Transfusion and Apheresis Science 61 (2022) 103367

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

# Defibrotide combined with triple therapy including posttransplant cyclophosphamide, low dose rabbit anti-t-lymphocyte globulin and cyclosporine is effective in prevention of graft versus host disease after allogeneic peripheral blood stem cell transplantation for hematologic malignancies

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ARTICLE INFO

*Keywords:*
Graft versus host disease
Prevention
Defibrotide
ATG
Cyclophosphamide
Cyclosporine

ABSTRACT

Endothelial dysfunction and damage play important roles in the pathophysiology of graft versus host disease (GvHD) and hepatic venoocclusive disease/sinusoidal obstruction syndrome (VOD/SOS). Preliminary evidence suggests that defibrotide (DF) may decrease the risk of GvHD. We speculated that DF prophylaxis may have a synergistic effect with other immunosupressive agents by decreasing the incidence of GvHD and retrospectively evaluated the impact of a DF prophylaxis on the development of GvHD. Thirty-eight adult patients with various hematological neoplasms who underwent peripheral blood allogeneic hematopoietic stem cell transplantation from all donor types were included. All patients received DF for prevention of VOD/SOS. GvHD prophylaxis included rabbit anti-T lymphocyte globulin (rATLG), posttransplant cyclophosphamide (PTCy) and cyclosporine (CsA). The median follow-up of the surviving patients was 484 (365−814) days. The cumulative incidence of grade III-IV acute GvHD and moderate/severe chronic GvHD requiring systemic immunosupression at 1 year were 20.6 % and 5.3 %, respectively. Non-relapse mortality, GvHD-relapse-free survival, and overall survival of the study cohort at 1-year were 21.1 %, 44.7 % and 57.9 %, respectively. Our preliminary results suggest that DF may act as a global endothelial protectant and decrease the risk of GvHD in combination with rATLG, PTCy and CsA.

## 1. Introduction

Graft versus host disease (GvHD) is one of the most important immunologic complication in the setting of allogeneic hematopoietic stem cell transplantation (allo-HSCT) contributing to increased transplant-related morbidity and mortality. Despite significant improvements in preventive strategies in the last decade, almost 40–50 % and 30–70 % of patients all destined to develop significant forms of acute (aGvHD) and/or chronic (cGvHD) GvHD following allo-HSCT, respectively [1]. The efficacy and tolerability of in vivo T-cell depletion with posttransplant cyclophosphamide (PTCy) for prevention of GvHD was shown first in haploidentical followed by matched donor settings in various hematological malignancies [2–4]. PTCy as a sole GvHD prophylaxis was effective in patients who received bone marrow grafts [5,6] but this strategy resulted in unacceptable high rates of aGvHD in matched related (MRD) and unrelated donor (MUD) settings using peripheral blood [7]. Therefore, a standard approach in the PTCy-based haploidentical HSCT (haplo-HSCT) setting was to add mycofenolat mofetil (MMF) plus calcineurin inhibitors (CNIs) for prevention of GvHD. Polyclonal rabbit anti-T lymphocyte globulin (rATLG) and anti thymocyte globulin (rATG) are also effective options for GvHD prophylaxis [8]. Recent data indicates that tripple or quadripple regimens including dual T cell depletion (TCD) using PTCy and rATG plus CNIs ± MMF were associated with low cumulative incidence of GvHD, increased GvHD/relapse free survival (GRFS) in MUD and haplo-HSCT settings using peripheral blood as the stem cell source (PBSCT) [9,10].

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https://doi.org/10.1016/j.transci.2022.103367

Available online 24 January 2022

Hepatic veno-occlusive disease/sinusoidal syndrome (VOD/SOS) is another life-threatening complication of endothelial origin observed in the early time period following allo-HSCT. Defibrotide (DF) is indicated in the treatment of patients who developed severe/very severe forms of VOD/SOS. A prospective, randomized, phase 3 study in the pediatric population with high-risk features for development of VOD/SOS showed efficacy of DF in reducing the risk of this complication [11]. Although prospective, randomized data in the adult population is lacking, the drug is also recommended for prevention of VOD/SOS in high-risk adult patients based on the benefit observed in adult retrospective studies and aforementioned phase 3 study in the pediatric population [12]. Endothelial dysfunction and damage play important roles in the pathophysiology of GvHD and VOD/SOS. Indeed, preliminary evidence suggests that DF prophylaxis also reduces the risk of aGvHD [11,13]. We speculated that DF prophylaxis may have a synergistic effect with other immunosupressive agents in decreasing the incidence of GvHD and retrospectively evaluated the impact of a quadruple prophylaxis on development of GvHD.

