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OVERCOMING DIFFICULTIES IN DONOR SELECTION FOR PEDIATRIC ALLOGENEIC TRANSPLANTATION IN A RESOURCE LIMITED COUNTRY

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ABSTRACT

Objective: Describe the actions taken by our program to gain access to worldwide transplant donors, select and procure the preferred donor for our patients, and perform the transplant timely. **Methods:** We worked on three aspects to gain unlimited access to unrelated donors: hiring and training transplant nurse coordinators, fluid communication and collaboration with registries and cord blood banks, and careful planning of the transplant procedure to avoid delays. We start a donor search immediately after we indicate the transplant. Our donor preference is matched sibling (MSD), matched unrelated (MUD), single antigen mismatched unrelated (MMUD), and cord blood (UCB). We gave a haploidentical donor transplant in case of no donor or procurement delays. We analyzed donor usage and time to transplantation in our program from 2014 through 2022. **Results:** We transplanted 166 children between 2014 and 2022. 19% of patients had an MSD, 28% found a MUD, 19% an MMUD, and 24% a UCB. 10% received a haploidentical transplant. Unrelated donors increased from 26% in 2014-2018 to 61% in 2019-2022. DKMS donor centers provided 60% of the products. The mean time to transplantation was 68 days for related donors (MSD and haploidentical) and 74 days for unrelated donors (MUD, MMUD, UCB). Conclusion: We overcame donor selection difficulties with specific actions, accessing all available donors and transplanting patients timely.

Keywords: Transplantation, Homologous. Pediatrics. Blood Banks.

INTRODUCTION

Allogeneic stem cell transplantation (SCT) is performed worldwide for the treatment of a wide variety of life-threatening blood-related diseases in children and adults. A matched sibling is the preferred donor, but only 20-25% of patients have such a donor. Alternative donors include matched and mismatched unrelated (MUD and MMUD), mismatched related (haploidentical), and unrelated umbilical cord blood (UCB). Choosing the best alternative donor for when more than one is available is a highly debated topic. MUDs are the first source of stem cells for pediatric ASCT in most centers and teams in developed countries where there is broad experience in children with results that match those with MSD . CBUs are used in children preferably for some diseases () and MMUD continue to be used in children with malignant and non-malignant diseases. Haploidentical transplant activity has increased rapidly, allowing patients without an unrelated donor to get a timely ASCT . Moreover, transplants with highly mismatched unrelated donors have proved encouraging results constituting a good alternative in pa-

tients without a MUD or haploidentical donor, especially in ethnic minorities. Many studies comparing survival for different donor options in children show similar results. Still, many other outcomes remain controversial, such as acute and chronic graft versus host disease (GvHD) incidence, the impact of disease stage and conditioning intensity on survival, non-relapse mortality, and relapse incidence . Ongoing prospective trials will answer some of these topics. Centers in resource-limited countries face many challenges when selecting unrelated donors. A perceived low chance for a match, lack of familiarity with the search process, complex logistics for countries far away from large donor centers, lack of trained staff in search and coordination, and high upfront cost are some of those challenges. Based on these issues, many centers in Latin America have moved away from unrelated donors to haploidentical SCT with post-transplant cyclophosphamide. Others do not consider or discourage unrelated SCT and thus limit options for patients in choosing the best donor. Hispanic minorities are historically underrepresented in international donor registries, but recent data from the NMDP has shown that up to 80% of Hispanic patients may find either a fully matched or one antigen/allele mismatched donor in the registry. On the other hand, several reports of haploidentical SCT in pediatric malignancies from centers in Latin America have shown its advantages, feasibility, and encouraging results[7,8]. As the field moves along, it is important for individual centers in the region to consider all transplant options and overcome the difficulties in accessing registries and procuring stem cell products, as well as gaining experience in transplantation with unrelated donors, allowing the best donor choice for each patient.

