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Brief Articles

A Case Series of Post-Transplantation Cyclophosphamide in Unrelated Donor Hematopoietic Cell Transplantation for Aplastic Anemia

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A B S T R A C T

Patients with severe aplastic anemia (SAA) who fail immunosuppressive therapy have a dismal prognosis. Hematopoietic stem cell transplantation (HSCT) from an unrelated donor (URD) is one of the most effective treatment options. Two institutions have independently adopted a post-transplantation cyclophosphamide (PTCy) approach for patients with SAA undergoing HSCT from a URD. Thirteen patients were included, 11 of whom had been treated with immunosuppressive therapy. Eight patients had a mismatched URD. All patients were conditioned with fludarabine, cyclophosphamide, and total body irradiation, in various dosage combinations. PTCy was given at a dose of 100 mg/kg. Two patients died, and overall survival was 85% at 2 years. All patients engrafted, but 1 patient developed secondary graft failure. Of the 11 patients alive after 2 years, 9 had complete donor chimerism. All surviving patients were transfusion-independent. Ten patients (77%) had cytomegalovirus reactivation, and 2 patients had more than 1 reactivation. No Epstein-Barr virus reactivation or post-transplantation lymphoproliferative disease was observed. Four patients had mild hemorrhagic cystitis. In summary, our findings show that PTCy is a promising treatment for patients with SAA undergoing URD HSCT.

INTRODUCTION

Immunosuppressive therapy has been the standard treatment for patients with severe aplastic anemia (SAA) lacking a matched sibling donor for hematopoietic stem cell transplantation (HSCT). The prognosis of patients who fail immunosuppression is poor, and HSCT from an unrelated donor (URD) is one of the most effective available options.

The most common conditioning regimens for URD HSCT for SAA have been antithymocyte globulin (ATG)-cyclophosphamide (Cy)-total body irradiation (TBI) [1] and ATG-Cy-fludarabine (Flu)-based regimens [2-5]. Both achieve relatively high overall survival rates in high-income countries. The former, with a total Cy dose of 200 mg/kg, has been associated with significant nonhematologic toxicity, whereas the latter, with a minimum of 50 mg/kg Cy, has overcome graft failure at the cost of a highly immunosuppressive regimen profile.

In low-income countries, including Brazil, lower-than-expected survival has been reported for matched related donor and matched unrelated donor HSCT [6-8]. In addition to the high toxicity of ATG-Cy conditioning regimens, extremely high cytomegalovirus (CMV) and Epstein-Barr virus (EBV) seroprevalences have been reported [9,10], which could partially explain that finding.

Nonmyeloablative haploidentical transplantation with post-transplantation cyclophosphamide (PTCy) has been used with relative success for patients with SAA [11]. Therefore, 2 Brazilian institutions independently adopted a Flu-Cy-TBI-based conditioning regimen with PTCy [12] for patients undergoing URD HSCT for SAA, with a few adaptations. Here, we report the results of the first 13 patients.

METHODS

We included all patients who underwent an URD HSCT for SAA using a PTCy platform at 2 Brazilian institutions. Our results are mainly descriptive. Patient baseline and transplantation characteristics were collected retrospectively, along with the following outcomes: survival, primary and secondary graft failure, acute and chronic graft-versus-host disease (GVHD), CMV reactivation, hemorrhagic cystitis, and BK viruria, the latter only in symptomatic patients. We report continuous variables as median and range and categorical variables as number of patients and percentage. Overall survival was estimated using the Kaplan-Meier method. The analysis of time to engraftment was performed with a Cox model. This study was approved by the institution's Ethics Committees.