## 2. Methods

### 2.1. Patients

All consecutive adult patients with hematological neoplasms who underwent a first allogeneic PBSCT from all donor types between March 2019 and October 2020 were included. In order to evaluate cGvHD development patients should have at least 1 year of posttransplant follow-up or until death.

### 2.2. Prophylaxis of VOD/SOS and GvHD

All patients received DF for VOD/SOS and rATLG (ATG-Grafalon®; formerly ATG-Fresenius®), PTCy 50 mg/kg posttransplant D + 3/D+4 and cyclosporine (CsA) for GvHD prophylaxis, respectively. Patients who had at least two major risk factors according to the recently published European Society for Blood and marrow Transplantation (EBMT-2020) criteria were defined as having very high-risk for development of VOD/SOS and received DF at 25 mg/kg daily dose DF beginning with a conditioning regimen for 3 weeks or until discharge. All others received 10 mg/kg daily DF initiated with conditioning for 2 weeks. Patients who developed VOD/SOS were treated with 25 mg/kg daily DF until resolution of symphoms or death. The total dose of rATLG was 5−10 mg/kg and was determined based on HLA match and remission status of patients at allo−HCT.

### 2.3. Definitions

We used established criteria proposed by the Mount Sinai Acute GvHD International Corsortium (MAGIC) and National Institutes of Health (NIH-2014) for definition/grading of aGvHD and cGvHD, respectively [14,15]. Matched related/unrelated donors had 10/10 HLA match considering HLA-A, -B, -C, DRB1 and DQB1 allelic typing. Patients having a 9/10 HLA matched related and unrelated donors were defined as well-matched related (WMRD) and well-matched unrelated (WMUD), respectively. Donor-recipient pairs with $\geq$ 2 HLA mismatches were treated as haplotransplants. The definition of the conditioning intensity (myeloablative-MA or reduced-intensity conditioning-RIC) is made according to widely accepted criteria [16]. In all patients HCT comorbidity index (HCT-CI) [17], comorbidity-age index (aHCT-CI) [18], EBMT score [19], disease-risk index (DRI) [20] and transplant-conditioning intensity [21] were calculated. Neutrophil and thrombocyte engraftment were defined according to standard criteria.

### 2.4. Endpoints

The primary endpoints of the study were cumulative incidence of aGvHD, cGvHD, non-relapse mortality (NRM) and GvHD/relapse-free survival (GRFS) at the first year after allo-HSCT. NRM was defined as death from any cause other than relapse. The composite endpoint GRFS was defined as survival without stage III/IV aGvHD, extensive cGvHD, relapse or death from any cause after transplantation.

### 2.5. Statistics

All statistical analysis were performed with the IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp) software. Frequency (percentage) and median (min-max) values were calculated as descriptive statistics for categorical and quantitative variables, respectively. Kaplan-Meier method was used to estimate GRFS and overall survival (OS- measured as the time from transplantation to death). NRM and cumulative incidence (CI) of aGvHD/cGvHD were estimated with competing risk analysis. Competing risks were relapse for NRM, relapse and death for aGvHD, cGvHD and GRFS. The median follow-up was calculated as the time from allo-HSCT to death or last follow-up for censored patients. All patients gave written informed consent for all aspects of allo−HCT before transplant. The study was approved by a local institutional review board and conducted in accordance with the declaration of Helsinki.

