Conditioning with TLI/ATG in Hematopoietic Stem Cell Transplantation from Haploidentical Donors with Post-transplant Cyclophosphamide in Children in a Single Center During 2015-2017

Catalina María Acevedo-HENAO[1,2], Nelson Romero-ROSAS[2], Estefania BELTRAN[3], Eliana MANZI[2,3], Alexis Antonio Franco MORENO[2,4], Mayra ESTACIO[3], Guillermo Potdevin STEIN[1,2], Diego Medina VALENCIA[2,4]

[1] Fundación Valle del Lili, Department of Radiotherapy, Cali
[2] Universidad Icesi, Faculty of Health Science, Department of Medicine, Cali
[3] Fundación Valle del Lili, Sub Directorate of Clinical Research, Center for Clinical Research, Cali
[4] Fundación Valle del Lili, Pediatric Stem Cell Transplant Service, Cali, COLOMBIA

ABSTRACT

Hematopoietic stem cell transplantation is a treatment alternative for some benign blood disorders. The use of nonmyeloablative conditioning with total lymphoid irradiation and anti-thymocyte globulin has decreased the incidence of acute graft-versus-host disease and can reduce the complications of total body irradiation and generate sustained chimerism. Posttransplant cyclophosphamide has also shown benefits. This is a retrospective, case-series study of pediatric patients with benign pathologies who were treated at Fundación Valle del Lili. A descriptive analysis was performed with measures of central tendency. Survival outcomes were calculated using the Kaplan-Meier estimator. Twelve patients (50% female) with benign blood disorders were included, with an average age of 8.2 ± 5.7 years. The type of donor was haploidentical in all cases; in half, the cellular source was bone marrow. Fifty percent had a diagnosis of immunodeficiencies. The average follow-up time was 28.9 months. The total lymphoid irradiation dose corresponded to a median of 750 centigrays (IQR: 400-750). Neutrophil grafting was achieved in 12/12 patients, and platelet grafting was achieved in 11/12 patients. The presentation of acute graft-versus-host disease was 58%. The transplant related mortality was 17%, and the 1-year overall survival was 83%. Conditioning with total lymphoid irradiation and anti-thymocyte globulin and the use of posttransplant cyclophosphamide is a viable alternative; however, it did not decrease the cases of acute graft-versus-host disease.

Keywords: Stem cell transplant, Thymoglobulin, Lymphatic irradiation, Child, Adolescent

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a curative treatment option for different hematological pathologies in pediatrics.[1-3] In 1968, a successful case of a pediatric patient treated for severe combined immunodeficiency (SCID) was reported.[4,5]; since 1976, different TLI-based conditioning strategies have been used in both adults and children with good results.[6] Among the main benign pathologies in which this conditioning regimen has been applied are primary immunodeficiencies, hemoglobinopathies, bone marrow failure syndromes (BMFSs), and others.[5,7,8]

In terms of the types of donors, the ideal donor is an identical family member; however, this situation is only found in approximately 30% of cases.[9] Therefore, alternative donors are usually required, and their selection depends on the availability and expertise of the transplant center.

Nonmyeloablative conditioning with TLI and anti-thymocyte globulin (ATG) has been shown to decrease the incidence of acute graft-versus-host disease (GVHD) and the complications of irradiation.

It also leads to sustained chimerism and protects against donor-recipient alloreactivity, with high rates of survival in murine models and humans through the depletion of T cell populations and the survival of natural killer T cells, which polarize donor T cells towards the type 2 helper phenotype (anti-inflammatory subtype). Additionally, donor regulatory T cells expand and secrete interleukin-10 (IL-10).[10,11] In addition, the use of TLI has been associated with minimal adverse effects, likely due to the lower amount of irradiated body area, especially when using intensity modulation and the volumetric modulated arc therapy (VMAT) technique.[12] This modality has also been used in HSCT of haploidentical donors with graft manipulation.[13]

Regarding the use of post-HSCT cyclophosphamide (Cy), there has been evidence of benefits in the modulation of GVHD in human leukocyte antigen-identical (HLA-identical) and haploidentical donors in different types of pathologies in both adults and children.[14,15] The use of post-HSCT Cy in a pediatric population with benign disorders undergoing haploidentical HSCT leads to high overall survival (OS), low rates of GVHD and complications and disease resolution.[14,16]

Knowing that post-HSCT Cy has been used in multiple conditioning strategies and different donor types and given the benefit of TLI in GVHD, it was hypothesized that this combination could benefit patients with benign pathologies.

