Establishment of a Pediatric HSCT Program in a Public Hospital in Chile

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Background. In Chile, survival estimates for pediatric patients with cancer are comparable to those in the United States and Western Europe. Approximately 80% of these patients are treated at government-supported centers, and an estimated 65% are cured. We reasoned that cure rates could be further improved if transplantation with hematopoietic stem cells were available for patients with chemotherapy-resistant malignancy. ***Patients and Methods.*** Physicians and nurses were selected to be trained in international centers, and a transplantation unit was developed at Luis Calvo Mackenna Hospital in Santiago. Between October 1999 and December 2003, 59 patients received transplants. Of these, 42 were from HLA-matched family members and 11 were autologous. ***Results.*** The 3-year event-free survival estimate was $72 \pm 10\%$ overall, and it was $81 \pm 10\%$ for the subgroup treated with matched related transplants. Peritransplant mortality was 6.6%. The average cost for an allogeneic transplant in our unit was US $50,000. ***Conclusions.*** We are encouraged by this experience as well as by the overall survival rates and hope to expand the program. Our goal is to extend treatment to all children in the country for whom HSCT is indicated, including those who do not have HLA-identical family donors.

Key words: Chile; hematopoietic stem cell transplantation; initial experience; pediatric program

INTRODUCTION

In Chile, a Latin American nation of 15 million people, approximately 500 new cases of pediatric cancer are diagnosed yearly. Approximately 80% of these patients receive free medical care at government-supported institutions. In 1988, Chilean pediatric oncologists founded a national cooperative group, termed PINDA. With the support of the Ministry of Health, investigators from PINDA promptly developed a National Pediatric Cancer Program and introduced common treatment protocols for all children with cancer in the country [1]. To ensure appropriate therapy, chemotherapeutic agents were made available at no cost as part of treatment. The protocols, which are based on American and European treatment regimens, result in overall 5-year event-free survival (EFS) estimates of approximately $65 \pm 5\%$, an outcome comparable to that of other countries [2,3]. We reasoned that cure rates could be further improved if children with chemotherapy-resistant malignancies could be treated with transplantation, and began efforts to establish a pediatric hematopoietic stem cell transplant (HSCT) program.

After a detailed cost study, the Ministry of Health in Chile approved additional funding for pediatric transplantation. An HSCT unit was developed in the department of pediatric oncology at the Luis Calvo Mackenna Hospital (LCMH), a 220-bed pediatric hospital, where liver and kidney transplant programs had been under way for the last 15 years [4–7]. Establishment of our pediatric HSCT program in Chile took approximately 2 years. We report here our initial results on 60 transplants performed on 59 patients between October 1999 and December 2003.

PATIENTS AND METHODS

Training of Staff

Because a similar transplant program had never existed in Chile, it was necessary for the medical staff to be trained in other countries. To this end, PINDA initiated a collaborative effort with St. Jude Children's Research Hospital (Memphis, TN), and a group of physicians was selected to receive training in HSCT at international transplant centers. Three pediatric oncologists from Santiago were trained for 1 year at Vall d'Hebron Hospital in Barcelona, Spain, where approximately 50 transplants per year are performed. This center was selected on the basis of its excellent HSCT program and the similarities of the languages and cultures of Chile and Spain [8–10]. Other pediatric specialists were trained at St. Jude, including an immunologist, a hematologist, an intensivist, and a pathologist; as well as medical technologists. Three nurses were trained at the Hospital de Clinicas in Curitiba, Brazil.

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Unit Description and Accreditation

The unit comprises four isolation rooms with positive-pressure and high-efficiency particulate arrest (HEPA) air filtration systems, which were tested by staff from St. Jude. Guidelines for preventing opportunistic infections followed recommendations of the Centers for Disease Control and Prevention, the Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation [11]. Each patient has a private room, entrance to the unit is restricted, and hand-washing and isolation measures are strictly enforced. In July 1999, shortly before the unit opened, it was accredited by the Chilean Ministry of Health based on Joint Accreditation Committee of ISHAGE-Europe (JACIE) and European Group for Bone Marrow Transplantation (EBMT) regulations [12]. A transplant expert from Fullbourn Hospital in Cambridge, UK, traveled to Santiago to supervise the accreditation procedures.

