remission	37 (72.5%)
CR1	27 (53%)
CR \geq 2	10 (19.5%)
Partial remission	6 (12%)
Active/progressive disease	8 (15.5%)
Disease risk index , n (%)	
Intermediate	35 (68.5%)
High	14 (27.5%)
Very-high	2 (4%)
Number of previous therapy lines , n (%)	
0	2 (4%)
1	28 (55%)
2	10 (19.5%)
\geq 3	11 (21.5%)
Previous autologous HSCT , n (%)	6 (12%)
Previous allogeneic HSCT , n (%)	3 (6%)
Donor-recipient CMV serostatus match , n (%)	
Donor negative/recipient negative	13 (25.5%)
Donor negative/recipient positive	11 (21.5%)
Donor positive/recipient negative	1 (2%)
Donor positive/recipient positive	26 (51%)
Stem cell source , n (%)	
PBSC	42 (82%)
BM	9 (18%)
Median CD34+/Kg (range)	5 (1.02-9.74)

Abbreviations: AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, NHL: Non-Hodgkin lymphoma, DLBCL: Diffuse large B-cell lymphoma, MCL: Mantle cell lymphoma, T NOS: lymphoma T not otherwise specified, ATLL: acute T-cell leukemia/lymphoma, CR: complete remission, HSCT: hematopoietic stem cell transplantation, CMV: cytomegalovirus, PBSC: peripheral blood stem cells, BM: Bone marrow.

Table 2. Conditioning regimen

	n (%)
Thiotepa and busulfan doses	
T1B2F	26 (51%)
T1B3F	12 (23.5%)
T2B2F	1 (2%)
T2B3F	12 (23.5%)
ATG	
No	12 (23.5%)
Yes	39 (76.5%)
2.5 mg/kg	29 (57%)
5 mg/kg	10 (19.5%)
PT-Cy	
No	0 (0%)
Yes	51 (100%)
PT Cy D+3 only	10 (19.5%)
PT Cy D+3 and D+5	41 (80.5%)

Abbreviations: T1B2F (thiotepa 5mg/kg/day for 1 day, Busulfan 3.2mg/kg/day for 2 days, fludarabine 150mg/m²); T1B3F (thiotepa 5mg/kg/day for 1 day, Busulfan 3.2mg/kg/day for 3 days, fludarabine 150mg/m²); T2B3F (thiotepa 5mg/kg/day for 2 days, Busulfan 3.2mg/kg/day for 3 days, fludarabine 150mg/m²); ATG: Antithymocyte globulin, PT-Cy: post-transplant cyclophosphamide, D: Day.

Table 3. Engraftment and clinical outcomes

	Total (n=51)
Median time to neutrophil > 0.5 x10⁹/L, day (range)	17 (12-34)
Median time to platelet > 20 x10⁹/L, day (range)	18 (7-130)
Platelet > 50x10⁹/L, n (%)	45 (88%)
Median time to Platelet >50x10⁹/L, day (range)	28 (9-406)
Acute GVHD, n(%)	
Grade II-IV	14 (27.5%)
Grade III-IV	7 (13.5%)
Systemic steroid treatment for acute GVHD	14 (27.5%)
Steroid refractory acute GVHD	8 (16%)
2-year CI of Chronic GVHD, n (%)	15 (29%)
Mild	9 (17.5%)
Moderate	2 (4%)
Severe	4 (7.5%)
NRM	
CI at day+100, % (confidence interval)	6% (1.9-17.8)
CI at 2 years, % (confidence interval)	20% (11.2-34.4)
Relapse	
CI at day+100, % (confidence interval)	4% (1.0-15.5)
CI at 2 years, % (confidence interval)	22.5% (13.2-38.5)
2-year OS, % (confidence interval)	67% (60-74)
2-year DFS, % (confidence interval)	58% (51-65)
Median follow-up (range)	25 months (12-62)

Abbreviations: GVHD: graft-versus-host disease, CI: cumulative incidence, OS: overall survival, DFS: disease free survival.