## 3. Results

The study included a total of 38 patiens (19 males, 19 females). The median age of the study cohort was 44 (20−68). The demographic and clinical features of the patients are summarized in Table 1. The dose of DF was 10 mg/kg and 25 mg/kg in 36 (94.7 %) and 2 (5.3 %) patients, respectively. HSCT-associated outcomes are presented in Table 2. The median follow-up of surviving patients was 484 (365−814) days. Four (10.5 %) patients suffered from grade III-IV aGvHD (Fig. 1). The cumulative incidence of grade III-IV aGvHD and moderate/severe cGvHD requiring systemic immunosupression at 1 year were 13 % and 5.3 %, respectively (Fig. 2). NRM, GRFS and OS of the study cohort at 1-year were 21.1 %, 44.7 % and 57.9 %, respectively (Figs. 3 and 4).

## 4. Discussion

The preliminary results of quadruple GvHD prophylaxis were impressive with 13 % and 5.3 % grade III-IV aGvHD and moderate/severe cGvHD, respectively. Our findings indicate that dual T-cell depletion with PTCy/low-dose ATLG combined with CsA and DF was associated with accep Table 1-year NRM, GRFS and OS rates in a wide range of patients with hematological malignancies who underwent PBSCT from different types of donors. A recently published study from the Acute Leukemia Working Party-European Society of Blood and Marrow Transplantation (ALWP-EBMT) analyzed outcomes of adult ALL patients in first complete remission who underwent HSCT with PTCy-based GvHD prophylaxis from MRD, MUD and haploidentical donors. 62 % of patients received PBSCT. The CIs of grade III-IV aGvHD and extensive cGvHD based on donor types were 13–15 % and 11–21 %, respectively. GRFS of the study cohort was 35–46 % [2]. Sin et al. reported their experience with dual TCD (low-dose rATG/PTCy) combined with CsA and MMF for prevention of GvHD after MUD-PBSCT in 51 patients presenting with various hematological malignancies. CIs of grade II—IV aGvHD and mild-moderate cGvHD were 6.2 % and 11.5, respectively. The quadruple prevention strategy using total doses of 5 mg/kg rATG and 50 mg/kg PTCy resulted in 70.6 % 1-year GRFS [10]. Another retrospective study included 95 patients with different types of hematological malignancies who underwent haploidentical PBSCT using in-vivo TCD (PTCy/rATG) combined with CsA for prevention of GvHD. The authors evaluated the impact of reduction of cumulative rATG dose from 4.5 mg/kg to 2 mg/kg on outcome parameters. Eighty-six (90.5 %) of the study cohort received RIC. CIs of grade III-IV aGvHD and mild-moderate cGvHD were 11.1 % and 20.2, respectively.

**Table 1**
Demographic and clinical features of the study cohort.

| Variable | Results |
|---|---|
| Age (years) (median; range) | 44 (20–68) |
| Gender (female; male) (n; %) | 19 (50 %) / 19 (50 %) |
| Primary diagnosis (n; %) | |
| Acute myeloid leukemia | 20 (52.6 %) |
| Acute lymphoblastic leukemia | 12 (31.6 %) |
| Myelodysplastic syndrome | 2 (5.3 %) |
| Multiple myeloma | 2 (5.3) |
| Non-Hodgkin lymphoma | 2 (5.3 %) |
| Donor type (n; %) | |
| MRD | 19 (50 %) |
| MUD | 6 (15.8 %) |
| WMUD | 8 (21.1 %) |
| Haplo | 5 (13.2 %) |
| Donor-recipient sex mismatch (n; %) | |
| Yes | 21 (55.3 %) |
| No | 17 (44.7 %) |
| ABO mismatch (n; %) | |
| Yes | 19 (50 %) |
| No | 19 (50 %) |
| Infusion modality of HSCT product (n; %) | |
| Fresh | 32 (84.2 %) |
| Cryopreserved | 6 (15.8 %) |
| Infused $CD34^+$ cells ($10^6$/kg) (median; range) | 8.05 (4.1–9.4) |
| Conditioning regimen (n; %) | |
| Busulfan-Fludarabine | 21 (55.2 %) |
| Total body irradiation-Etoposide | 15 (39.5 %) |
| Treosulfan-Fludarabine-Total body irradiation | 2 (5.3 %) |
| Conditioning intensity (n; %) | |
| MAC | 36 (94.7 %) |
| RIC | 2 (5.3 %) |
| TCI score (n; %) | |
| 2.5-3.5 | 26 (68.4 %) |
| 4-6 | 12 (31.6 %) |
| EBMT score (n; %) | |
| 1 | 5 (13.2 %) |
| 2 | 10 (26.3 %) |
| 3 | 15 (39.5 %) |
| 4 | 6 (15.8 %) |
| 5 | 2 (5.3 %) |
| HCT-CI (n; %) | |
| 0 | 12 (31.6 %) |
| 1-2 | 17 (44.7 %) |
| $\geq 3$ | 9 (23.7 %) |
| aHCT-CI (n; %) | |
| 0 | 4 (10.5 %) |
| 1-2 | 16 (42.1 %) |
| 3-4 | 17 (44.7 %) |
| $\geq 5$ | 1 (2.6 %) |
| DRI | |
| Low | 3 (7.9 %) |
| Intermediate | 20 (52.6 %) |
| High | 12 (31.6 %) |
| Very high | 3 (7.9 %) |

