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ORIGINAL ARTICLE

Directed sibling donor cord blood donation in the Chilean Public Health System

Donación dirigida de sangre de Cordón Umbilical de Hermano Compatible en el Sistema de Salud Público de Chile

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What do we know about the subject matter of this study?

Umbilical cord blood collected from directed donors is a standard source of hematopoietic stem cells for transplantation. Among the directed umbilical cord blood units collected, 7.5 to 16.0% are used in patients. Hence, these patients recived the best possible donor.

What does this study contribute to what is already known?

We report the results of the Chilean public program of umbilical cord blood collection from directed donors for hematopoietic stem cell transplantation. Collections performed achieved international standards and four patients have been treated so far.

Abstract

Introduction: Cord blood (CB) as a source of Hematopoietic Stem Cells for Transplantation (HSCT) is well established. Worldwide, nonetheless, less than 10% of the CB HSCTs are performed with a match sibling donor. Since 2004, the Chilean National Childhood Cancer Program (PINDA) network, has established a CB directed donation program for HSCT. **Patients and Method:** An observational, descriptive and retrospective study was designed to assess the number and characteristics of the CB units collected in the program as well as the number, clinical characteristics and follow-up of the patients who received an HSCT from those CB units between January 2004 and October 2018. **Results:** Sixty CB units have been collected; 55 of them with full records and stored. The median volume collected was 74.8 ml (30.0-170.8), the median number of total nucleated cells was 7.6 x 10e8 (2.0-21.1), and the median of CD34+ cells was 1.6 x 10e6 (0.2-11.6). Four high-risk leukemia patients received HSCT, all of them developed severe complications after transplantation and one patient died due to relapse. Those patients currently alive have a 100% Karnofsky/Lansky score. The median follow-up time was 8 years. **Conclusion:** The PINDA program has allowed 4 patients to be transplanted who otherwise would not have had access to a donor. This directed donation program could be seen as a model for the development of a public cord blood bank in Chile.

Keywords:
Cord Blood Stem Cell Transplantation; Directed Tissue Donation; Cord Blood; Hematopoietic Stem Cell Transplantation

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Introduction

The first successful hematopoietic stem cell transplantation (HSCT) using umbilical cord blood (UCB) was reported in 1991[1]. Currently, the use of UCB is indicated for children[2] and adults[3] and it is a common procedure in Chile and worldwide[4]. In 2011, a constant increase in UCB use was reported but less than 10% came from a match siblings[5]. Since 2013, the use of UCB has decreased[6], probably due to new haploidentical stem cell transplantation techniques. New applications of the UCB are under study and we expect an increase in its use in years to come[7].

The results of HSCT using UCB of a match sibling are promising[8]. Eurocord reported better overall survival, shorter engraftment time, and less acute graft-versus-host disease (GVHD) compared with an unrelated UCB donor[9]. In addition, when comparing UCB and bone marrow form a match sibling, similar overall survival is observed but lower incidence of acute or chronic GVHD using UCB[10]. Both reports present methodological problems, thus their conclusions should be considered cautiously[11]. Despite this, directed donation of UCB for a family member with a potentially curable disease through HSCT is highly recommended by both pediatricians[12,13] and obstetricians[14].

The Pediatric National Cancer Program (PINDA), started its HSCT from UCB program at the Bone Marrow Transplant Unit (BMTU) of the *Hospital Dr. Luis Calvo Mackenna* (HLCM), in May 2003[15], to date, more than 140 such transplantations have been performed. In January 2004, we started the collection of UCB from siblings of PINDA patients with a possible indication of HSCT. Subsequently, it was extended to patients without oncological pathology treated in the Public Health System. The BMTU HLCM-PINDA assumed the coordination of the PINDA centers distributed throughout the country and the maternity ward of the *Hospital Dr. Luis Tisné Brousse* was established as the only collection center. All collected UCB units were stored in the *Clínica Alemana*'s Laboratory and Blood Bank in Santiago.