The pediatric SCT program at our institution started with MSD transplants in 1989. Cord blood became available in 1996 and became our only source of alternative donors. Unrelated donor registries were reluctant to work with new centers in Latin America until 2008, when National Marrow Donor Program (NMDP) accepted us as a non-network center. This collaboration opened the doors of every donor center and registry in the USA and Europe, and we could access the World Marrow Donor Association (WMDA) database. We began with haploidentical donor transplants after the technique was proven safe and effective in children in 2014. In order to expand our options and procure stem cell products from all registries and cord blood banks, we took specific actions:

Hire and train dedicated transplant nursing coordinators. They are involved from the beginning, educating parents and children about the steps of getting to transplant. They participate actively in donor search and contact the donor center, registry, or cord blood bank. When we identify a donor, nursing coordinators request confirmatory typing and workup of the donor. They coordinate the procedure with the medical team, bone marrow transplant ward, hospital administrators, and ancillary services when needed (radiation oncology, blood bank, among others)

As in most resource-limited countries, no donor registry in Chile provides search and procurement services. We established a collaboration and fluid communication with donor registries and cord blood banks outside our country. Large registries such as Deutsche Knochenmarkspenderdatei (DKMS) and NMDP regularly assign a search coordinator to communicate with the transplant center and respond to requirements during the search process. They also provide expert advice regarding donor-patient matching.

Careful planning of the transplant procedure: in order to get the patient expeditely to transplant from an unrelated donor, we begin the search and procurement as soon as we make the indication, allowing time to complete the process timely. Patients with malignancies receive protocol chemotherapy to obtain or maintain remission, and patients with other diseases, such as aplastic anemia and immunodeficiencies, receive supportive care until conditioning starts.

We report the result of our actions and usage of different donor sources for children transplanted in our center from 2014 through 2022. We compare the search process results over two periods and the time from indication to transplant between related and unrelated donors for patients with aplastic anemia, acute leukemia, and lymphoma.

SUBJECTS AND METHODS

A donor search is initiated in our center as soon as the transplant team reviews the patient's history and the SCT indication is confirmed. We perform high-resolution typing for HLA A, B, C, DRB1, DQB1, and DPB1 on the patient, siblings and parents. We refer samples to the DKMS Life Science Laboratories (Dresden, DE) and receive results in 7 to 10 working days. If an MSD is unavailable, we immediately search for an unrelated donor or cord blood unit in WMDA (https://searchmatch.wmda.info/). We base our search algo-

rithm on donor type, underlying disease, and the expected time to transplant . In brief, our first choice is a fully matched unrelated donor (MUD) followed by either a one antigen/allele mismatched donor (MMUD) with a permissive DPB1 TCE3 mismatch or a cord blood unit with ≥ 5/8 loci high-resolution match and an adequate cell dose (TNC 10e7/kg and CD34 2 x 10e5/kg). We prefer cord blood for infants and small children when we identify a fully matched unit or expect delays in procuring unrelated donors. Other criteria for choosing are younger donor age, no ABO incompatibility, CMV status (we try to avoid negative donors for positive patients), and gender.

The best unrelated donor or cord blood unit is then selected, and we set a tentative date for the transplant according to the disease type and stage. Patients with malignant diseases receive chemotherapy according to the institution's protocol, and those with non-malignant diseases receive supportive care according to the disease. If no unrelated donor or cord blood unit is available in the initial search or stem cell procurement is delayed beyond the defined date, we test the patient for anti-HLA antibodies. Haploidentical donors considered are a sibling, father, or mother in that order. We select donor centers providing the product according to the expected time for collection and shipping and the cost of the product.

We analyzed the distribution of donor types in the entire cohort and compared two periods, 2014 to 2018 vs. 2019 to 2021. We choose the periods coinciding with the establishment of DKMS in Chile, and we compared the distribution of donor types by Fisher exact test.

Time to transplantation was defined as the number of days from transplant indication to stem cell infusion. We analyzed the difference between related (MSD, haploidentical) and unrelated donors (MUD, MMUD, UCB) between 2016 and 2022 for patients with acute leukemia, lymphoma, aplastic anemia, and Severe Combined Immunodeficiency (SCID).