The objective of this study was to describe the treatment modality and outcomes of pediatric patients treated with TLI/ATG conditioning and post-HSCT Cy for hematological benign disorders between 2015 and 2017 at a tertiary care center.

MATERIAL AND METHODS

An observational, retrospective, case-series study of pediatric patients with benign pathologies treated at Fundación Valle del Lili between 2015 and 2017 was conducted. The information was collected through the institutional database of transplants, selecting the transplant patients with benign hematological pathologies recorded in their medical history. Subsequently, the following selection criteria were applied: patients younger than 18 years of age with a diagnosis of benign hematological pathology based on clinical symptoms and paraclinical studies who had received pretransplant conditioning based on TLI/ATG and post-HSCT Cy, had a haploidentical donor, and had undergone transplant at the institution. Patients were excluded whenever data were incomplete. One patient was excluded for malignant pathology and another for having an identical-matched relative. This study was approved by the institutional ethics committee.

Transplantation

Conditioning regimen: Reduced-intensity protocols based on fludarabine (Flu) 30 mg/m^2 on days -5 to -2, Cy 15 mg/kg days -6 to -5, rabbit ATG 5 mg/kg cumulative dose and, in one case, horse ATG 30 mg/kg days -9 to -7, and TLI on day -8 or -1. This variation occurred because, in some cases, the intention was an early application to avoid the inconveniences with edema after ATG, which could affect the initial simulation of the procedure. Furthermore, the dose administered in centigrays (cGy) was according to age. In two cases, additional medicines were added: Busulfan (BU) according to weight on days -4 to -2 and, in one case, Rituximab 375 mg/m^2/dose since day -9.[17]

Prophylaxis for graft-versus-host-disease: A regimen based on posttransplant Cy on days +3 and +4 was used at a dose of 50 mg/kg/day[18], with cyclosporine (CsA) every 12 hours beginning on day +4 while monitoring CsA levels to maintain a level of approximately 200 ng/Ml. The CsA start day was a local decision in order to obtain better and early levels and decrease GVHD presentation. In some cases, sirolimus (Srl) was added for 4 days according to the pharmaceutical recommendation; mycophenolate mofetil (MMF) was added at a dose of 15 mg/kg every 8 hours orally from day +4 until +30; or methotrexate (Mtx)[19] was added at a dose between 5 and 7.5 mg/m^2 on days +5, +7, +10 and +15 with calcium folinate as the rescue agent.

TLI/ATG regimen: The procedure performed at the institution began with intravenous administration of ATG pre-HSCT. Next, a total dose of TLI between 400 and 750 cGy was administered in a single dose on day -1 and, in two cases, was performed on day -8 of HSCT using the Artiste Sie-

Table 1. General characteristics of the patients

ID	Age	Gender	DX	Conditioning Regimen	AGVHD	CGVHD	Infections	Follow-up*	Vital Status
1	6	F	SCA	Cy, Flu, ATG, TLI (750 cGy)	No	No	No	25	Alive
2	10	F	SCA	Cy, Flu, ATG, TLI	No	No	Bacterial, Fungal, Viral	55	Alive
3	12	F	SCA	Cy, Flu, ATG, TLI (750 cGy)	GII Hepatic	No	Bacterial	32	Alive
4	14	F	SCA	Cy, Flu, ATG, TLI (750 cGy)	GII-Gastro-intestinal	No	No	49	Alive
5	0.5	M	CGD	Cy, Flu, ATG, TLI (400 cGy)	No	No	Bacterial, Fungal	1.5	Dead
6	1	M	CGD	Cy, Bu, Flu, ATG, TLI (400 cGy)	No	Severe	No	43	Alive
7	1	F	CGD	Cy, Bu, Flu, ATG, TLI (400 cGy)	GI-gastro-intestinal	Moderate	No	39	Alive
8	3	M	ID1	Cy, Bu, Flu, ATG, TLI (750 cGy)	No	Moderate	Bacterial	44	Alive
9	3	M	ID2	Cy, Bu, Flu, ATG, TLI (750 cGy)	GII-skin, GIII-gastro-intestinal	Moderate	Bacterial, KPC, Viral	18	Alive
10	4	M	ID3	Cy, Bu, Flu, ATG, TLI (450 cGy)	GII-skin, GI-hepatic	No	Fungal.	34	Alive
11	9	M	FA	AraC, Flu, ATG, TLI (400 cGy)	GII-skin,	Mild GI-gastro-intestinal	Viral	23	Alive
12	13	F	FA	AraC, Flu, ATG, TLI (400 cGy)	GIII-gastro-intestinal	No	Bacterial, Viral	2.4	Dead