There are few reports on the use rate of directed UCB units and even fewer that analyzed the outcome of transplanted patients with them. There are no reports of this type of transplantation in Chile. The objective of this study is to report the experience of PINDA's UCB collection program.

Patients and Method

A retrospective study of clinical records from patients transplanted using directed UCB units, was design. Its aim was to identifying the number, characteristics, and evolution of them. . This study follows the ethical standards of the Declaration of Helsinki and was approved by the HLCM' Dicrector and a scientific ethics committee, Comité de Ética Científico del Servicio de Salud Metropolitano Oriente. We reviewed the records of the UCB units collected at the *Hospital Dr. Luis Tisné Brousse* for patients in the PINDA network between January 2004 and October 2018. Before accessing to the records, we obtained an informed consent from patients if over 18 year old at the time of the study or her/his legal guardian if still a minor. Informed assent was also obtained if the patient was between12 and 18 years old years at the time of the study.

We registered the total number of cord blood units collected, their volume, patient's diagnosis, referral hospital, total nucleated cells (TNC) and CD34+ cells counts. From the clinical record of the transplanted patients, the following data were recorded: diagnosis, sex, treatment and complications before transplantation, blood type, conditioning, age, weight, stem cell dose, and engraftment of erythrocytes , leukocytes and platelets. In the follow-up, we evaluated bone marrow aspirate, chimerism lymphocyte subpopulations, immunoglobulins, Karnofsky/Lansky score according to age, post-transplantation complications, current status, time of follow-up, and donor data (blood type and age at transplantation).

Results

In the study period, 60 UCB units were collected, 31 of them between 2014 and 2018. Out of the 60, 3 were excluded, the first one due to low volume extracted, the second one due to low cellularity, and the third one due to not compliance with the proper extraction procedure. Out of the remaining 57, the record of two of them was incomplete which correspond to the first two units extracted thus they were excluded from the analysis. Table 1 summarized the characteristics of the 55 stored UCB units analyzed.

Out of the five UCB units stored for patients with non-oncological pathology, none has been used. Out of the UCB units stored for patients with oncological pathology, four of them have been used in four patients. This represents 6.7% of the 60 units collected, 7.0% of the 57 stored, and 8.0% of the 50 stored for oncological pathology.

Before transplantation, two of the four transplanted patients were treated at the HLCM in Santiago, one at the *Hospital Dr. Sótero del* Río in Santiago, and the last one at the *Hospital Dr. Gustavo Fricke* in Viña del Mar. Table 2 shows the evolution of patients before transplantation.

Table 1. Characteristics of the stored umbilical cord blood units

Characteristics	Years			Total
	2004-2008	2009-2013	2014-2018	
Number	6*	18	31	55
Diagnosis for collection				
Non malignancy	2	2	1	5 (9%)
Malignancy	4	16	30	50 (91%)
Referral hospital location				
SMR	3	14	27	44 (80%)
No SMR	1	1	4	6 (11%)
No data	2	3	0	5 (9%)
Median volume (ml)	70.0** (rango 60.5-91.0)	73.7 (rango 31.5-125.3)	80.6 (rango 30.0-170.8)	74.8 (rango 30.0-170.8)
Median TNC ($x10^8$)	6.5 (rango 5.3-14.1)	7.8 (rango 2.7-16.5)	7.9 (rango 0.2-21.2)	7.6 (rango 2.0-21.1)
Median CD34 ($x10^6$)	1.0 (rango 0.5-8.6)	1.6 (rango 0.4-3.7)	1.6 (rango 0.2-11.2)	1.6 (rango 0.2-11.2)

SMR: hospital from Santiago's Metropolitan Region, No SMR: hospital not from Santiago's Metropolitan Region, TNC: Total Nucleated Cells, CD34: CD34 + Cells. *2 units excluded due to incomplete record. **Data available only in 5 of the 6 units.