Estimated Costs and Number of Patients

The cost study presented to Chile's National Health Fund covered pre-transplant evaluations of donors and recipients, transplantation, tissue typing, chemotherapy, hospital care, and post-transplant follow-up. The Ministry of Health approved an amount equivalent to US $50,000 for each allogeneic transplant and US $25,000 for each autologous HSCT. On the basis of enrollment in PINDA protocols, we estimated that in Chile 60 pediatric patients per year would be eligible for HSCT (40 oncology and 20 non-oncology patients) and that approximately one third would have an HLA-compatible sibling and could be treated with HSCT.

To ensure that patients from all areas of Chile have equal access to participation in the program, cases are reviewed by the PINDA HSCT selection committee, whose 10 members represent all main pediatric oncology centers. Guidelines for selecting the patients for HSCT in the PINDA program are based on those of the European Group for Blood and Marrow Transplantation [13].

Support Outside LCMH

Initially, several types of laboratory procedures were performed at private clinics. For example, radiation therapy and cryopreservation technology were provided at *Clinica Alemana*, in Santiago. Chimerism studies and evaluation of immune reconstitution were performed at the Laboratory of Genetics and at the University of Los Andes, respectively. Currently, the only laboratory procedures being conducted outside LCMH are high-resolution HLA typing, total body irradiation (TBI), and molecular biology testing.

Types of HSCT Offered

Patients who could be treated with the types of HSCT routinely offered (mainly autologous and matched related allogeneic grafts) underwent transplantation at the beginning of the program. Our definition of routinely offered types of HSCT also followed the recommendations of international groups [13]. As a pilot program, we performed haploidentical transplants in four children with pediatric immunodeficiency and unrelated cord blood transplants in two patients who had very high-risk ALL and no family donor.

Stem Cell Sources

HSC harvested from peripheral blood were used for autologous transplants. Bone marrow was the preferred source for allogeneic transplants. G-CSF was not used routinely; only two patients received G-CSF. The first child was a pediatric donor (4 years), very small compared to recipient, and G-CSF was administered to boost white blood cell production. The second was an adult donor for a child who had to receive a second transplant due to engraftment failure. HSC were obtained by bone marrow aspiration in the operating room under general anesthesia. Peripheral blood stem cells were collected by apheresis. We used T-cell-depleted bone marrow from parents for haploidentical grafts, after T-cell depletion by soybean lectin agglutination. Cord blood was used for unrelated donor transplants.

Evaluation for HSCT and Routine Management

Donors and recipients were evaluated before transplants in accordance with International Bone Marrow Registry guidelines [14]. Transfusion procedures and prophylaxis of infections, veno-occlusive disease, and GvHD also followed international standards [11,15,16]. All allogeneic transplant recipients received cyclosporin A (CSA) (5 mg/kg on day -1, 4 mg/kg on day 0, and 3 mg/kg thereafter) $\pm$ methotrexate (15 mg/m^2 on days $+1$, $+5$, and $+11$) as GvHD prophylaxis. CSA doses were adjusted according to CSA serum levels.

Conditioning Regimens

Table I illustrates conditioning regimens administered according to diagnoses and type of HSCT.

HSC Infusion

After administration of methylprednisolone and antihistamines, patients received infusions of peripheral blood or cord blood HSC through a double-lumen Hickman catheter for a period of 10 to 15 min. Infusion of bone marrow cells lasted 4 to 6 hr.