* Follow up in months. *DX= diagnosis, CGD= Chronic Granulomatous Disease, ID1= immunodeficiency associated with Epstein Barr Virus, ID2= Severe combined immunodeficiency, ID3= Leukocyte adhesion deficiency type 1 (LAD-1) Immunodeficiency, FA= Fanconi anemia*

mens linear accelerator with intensive modulated radiation therapy (IMRT) techniques with 6 MV energy and a dose rate of 50 MU/min. In all patients, the treatment session was performed under anesthesia. Patients were treated in the supine decubitus position on a vacuum mattress and with a thermoplastic mask. The treatment region included the lower mandibular, supra- and infraclavicular, axillary, mediastinal, hilar, paraaortic, pericaval, iliac, and inguinal lymph nodes; splenic hilum; spleen; and thymus. Risk organs were defined as the bone marrow, mandible, parotid, larynx, thyroid, humeral heads, lungs, heart, kidneys, intestinal loops, liver, bladder, rectum, femoral heads, mammary gland, ovaries, and testes.

Antimicrobial Prophylaxis

All patients received voriconazole, itraconazole or posaconazole as antifungal prophylaxis; trimethoprim/sulfamethoxazole as prophylaxis for Pneumocystis jirovecii; fluoroquinolones as antimicrobial prophylaxis; and acyclovir as antiviral prophylaxis. Doses and schedules were adjusted individually according to current international guidelines.[20]

Statistical Analysis

A descriptive statistical analysis was performed for all variables considered. Categorical variables are summarized in proportions, and continuous variables are expressed as the means ± standard de-

viations (SDs) or medians with interquartile ranges (IQRs) according to the distribution of the variable. The primary outcomes of the study were treatment, complications, and OS in months calculated from the date of diagnosis or date of transplantation to the date of death or last follow-up at the institution. These outcomes were analyzed with the Kaplan-Meier method using the statistical software STATA® 12.1.

RESULTS

Description of the Case Series

Twelve patients fulfilled the selection criteria from 2012-2017. An equal distribution was found between males and females, with an average age of 8.2 ± 5.7 years. The most frequent diagnostic group that required transplantation of hematopoietic cells was immunodeficiencies (50%), followed by hemoglobinopathies (33%). The average follow-up time was 28.9 months (Tables 1 and 2).

Table 2. Characteristics of patients undergoing non-myeloablative conditioning with TLI / ATG for HSCT in benign diseases

Characteristics	Total (n= 12)
Age in years, Median (RIC)	7.9 (3.3-13.4)
Male, n (%)	6 (50)
Weight in kg	
Average ± Sd	27±16
Range	6.9-59.5
Diagnosis	
Fanconi anemia, n (%)	2 (17)
Sickle cell disease, n (%)	4 (33)
Immunodeficiency, n (%)	6 (50)
Source Cells	
Bone marrow, n (%)	6 (50)
Peripheral blood, n (%)	4 (33)
Bone marrow + Peripherally Blood, n (%)	2 (17)
Follow up time in days, Median (RIC)	28.6 (19.5-42.4)

Table 3. Characterization of non-myeloablative TLI / ATG conditioning for HSCT

Characteristics	Total (n= 12)
Time of treatment with Tli	
30-60 Min, n (%)	1 (8)
60-90 Min, n (%)	4 (33)
> 90 Min, n (%)	7 (59)
Number of irradiated fields	
20-30, n (%)	3 (25)
30-40, n (%)	5 (42)
> 40, n (%)	4 (33)
Radiotherapy Dose In Cgy, Median (Ric)	750 (400-750)
Gvhd Prophylaxis	
Csa-Mtx-Cy, n (%)	7 (59)
Mmf-Cy-Srl, n (%)	1 (8)
Mtx-Cy-Tac-Srl, n (%)	3 (25)
Mtx-Mmf-Cy-Srl, n (%)	1 (8)
Nucleated, Average ± Sd	153±58
Range	81-271
Cd34, Average ± Sd	98±56
Range	21-192
Condicioning Regimen	
Flu – Cy, n (%)	5 (42)
Arc – Flu, n (%)	2 (16)
Bu - Flu-Cy, n (%)	5 (42)

TLI Radiotherapy

The time of treatment with TLI in the majority of patients (seven patients) was more than 90 min. The number of irradiated fields was between 20 and 40. The dose of radiotherapy received corresponded to a median of 750 cGy (IQR: 400-750). Overall, 83.3% of patients received TLI on day -1, and the remaining patients were treated on day -8 (Table 3).