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Table 1 presents patient and transplantation characteristics. In brief, 11 patients had failed previous immunosuppressive therapies, which included cyclosporine (CSA) with or without rabbit ATG (horse ATG is not available in Brazil) and with or without eltrombopag, and 2 had been treated only with danazol. Patients 4 and 8 had progressed from a presumed diagnosis of amegakaryocytic purpura. Patient 4 had a history of anemia and thrombocytopenia since age 2 years. A bone marrow biopsy had shown the absence of megakaryocytes, which progressed to aplastic anemia by age 7 years. Patient 5 had a history of thrombocytopenia since birth, and a bone marrow biopsy showed absence of megakaryocytes. This patient progressed to aplastic anemia age 3 years. All patients had been screened for Fanconi anemia (with the diepoxybutane test). Dyskeratosis congenita screening (ie, telomere length testing) was available only in 1 center, for patients 1 to 5, 12, and 13; all tested negative. Patient 11 had 7% paroxysmal nocturnal hemoglobinuria clone in neutrophils and 14% in monocytes. Eight patients had a 9/10 HLA-matched unrelated donor, and the other 5 had a 10/10 HLA-matched (high-resolution HLA-A, -B, -C, -DR, and -DQ) donor. The median patient age was 9 years (range, 2 to 52 years), and the median donor age was 28 years (range, 19 to 53 years). Not surprisingly, all patients were CMV IgG-positive. The long interval between diagnosis of SAA and HSCT (median, 19 months; range, 7 to 100 months) was reflected in the high pretransplantation serum ferritin levels (median, 2242 ng/mL; range, 250 to 8500 ng/mL).

We adapted the original Flu-Cy-TBI with PTCy protocol for all patients, which included higher pretransplantation Cy (50 mg/kg) or TBI (400 cGy), or the addition of ATG (4.5 mg/kg) before starting the conditioning regimen, as outlined in Table 1. GVHD prophylaxis consisted of PTCy 50 mg/kg on days +3 and +4 (100 mg/kg total dose) and mycophenolate mofetil (MMF; 30 or 45 mg/kg/day), along with a calcineurin inhibitor (CSA or tacrolimus), starting on day +5 (Figure 1). Granulocyte colony-stimulating factor was started on day +5. The graft source was bone marrow for all patients. The median infused total nucleated cell (TNC) and CD34 cell doses were 5.1×10^8/kg (range, 3.1 to 10.6 $\times$ 10^8/kg) and 3.2×10^6/kg (range, 1.1 to 8.9$\times$ 10^6/kg), respectively. Patient 2 had high donor-specific anti-HLA levels and underwent a desensitization protocol that included tacrolimus, rituximab, and mycophenolate, with plasmapheresis before transplantation. Patients were monitored for CMV and human herpesvirus 6 (HHV-6) reactivation weekly or twice weekly by PCR.

RESULTS

With a median follow-up of 30 months (range, 7 to 55 months), 2-year overall survival was 85% (Figure 2), and all the surviving patients were transfusion-free at last contact. Two patients had grade I and grade II acute GVHD, and another patient had severe chronic GVHD. Two patients died, 1 from interstitial pneumonia (CMV- and respiratory syncytial virus-positive in bronchioloalveolar lavage fluid) and the other following secondary graft failure. Table 2 summarizes the main outcomes.

All patients had neutrophil and platelet engraftment, at a median of 17 days (range, 14 to 20 days) and 21 days (range, 15 to 30 days), respectively. Infused TNC dose was correlated with both neutrophil engraftment (hazard ratio, 1.69 for each 1×10^8/kg higher TNC; $P = .02$) and platelet engraftment (hazard ratio, 2.14 for each 1×10^8/kg higher TNC; $P = .01$) engraftment (Table 3). After achieving 139.000 platelets/μL and 100% donor chimerism on 2 different measures, patient 9 had an asymptomatic HHV-6 reactivation (which was not treated), stopped taking CSA on his own, and had secondary graft failure diagnosed on day +54; he was deemed ineligible for a second transplantation and died on day +74 due to infection.

There were 12 CMV reactivations in 10 patients (77%) at a median of 48 days (range, 34 to 91 days). Four patients had mild hemorrhagic cystitis, and BK virus was identified in all of them. There was no EBV reactivation.

The conditioning regimen was well tolerated. Only 1 patient had mucositis greater than grade II, and no patient had sinusoidal obstruction syndrome.