Follow-up Evaluation

Patients were followed weekly until day $+60$ post-HSCT, twice monthly until day $+90$, and monthly until 1 to 2 years

TABLE I. Conditioning Regimens

Type of disease	Type of transplant		Type of therapy
Oncologic diseases			
Lymphoma	Autologous	BEAM chemotherapy	
		BCNU	300 mg/m^2 × 1
		Etoposide	100 mg/m^2 q 12 hours × 4 days
		Cytarabine	100 mg/m^2 q 12 hours × 4 days
		Melphalan	150 mg/m^2 × 1
AML	Autologous	Bu	4 mg/kg daily × 4
		Cy	60 mg/kg daily × 2
Neuroblastoma	Autologous	Melphalan	140 mg/m^2 × 1
		Bu	4 mg/kg daily × 4
AML > 3 years old	HLA-matched sibling	TBI	12 Gy total dose (bifractionated in 3 days)
		Cy	60 mg/kg × 2 days
AML < 3 years old	HLA-matched sibling	Bu	4 mg/kg daily × 4
		Cy	60 mg/kg daily × 2
ALL	HLA-matched sibling	Conditioned similarly to AML + Etoposide	30 mg/kg × 1
CML/MDS	HLA-matched sibling	Bu	4 mg/kg daily × 4
		Cy	60 mg/kg daily × 2
Non-oncologic diseases			
SAA	HLA-matched sibling	Cy	30–50 mg/kg, daily × 4
		Or	Cy as above + ATG or TNI: 7 Gy
SCID	Haploidentical	Bu	4 mg/kg daily × 4
		Cy	60 mg/kg daily × 2
		With or without ATG	
Chédiak-Higashi syndrome in accelerated phase	HLA-matched sibling	Bu	4 mg/kg daily × 4
		Cy	60 mg/kg daily × 2
		Etoposide	30 mg/kg × 1
Fanconi anemia	HLA-matched sibling	Cy	5 mg/kg daily × 4
		TNI	5 Gy
Kostmann syndrome	HLA-matched sibling	Bu	4 mg/kg daily × 4
Blackfan Diamond	HLA-matched sibling	Cy	60 mg/kg daily × 2
Osteopetrosis	HLA-matched sibling	Bu	150 mg/m^2 daily × 4
		Cy	50 mg/kg daily × 4

BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; Bu, busulfan, CML, chronic myelocytic leukemia; MDS, myelodysplastic syndrome; SAA, severe aplastic anemia; SCID, severe combined immune deficiency; TNI, total nodal irradiation.

after transplant. Pulmonary function studies, echocardiogram, and endocrinological and ophthalmological evaluations were performed 1 year after HSCT. Chimerism was evaluated for 12 months. Immunologic recovery was evaluated for 24 months or until immune system recovery.

Chimerism. Chimerism was studied by DNA polymorphism analysis based on PCR amplification of nine short tandem repeat loci. The DNA was extracted by using the Comey method [17] and quantified by using 1% agarose gel electrophoresis with ethidium bromide staining. We used Applied Biosystem's AmpFLSTR Profiler Plus to amplify the amelogenin locus, which is used for sex identification, and the STR loci, which include the following markers: D21S11, D3S1358, D5S818, D7S820, D8S1179, D13S317, D18S51, vWA, and FGA. Some samples were amplified by using Promega Corporation's PowerPlex 16 System, which has a discrimination power of 1.48×10^{11}. Chimerism was evaluated weekly for the first month after HSCT, and then on months 6 and 12 after HSCT.

Immune reconstitution. From October 1999 to August 2003, patients were sequentially studied for a period of 24 months or until immune system recovery (at 1, 3, 6, 12, 18, and 24 months after HSCT). Immune reconstitution was defined on the basis of absolute counts of peripheral blood lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and $CD56^+$) and serum immunoglobulin concentration. Peripheral blood lymphocyte subsets were identified in 2-ml whole blood preserved with ethylenediaminetetraacetic acid (EDTA), according to the surface expression of lineage-specific antigens after 2-color immunostaining (fluorescein isothiocyanate [FITC] and phycoerythrin [PE]). We used a previously reported immunophenotyping protocol [18]. Serum concentration of immunoglobulin (Ig) G, M, and A was assayed by nephelometry. Normalization of serum concentration was defined as the minimal normal value of age-matched reference values.