Hematopoietic Cell Transplantation

The most commonly used source of cells was bone marrow in 6/12 patients, followed by peripheral blood in 4/12 patients, and both in two patients according to the medical decision. The average number of nucleated cells was 153 ± 58 per 107, with a range of 81 - 271, and the average number of CD34+ cell was 98 ± 56 per 105/kg, with a range of 21 - 192. On average, all patients had a neutrophil graft at 16 ± 3 days. One patient had failure of primary platelet grafting, and the average platelet graft in 11/12 patients was 15 days (IQR: 14-18). Three patients with hemoglobinopathies had graft failure followed by autologous recovery.

Table 4. Description of acute and chronic GVHD in patients with HSCT who received TLI/ATG as non-myeloablative conditioning

	Total (n= 12)
Acute Gvhd Per Grade, n (%)	7 (58)
Grade I, n	7
Grade II, n	4
Grade III, n	2
Grade IV, n	0
Acute GVHD per organs affected	
Gastrointestinal, n (%)	5 (71.5)
Skin, n (%)	3 (43)
Liver, n (%)	2 (28.5)
Chronic GVHD, n (%)	5 (55)
Severe, n (%)	1 (11)

Table 5. Outcomes in patients undergoing non-myeloablative conditioning with TLI/ATG

Outcomes	Total (n= 12)
Infections	
Bacterial n (%)	6 (50)
Viral n (%)	4 (34)
Fungal n (%)	3 (25)
Mucositis, n (%)	5 (42)
100% donor chimerism at day 180, n (%)	5 (42)
Days until donor chimerism 100%	
Average ± Sd	106±53
Range	30-180
Time of neutrophil engraftment, Median (RIC)	16 (15-18)
Time of platelet engraftment, Median (RIC)	15 (14-18)
Primary graft failure, n (%)	1 (8)
Autologous recovery, n (%)	3 (25)
Mortality, n (%)	2 (17)
Fungal Infection, n	1
Viral Infection, n	1

Posttransplant Complications

Approximately 58% presented acute GVHD, mostly Grade II (57%), followed by grade III (28%). The system with the greatest compromise was the gastrointestinal system (71%). Chronic GVHD was documented in 5/12 patients; of these, one was diagnosed with severe chronic GVHD (Table 4).

The main cause of infection was bacteria in half of the cases, followed by viral and fungal infections. In this last group, there were three cases of Aspergillus. Mucositis occurred in less than half of patients (5/12) (Table 5).

The two-year nonrelapse mortality was 17% and was due to infectious cause, which occurred in the first 100 days after transplantation, one for fungal infection and one viral infection (Table 5).

Peripheral Blood Chimerism

On day 180, 5/12 patients reached 100% chimerism of the donor cells, 1/12 reached 80%, 1/12 reached 60%, 1/12 reached 20%, and 2/12 reached 0%; two patients died before 180 days (Table 5).

Survival

The OS was 83% at one year and at five years. The event-free survival was 58% at both one year and five years (Figures 1 and 2).

DISCUSSION

This case series summarizes the experience of pediatric patients diagnosed with benign pathologies who were treated with allogenic HSCT using a TLI/ATG conditioning regime and post-HSCT Cy with haploidentical donors at a tertiary care institution from 2015 - 2017. The results presented show a favorable outlook with the use of this combination, offering the possibility of irradiating fewer body areas. However, the GVHD decrease was not expected. To our knowledge, there are few publications with the characteristics of this study, especially regarding the use of posttransplant Cy; therefore, it is necessary to continue studying this population.

The most common benign pathologies reported in this study were immunodeficiencies, sickle cell anemia, and Fanconi anemia, similar to other reports in the literature.[21,22] Characteristically, we described three cases with graft failure, all related to patients with sickle cell anemia. We considered this to be associated with the high rates of failure in these pathologies.[23]

The literature has described the use of TLI and ATG as conditioning prior to the first and/or sec-

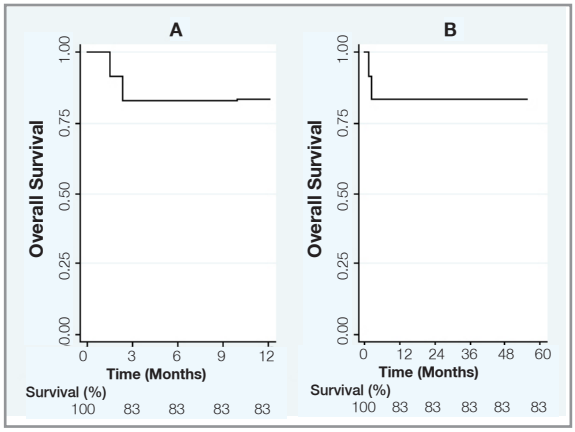

Figure 1. Overall survival in post-Hematopoietic stem cell transplantation patients during the first twelve months **(A)** and by year until fifth-year **(B)**.