DISCUSSION

Our results show that Flu-Cy-TBI-based conditioning regimen with bone marrow grafts and a PTCy-based GVHD

Table 1
Patient and Transplantation Characteristics

Patient	Patient Age, yr	Donor Age, yr	Sex, D→R	HSCT Year	Previous Therapy	Δt Dx → HSCT, mo	Ferritin, ng/mL	ABO Mismatch	Previous Transfusions, n	HLA Match (Mismatch)	Conditioning*	CI	MMF, mg/kg
1	3	38	F→M	2015	CSA + PDN	7	2242	No	25	12/12	Cy50-Flu150-TBI400	CSA	45
2	9	46	M→F	2017	ATG + CSA + PDN	18	5624	Minor	>25	10/12 (B, DP)	Cy50-Flu150-TBI200	CSA	45
3	9	28	M→M	2018	CSA + PDN	11	839	Major	12	12/12	Cy50-Flu150-TBI200	CSA	45
4	10	27	M→F	2016	Danazol	41	2500	No	>25	11/12 (A)	Cy50-Flu150-TBI400	CSA	45
5	9	53	M→F	2016	Danazol	39	278	No	12	11/12 (DP)	Cy50-Flu150-TBI200	CSA	45
6	20	19	M→M	2017	ATG + CSA + PDN	27	4812	Minor	>25	9/10 (B)	Cy29-Flu150-TBI400	FK	30
7	23	22	M→M	2017	ATG + CSA + PDN	7	1902	Minor	>25	10/10	Cy29-Flu150-TBI400	FK	30
8	4	26	F→F	2017	CSA + PDN	48	1179	Minor	15	10/10	ATG4.5-Cy29-Flu150-TBI400‡	FK	30
9	19	29	M→M	2017	CSA + PDN†	100	2231	Minor	>25	9/10 (A)	Cy29-Flu150-TBI400	CSA	30
10	15	24	F→M	2018	ATG + CSA + PDN	14	250	Minor	10	9/10 (A)	Cy29-Flu160-TBI400§	CSA	30
11	52	31	F→M	2015	ATG + CSA + PDN	9	3799	Major	>25	11/12 (C)¶	Cy29-Flu150-TBI400	CSA	45
12	8	26	M→M	2019	CSA + PDN	33	7323	Minor	>25	11/12 (DR)	Cy50-Flu150-TBI400	CSA	45
13	6	28	F→M	2019	CSA + PDN + eltrombopag	19	8500	Minor	>25	10/12 (DQ, DP)	ATG4.5-Cy50-Flu150-TBI200‡	CSA	45

D→R indicates donor to receptor; Δt Dx→HSCT, interval between diagnosis and HSCT; CI, calcineurin inhibitor; FK, tacrolimus.
* Total doses, ATG and Cy doses in mg/kg, Flu doses in mg/m^2, TBI in cGy.
† Severe reaction to first ATG infusion.
‡ ATG from day 9 to day 7 or from day 8 to 7.
§ Flu 40 mg/m^2 daily from day 6 to day 3.
¶ There was also a permissive DP mismatch.

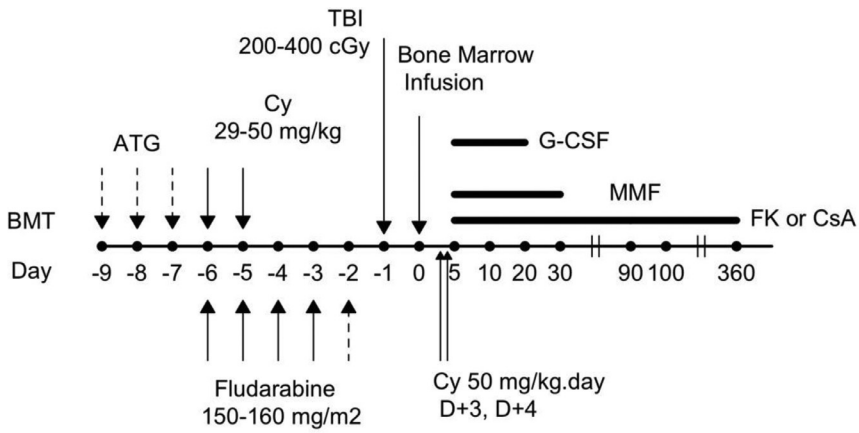

Figure 1. Conditioning regimens and GVHD prophylaxis.

prophylaxis strategy for SAA undergoing URD HSCT is safe and well-tolerated and yields high engraftment rates, even in a highly transfused and previously treated population. Mortality and GVHD were low. To our knowledge, this is the largest study with PTCy-based GVHD prophylaxis for SAA in the URD HSCT setting reported to date.