Table 4. Transplant-related complications and infections

	n (%)
Mucositis	
Grade I-II	28 (55%)
Grade III-IV	16 (31%)
Organ toxicity grade ≥ 3	
Hepatic	5 (10%)
Cardiac	4 (8%)
Neurological	1 (2%)
Pulmonary or renal	0
VOD	2 (4%)
TMA	8 (16%)
Viral infections	
BK virus hemorrhagic cystitis	24 (47%)
Grade 2	11 (21.5%)
Grade 3	11 (21.5%)
Grade 4	2 (4%)
CMV reactivation	27 (73%)
EBV reactivation > 5000 UI/mL	30 (59%)
EBV-related lymphoproliferative disease	2 (4%)
HHV6 reactivation (46 evaluable patients)	31 (67%)
Adenovirus infection	2 (4%)
Varicella Zoster reactivation	5 (10%)
Bacteriemia	33 (64%)
Gram positive	23 (45%)
Gram negative	10 (20%)
Severe sepsis during aplasia	9 (18%)
Sepsis requiring ICU admission	8 (16%)
Invasive fungal infections	
Aspergillus spp	2 (4%)
Candida spp	1 (2%)
Fusarium	1 (2%)
Mucor	1 (2%)
Pneumocystis pneumonia	2 (4%)
Toxoplasmosis	2 (4%)

Abbreviations: VOD: veno-occlusive disease, TMA: thrombotic microangiopathy, CMV:

cytomegalovirus, EBV: Epstein-Barr virus, HHV6: human herpesvirus 6, ICU: intensive care unit.

Table 5. Univariate analysis

		DFS at 24 months			OS at 24 months			2-year RI		
Variables	Value	%	Error +/-	p	%	Error +/-	p	%	95% CI	p
Recipient age	<=54.9 years	49	10	0.2	65	10	0.57	28	14.5 - 53.8	0.35
	>54.9 years	68	9		68	10		16	6.4 - 40.2	
Recipient sex	male	57	9	0.93	72	8	0.85	24	12 - 47.7	0.86
	female	58	11		62	11		21	8.5 - 52	
Diagnosis	others	47	12	0.09	53	12	0.06	24	9.6 - 57.5	0.72
	Acute leukemia	63	9		74	8		22	11.2 - 44	
Disease status	others	43	13	0.04	43	13	0.003	21	7.5 - 61.5	0.96
	CR	63	8		76	8		23	12.2 - 43.7	
DRI	intermediate	63	8	0.37	70	8	0.3	20	10.2 - 39.3	0.71
	high/very-high	48	13		61	13		27	10.9 - 65.8	
ATG	no	50	14	0.67	56	15	0.57	25	8.8 - 71.2	0.84
	yes	60	8		71	8		22	11.5 - 41.1	
ATG dose (mg/kg)	0	50	14	0.34	56	15	0.46	25	8.8 - 71.2	0.74
	2.5	67	9		79	8		19	8.4 - 44.8	
	5	40	15		50	16		30	10.7 - 83.9	
Thiotepa dose (mg/kg)	5	65	8	0.37	76	7	0.11	19	9.6 - 37.3	0.62
	10	43	13		50	13		29	11.8 - 68.9	
Graft source	BM	56	17	0.97	56	17	0.73	22	5.9 - 83.2	0.97
	PBSC	58	8		71	7		23	12.6 - 41.8	
Year of HSCT	<=2015	44	10	0.05	56	10	0.07	29	16.3 - 53.9	0.19
	>2015	75	8		83	8		13	4.2 - 37	