RESULTS

One hundred sixty-six children received an allogeneic SCT at our center from 2014 through 2022. Diagnosis and disease stage are shown in table 1. 106 had malignancies, and 60 had nonmalignant diseases.

Table 2 shows the donor distribution for the entire population divided by period. As expected, 19% of patients had an MSD. We found matched and mismatched unrelated donors for 47% of our patients and a UCB for 24%. Sixteen patients (10%) received a haploidentical transplant. Noticeably, the proportion of unrelated adult donors increased from 26% to 61% in both periods, while the UCB proportion fell from 44% to 11%.

The origin of stem cell products is listed in table 3. We procured 61% of unrelated donors from DKMS. DKMS Chile provided a sizable proportion of products considering that by December 2021, there were only 150.000 registered donors. 45% of our donors originated from Germany and Poland, and we obtained two-thirds of cord blood units from Spain and the US.

The mean time to transplantation in patients with severe aplastic anemia, SCID, acute leukemia, and lymphoma was calculated in 98 patients and compared between related (MSD and haploidentical) and unrelated donors (MUD, MMUD, CBU). The mean time to transplantation was 78 days (range 21 to 166), with no difference between both groups: 68 days for related donors (SD 33.8) and 74 for unrelated donors (SD 30.7). 46% of transplants were done within 60 days from the indication in the related donor group compared to 33% in the unrelated donor group (Fischer exact test p=0.26).

DISCUSSION

In the era of universal donor availability, transplant teams confront different options. Donor choice for patients without an MSD is a controversial topic. MUDs continue to be the preferred choice, as reported by CIBMTR and EBMT, both in children and adults [6,7]. Transplant teams in resource-limited counties face extra challenges when selecting an unrelated donor due to obstacles in procuring stem cell products from unrelated adult and cord blood donors. Haploidentical donor transplantation has emerged in Latin America as an alternative for those centers with limited access to donor registries and cord blood banks, limited search experience, delays in product procurement, and product cost. Haploidentical donors have allowed many more patients to access a transplant and are therefore being more used. Nevertheless, there is also broad experience with unrelated transplantation in the region, especially in countries with national registries, such as Brazil, Argentina, and Chile. Despite regional shortcomings, many centers continue to prefer unrelated donors for their patients when they are available. .

Few studies have directly compared outcomes with different donor types for pediatric transplantation. The Brazilian Society for Cell Therapy and Bone Marrow Transplantation recently published the overall activity and outcome for transplant indications in

the country from 2012 to 2022, reflecting the increase of haploidentical transplantation in children and adult patients. The authors found a trend for better survival in children with acute myeloid leukemia for haploidentical donors and for unrelated donors in lymphoblastic leukemia patients. However, the numbers were limited, follow-up was short, and differences were non-significant. Most studies of haploidentical donor transplants for pediatric malignancies in the region have been single-arm oriented to demonstrate the advantages and feasibility of the procedure, with promising results. Studies from Brazilian groups showed good outcomes of haploidentical ASCT in children with ALL, aplastic anemia and immunodeficiencies.[16,19] Other studies from Latin America have reported similar outcomes for transplants with MSD or URD[17]. Centers in countries with limited access to donor centers have recurred to haploidentical and cord blood transplantation [18,17].

Our report provides data to confirm that with a trained team, planning, and collaboration, we could overcome the obstacles to procuring stem cell products from donor centers, registries, and cord blood banks outside our country. Some authors have advocated for a restrictive approach to allogeneic transplantation in countries with limited resources where centers should avoid unrelated adult or cord blood donors in favor of haploidentical donors and prefer reduced intensity conditioning to avoid complications and cost (8). As attractive as this approach may look, we must compare its long-term survival outcomes against standard practice in our countries. This comparison should also look carefully at the relative costs of different procedures. The analysis must look not only at the product's upfront cost but also at short- and long-term post-transplant complications such as viral reactivation, hemorrhagic cystitis, and GvHD, for whom modern therapy in our countries may come at a high cost or not be available [17].