In November 2003, 3-color immunostaining of peripheral lymphocyte subsets began. $CD3^+CD45RA^+$ and $CD3^+$

$CD45RO^+$ subsets were added to the protocol. Immunostaining patterns were analyzed by using flow cytometry (Coulter Epics-XL). Normalization of lymphocyte subsets was defined as lymphocyte counts in the 5th percentile of the age-matched reference values [19].

Functional activation and proliferation of lymphocyte subsets were assayed by flow cytometry after 4 days of incubation with phytohemagglutinin (PHA). We used bromodeoxyuridine (BrdU) incorporation to determine proliferation (color 1), and CD71 monocolonal antibody (MoAb) to determine activation (color 2) [20]. Normalization of activation and proliferation was considered to have occurred when values reached the 5th percentile of control values.

Survival and Event-free Survival

Statistical methods. Survival was defined as the time from date of HSCT to death from any cause or to last follow-up. For EFS, an event was defined as a relapse, evidence of disease progression, or death (due to any cause). The date of first event was used in calculating EFS. For survival analysis, time was censored at the last follow-up date if no failure was observed. Kaplan–Meier survival estimates were obtained and survival distributions were compared by using the exact log-rank test. The cumulative incidence of relapse was estimated using Prentice's method (Biometrics, 1978). The length of time at risk for relapse was computed from the date of HSCT to the date of relapse, the date of death, or the date of last contact, whichever came first. Death from non-relapse was considered a competing event. The criterion for significance for all analyses was a *P*-value significant at level of $\alpha = 0.05$. All statistical analyses used SAS Release 8.2 (SAS Institute, Cary, NC). The final analysis of the data was performed on September 14, 2004.

Transplant-Related Mortality

Transplant-related mortality was defined as death before day +100 related to GvHD, toxicity, engraftment failure, or infection and not related to relapse of the primary disease.

RESULTS

Patients

Between October 1999 and December 2003, we performed 60 transplants in 59 patients, all at LCMH. One child received 2 allogeneic transplants from the same donor, 3 months apart; and only the first transplant was included in the analysis. Among 59 patients, 11 were autologous and 48 were allogeneic (42 HLA-matched family donor, 4 haploidentical, and 2 unrelated cord blood). All patients had been followed for 100 or more days at the time of this report. The median age at the time of transplantation was 8.3 years (range, 0.7–20.5 years), and 32 patients were boys. Table II lists the diagnoses.

TABLE II. Diagnoses in Patients Undergoing Transplantation

Oncologic diseases	Patients	Non-oncologic diseases	Patients
ALL			
CR 1	12	SAA	8*
CR 2	3	SCID	3
CR 3	1	Kostmann syndrome	2
AML			
CR 1	6	Fanconi	2
CR 2	6	Blackfan-Diamond syndrome	1
Neuroblastoma	4	Osteopetrosis	1
CML	3	Omenn	1
MDS	2	Chédiak-Higashi syndrome	1
NHL	2		
HD	1		
Total	40	Total	19

ALL, acute lymphoblastic leukemia; CR, complete remission; AML, acute myeloblastic leukemia; CML, chronic myelocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; SAA, severe aplastic anemia; SCID, severe combined immunodeficiency.
*One patient received two allogeneic transplants from the same donor.

The overall median hospital stay was 35 days (range, 11–153). The median hospital stay was 35 days (range, 27–153) for children who received an HLA-identical allogeneic transplant and 29 days (range, 11–44) for those who received an autologous transplant.

Stem Cell Sources

The main source of HSC was bone marrow (44 patients). Less commonly used were peripheral blood in 13 transplants (11 autologous and 2 allogeneic) and cord blood in 2. In 11 of 42 HLA-identical allogeneic procedures, the graft was manipulated ex vivo. (In 3, plasma was removed by centrifugation; in 7, red cells were removed; and in 1, plasma and red blood cells were removed.) The haploidentical grafts of four patients were depleted of T cells by soybean lectin agglutination and double rosetting. Table III shows the mean cell doses received by patients undergoing HSCT.