		100 day CI of aGVHD			2-year CI of cGVHD			2-year CI of NRM		
Variables	Value	%	95% CI	p	%	95% CI	p	%	95% CI	p
Recipient age	<=54.9 years	35	20.1 - 59.5	0.21	39	22.6 - 66.6	0.08	23	11.2 - 47.5	0.57
	>54.9 years	20	9 - 44.6		13	4.33 - 8.3		16	6.4 - 40.1	
Recipient sex	male	25	13.6 - 46.1	0.71	26	13.2 - 49.7	0.88	19	9 - 39.1	0.75
	female	32	15.9 - 62.5		30	13.3 - 66.3		21	8.6 - 51.7	
Diagnosis	others	29	13.7 - 63.1	0.83	26	10.5 - 65.9	0.94	29	13.6 - 63.5	0.19
	Acute leukemia	27	15 - 46.8		27	14.6 - 50.1		15	6.5 - 33.5	
Disease status	others	36	17.1 - 74.5	0.51	NA	NA	0.88	36	17 - 75.2	0.06
	CR	24	13.7 - 43.3		28	15.6 - 49.7		14	5.9 - 30.9	
DRI	intermediate	31	19.1 - 51.7	0.39	18	7.8 - 41.7	0.02	17	8.2 - 36	0.48
	high/very-high	19	6.5 - 53.9		47	26.2 - 83.8		25	10.3 - 60.5	
ATG	no	50	27.4 - 91.3	0.03	31	10.7 - 90.9	0.88	25	8.9 - 70.1	0.65
	yes	21	11 - 38.4		25	14 - 44.8		18	9.1 - 35.5	
ATG dose (mg/kg)	0	50	27.4 - 91.3	0.09	31	10.7 - 90.9	0.44	25	8.9 - 70.1	0.52
	2.5	17	7.6 - 38.9		20	8.7 - 44.5		14	5.4 - 34.9	
	5	30	11 - 82		40	17.5 - 91.5		30	10.8 - 83.3	
Thiotepa dose (mg/kg)	5	16	7.7 - 34.1	0.005	13	4.9 - 32.8	0.002	16	7.7 - 34.1	0.38
	10	57	35.3 - 92.4		57	35.1 - 93.2		29	12 - 68	
Graft source	BM	33	12.4 - 89.7	0.81	44	20 - 98.7	0.15	22	6 - 82.7	0.90
	PBSC	26	15.7 - 43.8		23	12.4 - 44.4		19	10.1 - 35.9	
Year of HSCT	<=2015	41	25.6 - 64.9	0.02	33	19.2 - 57.8	0.22	26	13.5 - 49.9	0.25
	>2015	13	4.2 - 36.9		NA	NA		13	4.2 - 37	

Abbreviations: DFS: disease free survival, OS: overall survival, RI: cumulative incidence of relapse, 95% CI: confidence interval of 95%, GVHD: graft-versus-host disease, CI: cumulative incidence, NRM: non-relapse mortality, CR: complete response, DRI: disease risk index, ATG: antithymocyte globulin, BM: bone marrow, PBSC: peripheral blood stem cell, HSCT: hematopoietic stem cell transplantation, NA: not applicable.

Table 6. Multivariate analysis

Variables	DFS				OS				Relapse			
	p	HR	95% CI		p	HR	95% CI		p	HR	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
Disease status (CR vs. others)	0.011	3.324	1.312	8.418	0.001	5.185	1.897	14.173	0.344	1.957	0.487	7.869
ATG (yes vs. no)	0.733	1.189	0.439	3.224	0.581	1.370	0.448	4.190	0.960	1.036	0.261	4.105
Thiotepa dose (10 vs. 5 mg/kg)	0.535	1.384	0.495	3.872	0.697	0.799	0.258	2.476	0.608	1.443	0.356	5.852
Year of HSCT (>2015 vs. ≤2015)	0.029	3.639	1.139	11.626	0.121	3.022	0.747	12.222	0.104	3.675	0.764	17.672
	acute GVHD				chronic GVHD				NRM			
Variables	p	HR	95% CI		p	HR	95% CI		p	HR	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
	Disease status (CR vs. others)	0.236	2.052	0.625	6.732	0.400	1.676	0.503	5.584	0.010	5.669	1.519
ATG (yes vs. no)	0.058	3.086	0.962	9.898	0.752	0.821	0.241	2.795	0.608	1.473	0.335	6.476
Thiotepa dose (10 vs. 5 mg/kg)	0.133	0.357	0.093	1.368	0.080	0.246	0.051	1.181	0.750	1.286	0.273	6.064
Year of HSCT (>2015 vs. ≤2015)	0.479	1.806	0.352	9.278	0.957	0.955	0.182	5.023	0.171	3.388	0.591	19.437