All our patients received bone marrow grafts, and only 1 had graft failure (secondary). Most patients achieved 100% chimerism, and those with mixed chimerism were transfusion-independent. The median infused TNC dose was 5.1×10^8/kg (compared with 2.9 and 3.1 in the 2 groups of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) study [2], and no patient received $<3 \times 10^8$ TNC/kg, which might have contributed to the low graft failure rate. On the other hand, the low median age of our cohort (9 years) favored high TNC harvests. Despite the relatively small number of patients in our study, we found a correlation between infused TNC dose and time to engraftment, suggesting that the quality of harvested marrow plays an important role in treating aplastic anemia with the PTCy approach. In addition, almost one-half of our marrow grafts were collected in the same city in which the transplantation was performed (6 donors; Supplementary Table S2). In fact, poorer results also have been reported in bone marrow graft recipients with a long interval from the end of collection to receipt at the transplantation center or a long interval from receipt to infusion [13]. Thus, the relatively low number of long-distance transportations might have positively impacted our results.

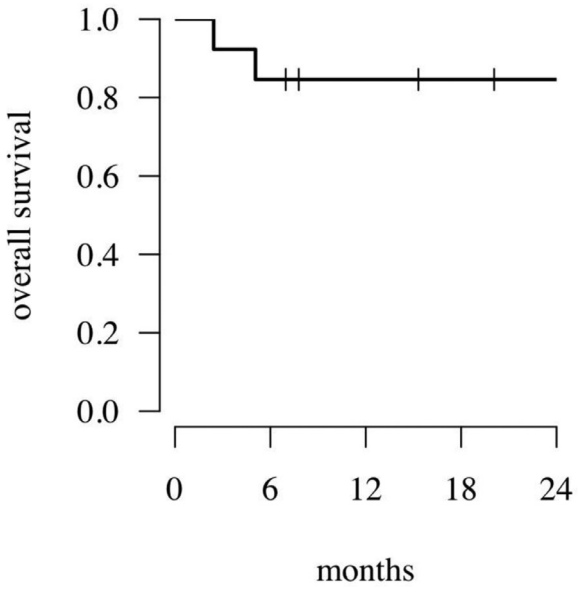

Figure 2. Overall survival.

Regulatory T cells, like $CD34^+$ cells, are resistant to Cy, and thus PTCy may promote a shift toward regulatory T cells, preventing immune-mediated graft rejection [14]. The total Cy dose in our study was 129 to 150 mg/kg (29 to 50 mg/kg pretransplantation and 100 mg/kg post-transplantation). BMT CTN 0301 [2] had a low 10% graft failure with 50 to 100 mg/kg pretransplantation Cy. Both BMT CTN 0301 [2] and the European Society for Blood and Marrow Transplantation SAA Working Party study [3,4] have established a minimum of 50 mg/kg Cy in ATG-Flu-Cy-based regimens to overcome graft failure. Thus, total Cy dose seems crucial to prevent graft failure with Flu-Cy-ATG-based conditioning.

Toxicity was low. Only 1 patient (patient 4), who had been screened for Fanconi anemia and dyskeratosis congenita, had grade IV mucositis and died due to pulmonary complications probably related to RSV and CMV. We cannot rule out Cy- or TBI-related lung injury. The BMT CTN 0301 study closed the 150 mg/kg cyclophosphamide arm due to excessive toxicity. The 50 and 100 mg/kg arms had a 15% rate of major regimen toxicity (with grade III-IV pulmonary toxicities the most frequent). We have not seen this level of toxicity in our patients, even considering that all patients who received the lower 129 mg/kg Cy dose, and 3 of the 7 patients who received the 150 mg/kg Cy dose, also received a higher TBI dose (400 cGy). The Cy dosing schedule in our study (29 to 50 mg/kg pretransplantation and 100 mg/kg 1 week post-transplantation) might have minimized the risk of toxicity.