Engraftment

Table IV summarizes the time to engraftment according to type of HSCT. Engraftment occurred within the expected time frames and in all but 1 patient, who required a second HSCT. Platelet reconstitution was defined as a platelet count >20,000/L in patients who had not received a transfusion for 7 consecutive days.

Complications

Acute complications (<100 days). The most frequent acute complication was febrile neutropenia, (49 patients, 83%). Bacterial organisms were isolated in the blood of

TABLE III. Cell Doses Received in Patients Undergoing Transplantation

Cell doses	Statistical measures	Allogeneic-matched related	Autologous	Haploidentical
NC $\times 10^8$/kg	N	40	9	4
	Mean (SEM)	4.21 (0.76)	9.49 (1.08)	9.31 (8.30)
	Median (range)	3.19 (0.90–32.00)	9.70 (4.53–13.76)	1.27(0.48–34.20)
MNC $\times 10^8$/kg	N	41	10	3
	Mean (SEM)	2.99 (0.75)	8.20 (1.23)	4.30 (3.65)
	Median (range)	1.40 (0.40–22.40)	7.52 (4.02–14.13)	0.83 (0.47–11.60)
CD34 $\times 10^6$/kg	N	42	11	4
	Mean (SEM)	2.27 (0.31)	3.89 (0.63)	5.01 (1.25)
	Median (range)	1.46 (0.22–8.34)	3.40 (1.70–9.08)	5.70 (1.43–7.20)
CD3 $\times 10^5$/kg	N	0	0	4
	Mean (SEM)	0	0	3.95 (1.12)
	Median (range)	0	0	3.99 (1.75–6.05)
CFU $\times 10^4$/kg	N	41	11	3
	Mean (SEM)	17.99 (3.63)	29.22 (6.57)	96.40 (69.80)
	Median (range)	10.62 (1.05-97.94)	28.18 (2.40–81.50)	53.00 (3.20–233.00)
Viability	N	22	1	3
	Mean (SEM)	99.55 (0.23)	98.00 (0)	94.67 (2.19)
	Median (range)	100.00 (96.00–100.00)	98.00	93.00 (92.00–99.00)

NC, nuclear; SEM, standard error of the mean; MNC, mononuclear; CFU, colony-forming units.

7 (14%) of these patients and in the urine of another 7. Twelve of the 49 developed hemo dynamic instability that was presumably secondary to sepsis; 11 responded favorably to antibiotic treatment. Thirteen patients (22%) developed cytomegalovirus (CMV) infection, and 1 invasive aspergillosis.

Twenty-three of 42 patients receiving HLA-identical sibling transplants developed acute GvHD, grade II-IV. The incidence and severity were higher among children treated with haploidentical transplants (4/4 grade III/IV). The two children receiving cord blood transplants also developed acute GvHD, both grade I. All patients with GvHD were treated with 1–5 mg/kg of methylprednisolone. Seven patients required additional treatment with anti-thymocyte globulin (ATG) and/or mycophenolate mofetil (MMF). Other acute complications included cyclosporine-related neurotoxicity in five patients and veno-occlusive disease in 1. Four patients (6.6%) died of transplant-related causes: 2 of acute GvHD after a haploidentical transplant and 2 of complications related to infection, 1 after an autograft, and 1after an HLA-identical sibling transplant.

Late complications (>100 days). The most common late complication was chronic GvHD, which occurred in 22 patients (37%) receiving HLA-identical sibling transplants. It was extensive in 17 patients, and 3 died. Treatment consisted of cyclosporine, steroids, and light therapy (psoralen plus ultraviolet A). Two patients developed bilateral aseptic necrosis of the hip as the result of steroid therapy and required medical treatment.