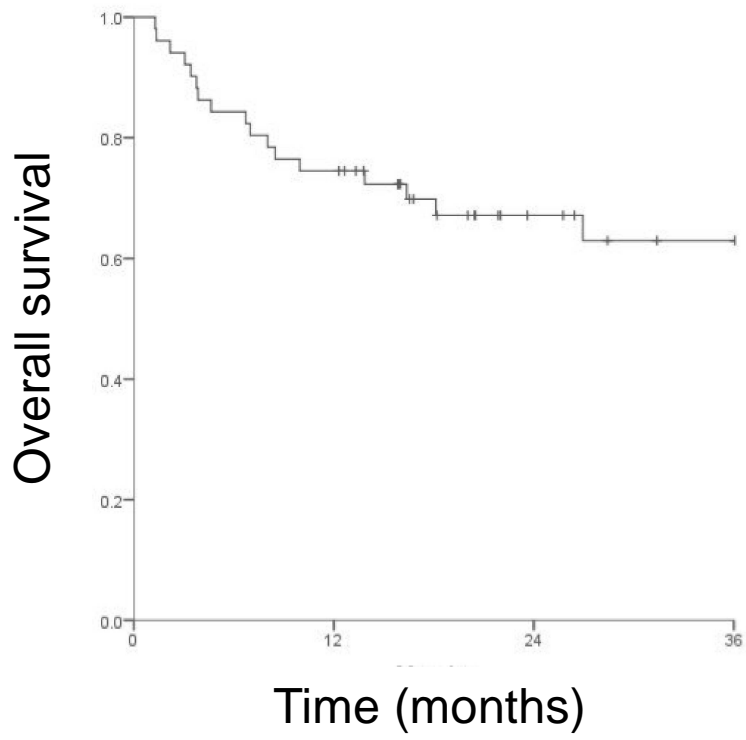
Abbreviations: DFS: disease free survival, OS: overall survival, RI: cumulative incidence of relapse, 95% CI: confidence interval of 95%, GVHD: graft-versus-host disease, NRM: non-relapse mortality, CR: complete remission, ATG: antithymocyte globulin, HSCT: hematopoietic stem cell transplantation.

Figure 1: Kaplan-Meier estimates of overall survival (A) and disease-free survival (B)

Figure 2: Kaplan-Meier estimates of overall survival according to disease status at transplant (CR: complete remission).

Figure 1

A



B

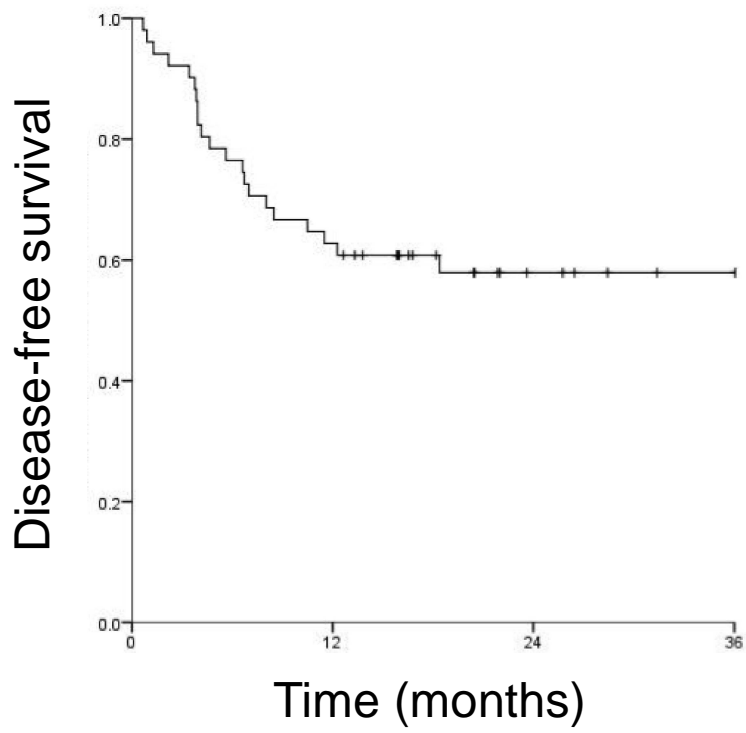


Figure 2