**Table 2**
HSCT-associated outcomes.

| Variable | Results |
|---|---|
| Neutrophil engraftment at D+28 (n; %) | |
| Yes | 34 (89.5 %) |
| No | 4 (10.5 %) |
| Platelet engraftment at D+28 (n; %) | |
| Yes | 33 (86.8 %) |
| No | 5 (13.2 %) |
| Neutrophil engraftment (days) (median; range) | 16 (12–26) |
| Platelet engraftment (days) (median; range) | 18 (6–55) |
| Cumulative incidence of aGvHD at 1 year (%) | 20.6 % |
| Cumulative incidence of grade III/IV aGvHD at 1 year (%) | 13 % |
| aGvHD grade (n; %) | |
| I | 1 (2.6 %) |
| II | 2 (5.3 %) |
| III | 3 (7.9 %) |
| IV | 1 (2.6 %) |
| Cumulative incidence of cGvHD at 1 year (%) | 5.3 % |
| Cumulative incidence of moderate/severe cGvHD at 1 year (%) | 5.3 % |
| cGvHD grade (n; %) | |
| mild | 0 (0 %) |
| moderate | 1 (2.6 %) |
| severe | 1 (2.6 %) |
| NRM at 1 year | 8 (21.1 %) |
| Median follow-up of surviving patients (days) (median; range) | 484 (365–814) |
| GRFS at 1 year (%) | 44.7 % |
| OS at 1 year (%) | 57.9 % |