Survival and Performance Status

EFS estimates for 59 patients treated in our unit are shown in Figure 1. The 3-year EFS survival estimate was $72 \pm 10\%$. EFS estimates for 42 patients who received an HLA-identical transplant and the 11 who received autografts are shown on Figure 2. Figure 3 compares the EFS estimates of patients

TABLE IV. Time to Engraftment According to Type of HSCT

		Number of days after HSCT		
Laboratory values	Statistical measures	Allogeneic-matched related (n = 41)*	Autologous (n = 10)	Haploidentical (n = 3)
ANC > 500 $\times$ mm^3	Mean (SEM)	17.68 (0.91)	15.20 (1.20)	12.33 (0.67)
	Median (range)	17.00 (10.00–34.00)	15.00 (9.00–22.00)	13.00 (11.00–13.00)
Platelets > 20,000 $\times$ mm^3	Mean (SEM)	18.44 (1.01)	16.10 (1.87)	14.67 (1.76)
	Median (range)	16.00 (10.00–42.00)	14.00 (12.00–32.00)	14.00 (12.00–18.00)
Platelets > 50,000 $\times$ mm^3	Mean (SEM)	23.63 (2.43)	18.50 (2.07)	33.33 (14.84)
	Median (range)	20.00 (13.00–109.00)	15.50 (14.00–32.00)	19.00 (18.00–63.00)
Reticulocyte > 1%	Mean (SEM)	16.35 (1.01)	14.80 (2.32)	12.33 (0.67)
	Median (range)	14.00 (11.00–47.00)	12.50 (9.00–34.00)	13.00 (11.00–13.00)

*Only 40 patients who received allogeneic-matched related transplants were assessed for recitulocyte counts. SEM, standard error of the mean.

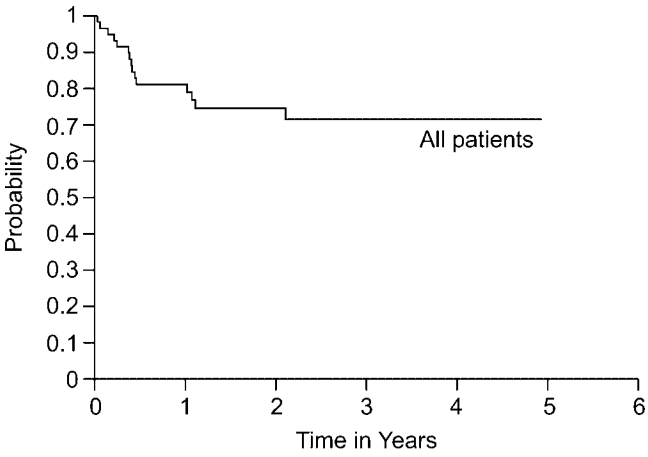

Fig. 1. EFS estimates for 59 patients who received HSCT.

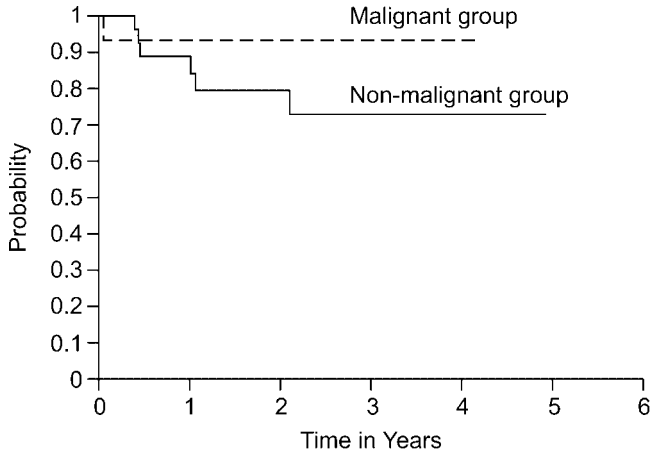

Fig. 3. EFS experience in pediatric patients who received HLA-identical transplants for malignant (n = 27) or non-malignant disease (n = 15).

receiving HLA-identical sibling transplants who had a malignancy (n = 27) with those who did not (n = 15). Four haploidentical transplant recipients and two cord blood transplant recipients were not included in the survival analysis.