Our team established collaborations with all donor centers where we found matching donors and obtained stem cell products on time. This work was done through direct contact and constant communication between our transplant coordinators, donor center staff, and cord blood banks. Most of our donors came from the most prominent donor centers in the world, DKMS and NMDP. As expected, we found a sizable number in DKMS Chile (23%). Nevertheless, 43% came from Germany and Poland, countries with a tiny Hispanic population, probably explained by the over 11 million donors in both countries, the relatively high proportion of western European ancestry of Chilean patients, and the preference of our center.

Time to transplantation is quoted by transplant centers as a crucial factor in the outcome, especially for patients who need an urgent or tightly scheduled transplant[7]. With an early start of the donor search and careful planning, we did not find a difference in time to transplantation between recipients of related and unrelated donors diagnosed with acute leukemia, severe aplastic anemia, or SCID. Scheduled chemotherapy protocols for leukemia before transplantation allowed us to complete the donor search, receive the unrelated donor product, and transplant the patient simultaneously as a related donor, either a sibling or haploidentical. 22 of 24 patients with aplastic anemia received a transplant as upfront therapy. We scheduled a haploidentical transplant if we could not identify an adequate unrelated donor on the patient's first search or if we projected the stem cell product shipment to be more than 60 days.

In conclusion, centers in resource-limited countries such as Chile may access unrelated adult donors and cord blood units with dedicated staff, fluid communication with donor centers, and careful planning of the search and procurement of the product. With the addition of haploidentical donors, every child needing a transplant should proceed to it, and regional centers should try to access all donor types as the field moves. Future studies in the region will need to compare outcomes considering multiple variables derived from the patient (age, disease, stage, conditioning, GvHD prophylaxis) and the donor (age, relationship, match grade). The analysis should include conventional outcomes (survival, relapse, GvHD), post-transplant complications, and cost, both upfront and related to post-transplant complications.

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TABLE 1. Patient´s diagnosis

Congenital hematologic diseases	Blackfan Diamond anemia	6
	Severe congenital neutropenia	2
	Chediak Higashi	1
	Familial Hemophagocytic Lymphohistiocytosis	2
Congenital immunodeficiencies	SCID	5
	Hyper IgM	4
	Wiskott Aldrich	3
	Chronic granulomatous disease	2
	APDS 1	1
	Cartilage Hair Hypoplasia	1
	Leukocyte adhesion deficiency	1
	IPEX	1
	GATA 2 Emerger	1
	X linked proliferative disease (EBV +)	1
	STAT 1 GOF	1
Inborn errors of metabolism	X linked adrenoleukodystrophy	2
	Mucopolysaccharidosis I	2
Severe aplastic anemia		24
Acute lymphoblastic leukemia	CR1	23
	CR2	27
	CR3, not in remission	18
Acute myeloid leukemia	CR1	16
	CR2	6
	Not in remission	3
Chronic myeloid leukemia	Chronic phase	2
Myelodysplasia		5
Hodgkin´s lymphoma		2
Non-Hodgkin´s lymphoma		4

TABLE 2. Donor selection by period

	Total population n	%	2014-2018 (65) n	%	2019-2022 (101) n	%	Difference between periods
MSD	32	19	14	23	18	17	P= 0.2
MUD	47	28	11	18	36	35	P= 0.0173
MMUD	31	19	6	10	25	24	P=0.0065
UCB	40	24	29	48	11	11	P<0.0001.
Haplo	16	10	5	8	11	11	P= 0.45

TABLE 3. Origin of stem cell products

DONOR CENTERS	n
DKMS Germany	27
DKMS Chile	18
Be the Match	17
ZKRD (Germany)	4
DKMS Poland	3
REDMO (Spain)	3
INCUCAI (Argentina)	2
Ezer Minion (Israel)	2
France Graffe de Moelle	1
Anthony Nolan (UK)	1
CEDACE (Portugal)	1
Cord Blood Banks	
Be the Match (US)	12
REDMO (Spain)	11
NCBP (New York)	4
Banco de Vida (Santiago)	3
France Graffe de Moelle	3
ZKRD (Germany)	3
Austria, Belgium, Canada, UK	1 each

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