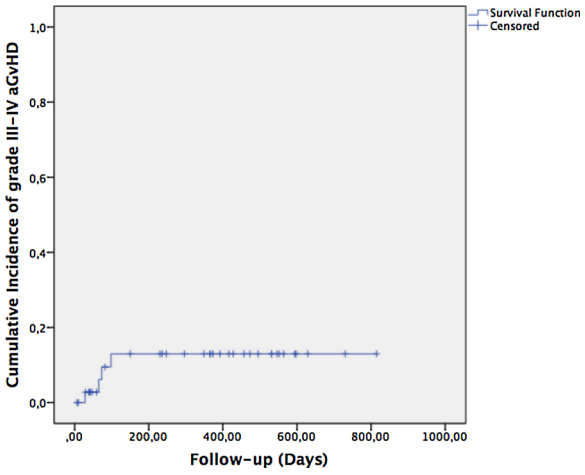


**Fig. 1.** Cumulative incidence of grade III-IV aGvHD.

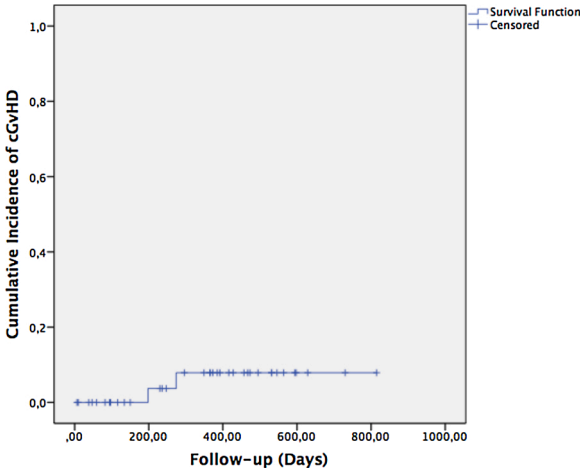


**Fig. 2.** Cumulative incidence of cGvHD.

Interestingly, the reduction of rATG dose significantly increased grade III-IV aGvHD (23.9 % vs 3.5 %; p = 0.006) without confering any advantage in terms of OS [9]. Researchers from China explored the impact of four-drug based prophylaxis of GvHD with or without PTCy in 239 consecutive patients presenting with various hematological malignancies who received BM driven haploidentical HSCT as part of MAC (Beijing-protocol). 125 and 114 patients received 10 mg/kg rATG, CsA, MMF, MTX (rATG-arm) and 29 mg/kg PTCy, 10 mg/kg rATG, MMF, MTX (rATG-PTCy arm) respectively. CIs of grade III-IV aGvHD (5% vs 18 %; p = 0.003) were significantly reduced and GRFS at 2 years (63 % vs 48 %; p = 0.039) increased in rATG/PTCy group compared to patients in the rATG arm. Although there was also a trend for decreased overall cGvHD at 2 years in rATG/PTCy arm (30 % vs 49 %; p = 0.007), CI of moderate/severe cGvHD were similar (17 % vs 16 %; p = 0.071) [22]. Although the impact of the five-drugs based prevention strategy of GvHD was impressive, 82 % of the study cohort had negative measurable residual disease status and belonged to the low/intermediate DRI

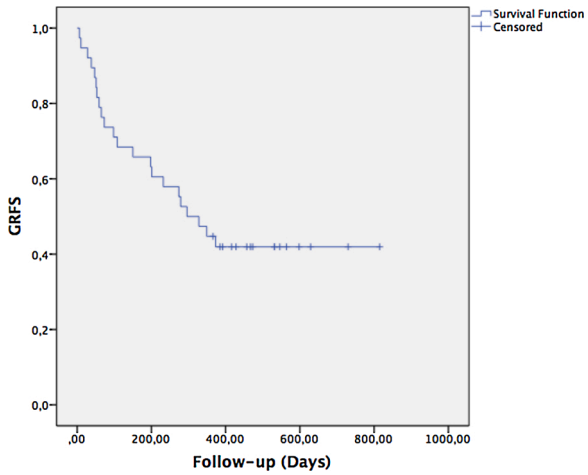


**Fig. 3.** GvHD and relapse-free survival.

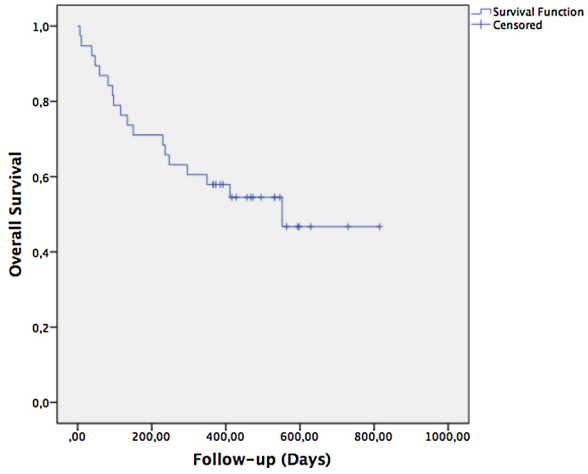


**Fig. 4.** Overall survival.

group at the time of HSCT. Head-to-head comparison of different GvHD prevention modalities is very difficult if not impossible because of differences in primary diseases, disease status at HSCT, conditioning intensity, stem cell sources and, donor types etc. Almost 40 % and 95 % of our study cohort had high/very-high DRI and received MAC, respectively. All patients received PBSCT. If we take the aforementioned facts into account, our findings suggest that a global GvHD prevention strategy including dual-TCD, CsA and DF may be used for all donor types with acceptable GvHD and GRFS rates.