The rate of CMV reactivation was extremely high, however, at 77% (n = 10 patients). Since Letermovir [15] is not available in Brazil, other strategies to reduce CMV reactivation are needed. The use of pretransplantation ganciclovir or valganciclovir in patients undergoing PTCy-based haploidentical transplantation have reduced the cumulative incidence of CMV disease [14], but this strategy was not used in any of our patients. Attempts to reduce total PTCy dose to 80 mg/kg or 50 mg/kg in have been reported, but CMV reactivation remained high [14,15]. Those 2 studies of reduced PTCy were performed in low miscegenated countries (Switzerland and Japan), and the impact of a reduced PTCy regimen on GVHD in a highly miscegenated population such as that of Brazil would

Table 2
Outcomes

Patient	Neutrophil Engraftment	Platelet Engraftment	Mucositis Grade	Acute GVHD	Chronic GVHD	CMV Reactivation	BK Virus Hemorrhagic Cystitis	Chimerism at Last Follow-Up, %	Outcome
1	+20	+19	I	No	No	Day +90	No	98	Alive at day +1673, transfusion independent
2	+17	+30	I	No	No	Day +67	No	100	Alive at day +1140, transfusion independent
3	+18	+25	I	No	No	No	Yes, day +40	100	Alive at day +611, transfusion independent
4	+14	+19	IV	Yes (grade II, day +22)*	No	Day +35	No	100	Dead on day +154, CMV pneumonitis
5	+15	+16	I	No	No	Day +49	Yes, day +95	100	Alive at day +1399, transfusion independent
6	+15	+29	I	Yes (grade I, day +19)*	No	No	Yes, day +47	100	Alive at day +819, transfusion independent
7	+19	+26	II	No	No	Day +49, day +81	No	100	Alive at day +953, transfusion independent
8	+17	+20	I	No	No	No	No	100	Alive at day +910, transfusion independent
9	+19	+27	I	No	No	Day +45	No	5	Dead on day +74, secondary graft failure
10	+15	+21	I	No	No	Day +34	Yes, day +38	100	Alive at day +466, transfusion independent
11	+17	+17	II	No	Yes	Day +91, day +129	No	100	Alive at day +1554, severe chronic GVHD
12	+15	+20	I	No	No	Day +46	No	63†	Alive at day +212, transfusion independent
13	+15	+18	I	No	No	Day +36	No	70‡	Alive at day +237, transfusion independent

NA indicates not available.
* Only skin.
† Chimerism performed in whole blood.
‡ In whole blood. In T cells, chimerism was 42%.

Table 3
Univariate Cox Models for Neutrophil and Platelet Recovery

Cells	Hazard Ratio	*P* Value
Neutrophils		
TNC ($\times 10^8$/kg)	1.69	.02
CD34 ($\times 10^6$/kg)	1.25	
Platelets		
TNC ($\times 10^8$/kg)	2.14	.01
CD34 ($\times 10^6$/kg)	1.03	.84

be unpredictable. Moreover, reduced PTCy in patients with SAA could compromise engraftment. Another possible intervention relates to the fludarabine schedule of the conditioning regimen. Fludarabine has a long half-life in adults, and adding another rest day would reduce donor graft exposure to fludarabine. This hypothesis remains to be tested in appropriate prospective trials, however. Finally, although MMF 45 mg/kg/day starting at day +5 have become the standard in the PTCy setting, MMF reduction to 30 mg/kg starting at day +1 has successfully prevented GVHD [16] and should be another area of research interest. A recent update of this study did not report CMV reactivation [17].

There was no EBV reactivation or grade III-IV hemorrhagic cystitis in our cohort. High rates of EBV reactivation and post-transplantation lymphoproliferative disease (PTLD) have been reported after URD HSCT for aplastic anemia [1-3]. We believe that both the infrequent use of ATG and the PTCy strategy, which has been associated with a near absence of EBV reactivation or PTLD in the PTCy-based haploidentical setting [18], contributed to this result. Actually, PTCy may deplete EBV-harboring lymphocytes, as is done by prophylactic rituximab [19].

Another option for these patients could be haploidentical transplantation, as described in 2 recently studies. Prata et al [20] reported a low engraftment rate of 67% in 33 patients who had mainly received previous ATG. On the other hand, De Zern et al [21] reported an encouraging graft failure rate of 11%. In 1 of the participating centers, the patients either had no haploidentical donor or had high levels of donor-specific anti-HLA antibodies. The other center was not performing haploidentical transplantation for aplastic anemia during this period.

Our study has some limitations. Although it is a retrospective study, all data collected were available except for telomere length testing, which was not available at 1 of the institutions. The number of patients was small, and the low incidence of graft failure could have been by chance. Nonetheless, to our knowledge, this is the largest series of URD HSCT with PTCy for SAA reported to date.

In conclusion, the PTCy strategy seems a promising approach for patients with SAA undergoing URD HSCT.

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