Table 2. Diagnosis and clinical evolution before transplantation

	Sex	Diagnosis	Treatment	Complications
1	F	ALL 2CR	LLA PINDA 2002 IDA-FLAG Consolidation TG y MTX	Recurrent Sinusitis *Clostridium difficile* Diarrhea Pneumonia *Pneumocystis jirovecii* with MV Candidemia: *Candida tropicalis* Upper gastrointestinal bleeding
2	M	ALL Phi(+) 1 CR	ESPHALL	Toxocariasis Positive Toxoplasma serology Pre transplant qualitative PCR BCR/ABL: +
3	M	CML 1 CP	Hydroxiurea Imatinib	Gastropathy due to prolapse Paresthesias due to Imatinib No stable molecular remission
4	M	JMML not in CR	Vall d´Hebron LMA PINDA 2006	Atopic dermatitis Toxocariasis Phimosis Recurrent bronchial obstruction Adverse reactions to blood products

F: female, M: male, ALL 2CR: acute lymhoblastic leukemia in second complete remission, LLA PINDA 2002: national treatment protocol. IDA-FLAG: treatment with idarrubicine, fludarabine, citarabine filgrastim. Consolidation: treatment with VP16 and citarabine. TG y MTX: maintenance treatment con methotrexate y tioguanine, MV: mechanical ventilation, 1CR: first complete remission, Ph (+): Philadelphia Chromosome positive, ESPhALL: international treatment protocol. CML 1CP: chronic myeloid leukemia in first chronic phase, JMML: juvenile myelomonocytic leukemia, CR: complete remission, Vall d'Hebron: treatment protocol[16], LMA PINDA 2006: national treatment protocol.

Table 3. Characteristics of the patients and their donors

	Patients				Donors			
	Sex	Age & weigth*	CMV	Blood group	TNC	Age*	Blood group	Sex
1	F	4.7 y.o. 15.0 Kg	(+)	A Rh+	3.5 x 10^7/Kg	8 m.o.	0 Rh+	F
2	M	14.0 y.o. 53.0 Kg	(+)	0 Rh+	1.9 x 10^7/Kg	3 m.o.	0 Rh+	M
3	M	17.9 y.o. 62.5 Kg	(-)	0 Rh+	SCU: 0.2 x 10^7/Kg MO: 11.8 x 10^7/Kg	3 y.o.	0 Rh+	F
4	M	2.0 y.o. 13.7 Kg	(-)	0 Rh+	4.3 x 10^7/kg	6 m.o.	0 Rh+	F

*at the time when transplantation was performed, CMV: cytomegalovirus serological status, y.o.: years old, m.o.: months old, TNC: total nucleated cells. F: female, M: male, UCB: umbilical cord blood, BM: bone marrow.

The age difference between donor and recipient ranged from 1.5 to 14.9 years. In adolescent transplant recipients, patients 2 and 3, the umbilical cord stem cell doses were low; patient 3 also received bone marrow to increase the stem cell dose. Table 3 shows the characteristics of patients and donors at the time of transplantation.

After transplantation, all four patients received the standard prophylaxis regime: Neomycin, Acyclovir, Fluconazole, Heparin, and Co-trimoxazole. The immunosuppressive therapy was based on Cyclosporine, however, in patient 4, the therapy was changed to Tacrolimus due to toxicity. All patients engrafted; however, patient 4 relapsed and died four months after the transplant. The three patients who have not relapsed had multiple complications, including uncommon ones such as stiff-person syndrome (patient 3) or severe ones such as secondary thyroid cancer (patient 1). Despite this, they are currently in good condition with Lansky/Karnofsky score 100% with an 8-years follow-up on average. All three patients have achieved adequate immune system recovery and have completed the post-transplant vaccination regime. Patients 2 and 3 are attending higher education and patient 1 is finishing high school. None of the patients lives in the Santiago´s Metropolitan Region. Table 4 shows the evolution of the patients.

Discussion

The match family donor is considered the ideal donor within allogeneic HSCT[17] and is preferred over other donors[18].