Haploidentical HSCT using PTCy-based GvHD prophylaxis resulted in similar OS compared to HLA fully-matched (MRD/MUD) or one antigen mismatched donors using a traditional GvHD prevention policy using CsA combined with short-term methotrexate/MMF with/without rATG in different types of hematological malignancies [23–27]. Encouraging results with PTCy-based GvHD prophylaxis in a haploidentical platform resulted in widespread use of this promising strategy also in matched/well-matched donor settings. Phase-2 studies using single agent PTCy for GvHD prophylaxis in matched-donor PBSCT were rather disappointing and resulted in 27–80 % of grade III-IV aGvGD [7,28]. A retrospective report of ALWP-EBMT indicated that the addition of two immunosupressive drugs to PTCy decreased the risk of cGvHD and mortality in 423 patients with acute leukemia who received matched donor HSCT [29]. The addition of rATG/rATLG for GvHD prophylaxis is recommended in patients undergoing MUD HSCT for hematological neoplasms and HSCT from all stem-cell sources for non-malignant diseases [30,31]. Retrospective analysis of EMBT comparing PTCy and rATG for GvHD prophylaxis in AML patients showed that both approaches were similar regarding posttransplant outcomes in MUD, but rATG significantly decreased overall and extensive cGvHD in the MRD setting [32,33]. On the other hand, another retrospective study including 76 AML/MDS patients who received WMUD (7/8 HLA-match) HSCT demonstrated that PTCy resulted in significantly lower rates of aGvHD, cGvHD and NRM compared rATG [34]. Although optimal GvHD prophylaxis is yet to be defined, dual in-vivo TCD combined with 2 or 3 immunosupressive drugs seems to be promising and may be used for every patient undergoing HSCT irrespective of donor type.

Multiple factors including but not restricted to conditioning regimen-associated toxicity, infections, use of colony-stimulating factors, alloreactivity, CNIs and engraftment result in endothelial activation which in turn lead to various endothelial complications in the early time period following allo-HSCT. Endothelial activation/dysfunction plays a pivotal role in development of early HSCT-drived complications like VOD/SOS, transplant-associated thrombotic microangiopathy, diffuse alveolar haemorrhage, GvHD [35]. Although the mechanism of action of DF is not fully elucidated, it seems to act through endothelial protection and restoration of thrombotic/fibrinolytic balance. A large meta analysis including 1230 patients showed that DF prophylaxis significantly decreased the mean overall incidence of VOD/SOS (4.7 % vs 13.7; $p < 0.005$) [36]. Although the recommended dose of DF for prevention of VOD/SOS is 25 mg/kg daily initiated with the start of the conditioning and administered at least D + 21 or until patient discharge [12], retrospective experience suggest that DF may also be effective at lower doses and treatment durations [37,38]. All but 2 patients (94.7 %) of our study cohort received 10 mg/kg DF for 2 weeks initiated with the first day of the conditioning regimen. On the other hand, the recommended dose of rATLG (ATG-Grafalon®) for prevention of GvHD in MAC HSCT is 30 mg/kg and 60 mg/kg in MRD and MUD settings, respectively, but the efficacy of lower doses at 15−30 mg/kg has been shown in non-randomized studies [30,31]. The optimal dose of rATLG as part of dual-TCD platform in different donor settings is still unknown. Optimizing the aATG/rATLG dose based on recipient absolute lymphocyte count (ALC) on the day of administration may be a practical solution to the problem [39]. But we did not evaluate the ALC of patients at the first day of rATLG. The doses of both DF and rATLG are lower than recommended. Whether standard doses of DF and rATLG will further decrease the incidence of GvHD and increase GRFS is unknown.

Our study has several limitations including a low number of the study population, retrospective single-center analysis, heterogenous donor and disease settings. As the number of patients in each subgroup was limited, we were unable to compare the impact of our GvHD prophylaxis on specific subgroups regarding primary diagnosis and donor match. But our preliminary results suggest that DF may act as a global endothelial protectant and decrease not only the the risk of VOD/SOS but also other early complications of allo-HSCT like GvHD. Future studies with homogenous patient populations in terms of primary diagnosis, donor match, stem cell source, conditioning intensity and, GvHD prophylaxis will probably define the role of DF in prevention of endothelium-derived early complications of allo−HCT.

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