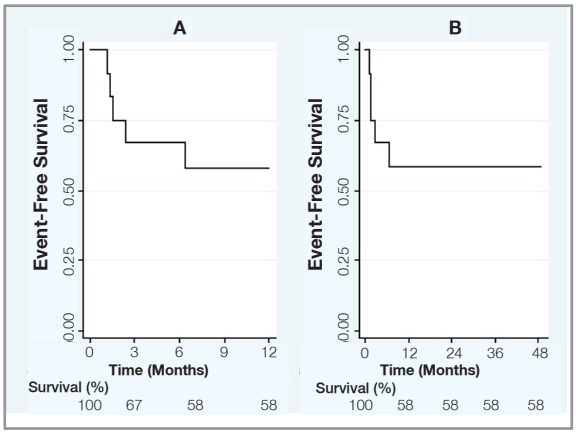

Figure 2. Event-free survival in post-Hematopoietic stem cell transplantation patients during the first twelve months **(A)** and by year until fourth-year **(B)**.

ond HSCT (24) in pediatric and adult populations with malignant and nonmalignant diseases with good results.[6,21,22,25-34] TLI has also been used in HSCT with different types of donors, as HLA-identical related and nonrelated donors for benign diseases.[6,12,21,25,28,29,32-34] In the case of haploidentical donors, the published literature refers mainly to protocols involving graft manipulation[13], but in our study, we used unmanipulated replete T cells.

This study showed an incidence of 58% and 42% of acute and chronic GVHD, respectively, which is similar to another study in our institution of patients with malignant pathologies treated with haploidentical HSCT with post-HSCT Cy and different conditioning regimens, in whom the incidence of acute GVHD was 59%.[35] This similarity is probably due to the low dose of ATG used. Other studies performed in pediatric patients with benign pathologies have shown a lower incidence of Grade II-IV acute GVHD between 0 and 17%.[28,36,37] However, these studies included patients with identical family donors, which was not our case. Experimental studies and reports in humans may suggest that post-HSCT Cy and the use of TLI have been associated with a lower risk of acute GVHD.[38] To our knowledge, there are no cases published regarding the combination of TLI with post-HSCT Cy in haploidentical HSCT.

The one- and five-year OS in this study was 85%, according to the range of values reported in other centers (83% -100%)[28,36] and the one- and five-year event-free survival was 61%, close to that reported in the literature (67% and 100%).[6,22,29,32-34] However, the comparable studies do not meet the same characteristics of our study due to the scarce information. The treatment-related mortality and GVHD in our patient were not decreased as expected. To the best of our knowledge, this is the largest series of patients with these characteristics.

This study has some limitations. The collection of retrospective data was limited to the information recorded in the medical records. Adverse events with TLI were not sought. The opportunity for HSCT in benign pathologies should continue to be studied. This study has a favorable impact and encourages researchers and practicing physicians to explore alternatives in the peri-transplant period to decrease the symptoms of underlying disease and posttransplant complications.

Conclusion

Pre-HSCT conditioning with TLI/ATG and the use of post-HSCT Cy in haploidentical HSCT is a novel approach to transplantation in benign disorders in children and should be explored in prospective studies. Further studies and long-term follow-up are required to evaluate this therapeutic option.

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Correspondence:

Dr. Diego Medina VALENCIA

Fundación Valle del Lili

Pediatric Stem Cell Transplantation Service

Carrera 98 No: 18-49

Cali 760032, COLOMBIA

Tel: 57 2 3319090 ext 8801

e-mail: diego.medina@fvl.org.co

ORCIDs:

Catalina María Acevedo-Henao	0000-0002-9559-0116
Nelson Romero-Rosas	0000-0001-8406-6848
Estefania Beltran	0000-0003-2438-8356
Eliana Manzi	0000-0001-5577-970X
Alexis Antonio Franco Moreno	0000-0002-3173-6059
Mayra Estacio	0000-0001-6908-2508
Guillermo Potdevin Stein	0000-0002-9876-4222
Diego Medina Valencia	0000-0002-1465-7957