Forty-five patients were alive 10–58 months after HSCT; they were recipients of 36/42 HLA-identical, 7/11 autologous, 1/4 haploidentical, and 1/2 cord blood transplants. Of the 14 who died, 10 had leukemia or lymphoma, 3 an immunodeficiency, and 1 aplastic anemia that developed after liver transplant. Altogether eight patients died of transplant-related complications (GvHD, bacterial or fungal infection), 4 within the first 100 days after HSCT and 4 after 100 days. Six patients died of recurrent malignant disease.

Performance status. Performance status was measured for the 45 surviving patients by using the Lansky scale: 32 patients scored 100%; 5, 90%; 3, 80%; 3, 60%, 1, 70%; and 1, 40%.

Relapse

The cumulative incidence of relapse among patients with a malignancy and who received grafts from an HLA-matched allogeneic donor is shown in Figure 4. As shown, at 3 years the incidence was 9.1% ± 5.2%.

Chimerism and Immune Reconstitution

To date, 27 patients who received allogeneic transplants have had chimerism studies on bone marrow samples. Twenty patients demonstrated complete donor chimerism. There were no cases of mixed chimerism. Samples from seven patients were not evaluable. Thirty-seven patients were followed for at least 6 months and were fully evaluable for immune reconstitution; 15 (40%) had normal immunoglobulin serum concentrations and absolute lymphocyte subset counts. Four (one autologous, three allogeneic) also had a normal lymphocyte proliferation response to PHA, indicating complete immune reconstitution. Twelve children died or

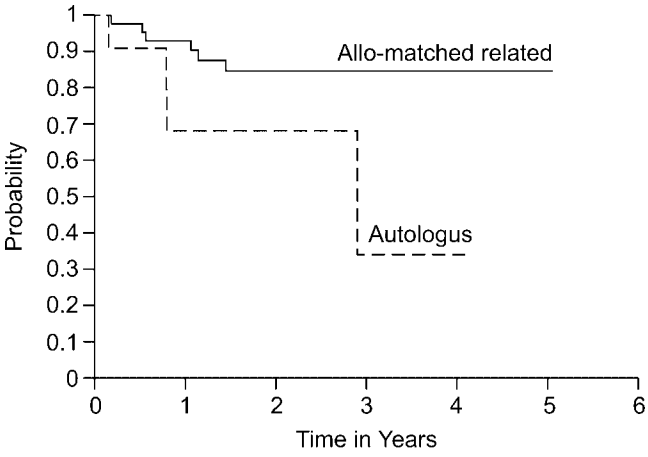

Fig. 2. Comparison of EFS estimates among children treated with autologous (n = 11) versus allogeneic HLA-identical transplants (n = 42).

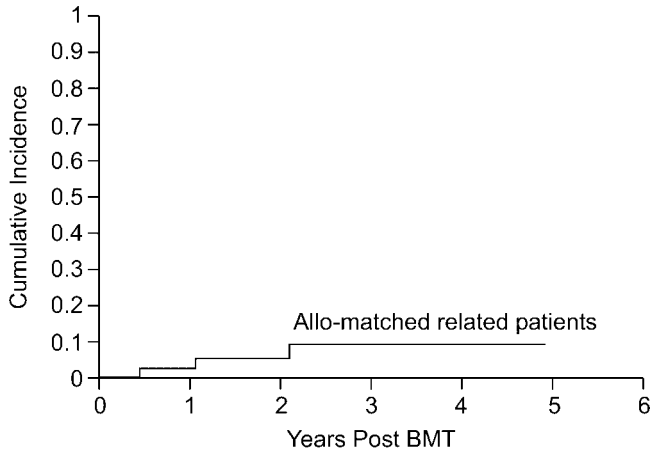

Fig. 4. Cumulative incidence of relapse among patients who received grafts from an HLA-matched allogeneic family donor.

experienced relapse before complete immune reconstitution. Studies are under way in 11. At the time of this report, one child with Omenn syndrome had normal lymphocyte counts and cell function but low serum immunoglobulin concentrations after a 46-month follow-up. Seventeen of the 37 patients followed had normal lymphocyte counts, a diminished $CD4^+/CD8^+$ ratio, and normal serum immunoglobulin concentrations. Lymphocyte proliferation was normal in 3 of 6 patients studied. Finally, 4/37 (one autologous, three allogeneic) patients had normal immunoglobulin serum concentrations, but incomplete immune reconstitution.