Our data show how UCB collection, in the program has increased over the years. Since PINDA is an oncology group, 91% of the UCB units stored were directed to patients with cancer, and 8% of them have been used. Greece reports the use of 2% of the units collected for malignant pathology and 16% in those collected for hemoglobinopathies[10]. In Italy, a 20 year old directed collection program uses 7.35% of the total collected units[21] but only 3.4% of them in leukemia[22].

In our program, the average volume and TNC are higher over the years, reflecting the experience achieved by the collecting teams; volumes and TNCs are similar to those reported elsewhere, but the content of CD34+ is lower[19-21,23]. Even when a unit has low CD34+, it should be stored since the simultaneous use of bone marrow and UCB of a match sibling seems to be beneficial[24] as seen in patient 3.

In our patients, the age difference with donors was such that the donation of stem cells would have been impossible. These 4 patients reflect the potentially severe complications of transplant recipients, some of them appearing in the very long-term. Extended follow-up and adequate transition to adult medicine care are necessary for childhood cancer survivors. This is an outstanding challenge in Chile.

The PINDA sibling directed donation program represents a challenge for the Chilean Public Health System, requiring network coordination of multiple teams for its success. At least 11% of the units stored come from referral hospitals outside the Santiago´s Metropolitan Region. The coordination has been possible thanks to over 20 years of operation of the PINDA's HSCT committee. We strongly recommend the directed donation of UCB to sick siblings and its expansion should be promoted in the future[5]. The collection and storage program can set a model for the development of a cord blood bank in the Public Health System.

Table 4. Transplantation procedure and follow up outcome

	Conditioning regimen	Engraft.	Early complications < 100 d post HSCT	Late Complications	Follow up
1	VP16 30 mg/kg Cy 200 mg /kg TBI 12 Gy	Leu +21 Ery +20 PLT +39	*S. mutans*, bacteremia All sinus sinusitis	SRV pneumonia Hypothyroidism Thyroid cancer	11,1 years post HSCT Chimerism 100% Lansky score 100% No GvHD CR booth cancers IR 1 year post HSCT
2	VP16 30 mg/kg Cy 120 mg /kg TBI 12 Gy	Leu +26 Ery +31 PLT +45	Focal seizure Septic shock due to *K. oxytoca* GvHD Ac Grade 2 CMV 2 episodes	Skin Ch GvHD CMV 3rd episode	9,3 years post HSCT Chimerism 100% Lansky score 100% No GvHD CR IR 1 year post HSCT
3	Bu 16 mg/kg Cy 120 mg /kg	Leu +13 Ery +15 PLT +29	CVC infection *S. epidermidis* MAS AKI Morphine abstinence syndrome	Lung Ch GvHD Stiff person syndrome Nephrolithiasis	6,6 years post HSCT Chimerism 100% Lansky score 100% No GvHD CR IR 1 year post HSCT
4	Bu 24 mg/kg Cy 120 mg/kg Mel 145 mg/m2	Leu +23 Ery +33 PLT N/A	Ac GvHD Grade 2 SIRS responsive to steroids CSA-TAM BK Hemorrhagic Cystitis BM HHV6 isolation Post HSCT relapse (day +73)	Not available	Dead 4 months post HSCT

Engraft.: engraftment, < 100 d: less than one hundred days, HSCT: hematopoietic stem cell transplant, VP16: etoposide, Cy cyclophosfamide, TBI: total body irradiation, Leu: leukocytes, Ery: erythrocytes, PLT: platelets, SRV: sincitial respiratory virus, GvHD graft versus host disease, CR: complete remission, IR: immunereconstitution, Ac: acute, Ch: chronic, CMV infection or reactivation of cytomegalovirus, Bu: busulfan (oral), CVC: central venous catheter, MAS: Macrophages activation syndrome, AKI: acute kidney injury Mel: melphalan, SIRS: systemic inflammatory response syndrome, CSA-TAM: cyclosporine associated thrombotic microangiopathy, BK: BK virus, HHV6: human herpes virus 6, BM: bone marrow.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

CS, JL, CA, PC and JP acknowledge as conflict of interest been the direct physicians involved in the treatment of patients.

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