DISCUSSION

On the basis of our initial experience, we contend that a pediatric HSCT program is feasible in a public hospital of a developing country such as Chile. Our success has been due in large part to an already established and well-organized pediatric oncology program. For example, because of procedures already in place and the organizational skills of investigators in the existing PINDA group, the Chilean government expanded funding for the treatment of pediatric malignancy to include transplantation. Since only one pediatric HSCT unit could be established to serve the country, a committee was created within PINDA to define transplant indications and to ensure appropriate patient referral throughout the country.

Several other important factors contributed to the development of our program. Chief among them was the establishment of a collaborative effort, which included the training of physicians and nurses at 3 well-known international institutions, that is, St. Jude Children's Research Hospital in Memphis, TN, Vall d'Hebron Hospital in Barcelona, Spain and Hospital de Clinicas in Curitiba, Brazil. Cooperation with St. Jude Children's Research has been facilitated through the institution's International Outreach Program, which was designed to help increase the survival of children with cancer in partner nations [21]. Although medical training is generally good in Chile, we had to send staff to be trained at these centers because the pediatric community had almost no experience in HSCT. Also contributing to the results has been the presence of 3 full-time physician-transplant specialists in the unit and effective 24-hr nursing care.

We were able to start our HSCT program without having to undertake new construction by remodeling an oncology ward in an existing hospital to meet current international standards. Remodeling costs to open the transplant unit within the LCMH were not prohibitive and were funded by AMICAM (Friends of Calvo Mackenna Hospital), a private fundraising foundation in Santiago. Public funds are always limited in developing countries; therefore, efforts to be cost efficient are almost mandatory.

Since its establishment, the program has grown in both the number of patients treated and in the types of transplants that are being performed. Because we had no local model to guide our efforts, we reviewed the literature and adapted existing protocols to local needs. During the first year of operation, we treated 10 patients, a number that has now grown to 20 per year. In the first phase of the program, we treated mainly children with HLA-matched siblings. In a recent pilot project, we performed haploidentical grafts in 4 children with immunodeficiency and cord blood transplants in 2 patients with very high-risk leukemia and no related donor.

The overall results of the HSCT program to date are comparable to those of other programs [22,23] with a 3-year EFS estimate exceeding 80% for allogeneic transplants and a low cumulative incidence of relapse. The results for patients with acute leukemia who received an HLA-identical graft are also similar to those reported [8–10]. Four children with high-risk neuroblastoma who received an autograft are also well [24]. The results obtained for patients with non-oncological diseases who received a transplant from an allogeneic-related donor are similarly encouraging. For example, only one of nine patients with severe aplastic anemia (SAA) has died. Overall, the rates of peritransplant morbidity and mortality (days 1–100) have been as low as those reported by others [25], validating the effectiveness of the guidelines and procedures that we have used.

Because some services were not initially available at LCMH, selected laboratory procedures and irradiation therapy were performed at *Clinica Alemana*, a private clinic in Santiago. We are in the process of transferring technology to our own center and acquiring the knowledge to use it to the best advantage. For example, we are now able to perform all procedures related to ex vivo graft manipulation.

At LCMH, allogeneic transplantation cost an amount equivalent to US $50,000 and autologous transplantation, US $25,000; these costs include evaluation of recipients and donors prior to the procedure, all hospitalization, and 1–2 years of clinical follow-up for those who received autologous and allogeneic transplants. On the basis of a cost comparison with other centers in the United States and Europe, our program has achieved good clinical results within a comparatively low budget [26].

We are encouraged by these results and hope to expand the HSCT program in the near future. To prepare for this possibility, we are undergoing additional training in higher-risk transplants such as those using unrelated or haploidentical donors. Our ultimate goal is to offer transplantation to all children requiring such treatment in the country, including those who do not have an HLA-identical family donor. We estimate that a total of 60 children per year may require HSCT in Chile.

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