original report

Importance of Nongovernmental Organizations for the Establishment of a Successful Hematopoietic Stem-Cell Transplantation Program in a Developing Country

abstract

Purpose In low- and middle-income countries with limited resources, the success of a hematopoietic stem-cell transplantation (HSCT) program relies directly on its affordability while obtaining similar outcomes to developed regions. The objective of this study was to describe the experience of a tertiary/referral center in Mexico City performing HSCT with the subsidy of a nongovernmental organization (NGO).

Patients and Methods We performed a retrospective analysis including 146 patients who underwent HSCT at the National Institutes of Health Sciences and Nutrition Salvador Zubiran and were subsidized by the NGO Unidos.

Results Seventy-five patients (51%) and 71 patients (49%) underwent autologous and allogeneic HSCT, respectively. The median age was 30 years, 56% did not obtain a bachelor's degree, 79% had a low socioeconomic level, and 75% were unemployed. None had any health coverage. According to the real patient out-of-pocket expense, the subsidy by Unidos corresponded to 88% and 72% in autologous and allogeneic HSCT, respectively.

Conclusion Our results highlight that undergoing an HSCT was feasible for vulnerable patients because of the subsidy of medications and chemotherapy by Unidos. Therefore, creating NGOs in developing countries is important to provide complex medical procedures, such as HSCT, at limited-resource centers to underserved populations while obtaining good outcomes.

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INTRODUCTION

For many years, nongovernmental organizations (NGOs) have endeavored to fill the gaps in health service delivery, research, and advocacy, especially in some developing countries where health services can be provided to improve access and quality of care.[1,2] In low- and middle-income countries with limited health care resources, the success of a hematopoietic stem-cell transplantation (HSCT) program depends directly on its cost and affordability while obtaining similar outcomes to developed regions. This challenge can be more critical for governmental hospitals caring for uninsured patients.[3-6] The first HSCT in Mexico was performed in the 1980s at our institution, the National Institute of Medical Sciences and Nutrition Salvador Zubiran. However, because of the lack of infrastructure, staff, and financial resources, fewer than 30 transplantations were performed during the following 18 years, and a low overall survival (OS) and high transplantation-related mortality were observed. In 1998, our HSCT program was restructured to improve outcomes. Some of the main goals associated with this restructuring were the development of new approaches to reduce transplant-related mortality while increasing the number of transplantations performed annually. However, because health care services in Mexico vary according to employment status, not everyone has health insurance, and procedures such as HSCT are hard to fund. For example, public institutions provide health care coverage for formally employed citizens. On the other hand, health care delivered through private insurances

is only available to those who can afford it. In 2004, the Catastrophic Expenses Protection Fund (Seguro Popular) was introduced, offering coverage to informally employed Mexicans, and this governmental program began to cover HSCT expenses in 2015. Therefore, the implementation of financial and medical strategies was mandatory to achieve our desired objectives regarding improvement of HSCT outcomes. In 2000, the NGO Unidos…Asociacion Pro Trasplante de Medula Osea Francisco Casares Cortina, A.C. (Unidos) was established in honor of a young patient with leukemia who underwent a transplantation, with the mission to increase the affordability of HSCT among Mexican adults. Ever since, Unidos has offered financial assistance and free support services to adult patients undergoing HSCT and their families, relying on private donations to provide these vital services. Although donations have been limited throughout the years, and Unidos remains a grassroots group, funds have helped cover chemotherapy, immunosuppressive, and other expensive medications not provided by our institution in a substantial number of patients undergoing HSCT. Furthermore, because our institution subsidizes inpatient hospitalization and further outpatient consultations according to a socioeconomic classification assigned during a first interview with social services, before the creation of Unidos, it was almost unattainable for patients to undergo HSCT because of the high costs related to chemotherapy and other medications. The objective of this study was to describe the experience of an HSCT program at a tertiary/referral center in Mexico with the support of an NGO.

PATIENTS AND METHODS

Patients

This is a retrospective analysis of patients who received subsidies from the NGO Unidos and underwent an HSCT at the National Institutes of Health Sciences and Nutrition Salvador Zubiran in Mexico City from March 2003 to June 2016. All adult patients without any health insurance registered at our institution requiring HSCT were candidates to apply for Unidos economic aid to afford chemotherapy and other medications. The information used for this study derived from patients' information collected from the transplantation program records, hospital official medical records, electronic records including imaging and pathology, and the NGO database. All patients signed an informed consent before undergoing HSCT. Our Institutional Review Board approved the usage of patients' information for this study.

Inpatient Procedure

For autologous HSCT, hematopoietic stem cells were collected by peripheral blood apheresis and for most allogeneic transplantations (allo-HSCT) by multiple aspirations of the iliac crests (bone marrow). All patients were admitted in rooms with high-efficiency particulate air filters 1 day before the beginning of the conditioning regimen. Patients undergoing autologous HSCT were conditioned with standard BUCY2 (busulfan 16 mg/kg orally and cyclophosphamide 120 mg/kg intravenously [IV]), BEAM (carmustine 300 mg/m^2 IV, etoposide 800 mg/m^2 IV, cytarabine 1,000 mg/m^2 IV, and melphalan 140 mg/m^2 IV), MEL-200 (melphalan 200 mg/m^2 IV), or etoposide and carboplatin (1,200 mg/m^2 IV and 1,500 mg/m^2 IV). Patients with malignant hematologic disorders undergoing an allo-HSCT received reduced BUCY2 (busulfan 12 mg/kg orally and cyclophosphamide 80 mg/kg IV), standard BUCY2, and reduced-intensity regimens (RIC; fludarabine 120 to 180 mg/m^2 IV and busulfan 16 mg/kg orally). Patients with aplastic anemia received conditioning regimens including antithymocyte globulin (60 mg/kg IV) and/or cyclophosphamide (200 mg/kg IV). Graft-versus-host disease (GVHD) prophylaxis, antimicrobial therapy (prophylactic and empirical), blood products, and nutritional support were provided according to institutional and international guidelines.

Outpatient Follow-Up

Patients were discharged when engraftment occurred and in the absence of infections or complications. For allo-HSCT follow-up, patients underwent weekly outpatient consultations for 2 to 4 months. Laboratories taken during every visit included: CBC count, comprehensive metabolic panel, cytomegalovirus antigenemia, cyclosporine levels, and magnesium. Chimerism was performed once monthly for 6 months. Medications included trimethoprim-sulfamethoxazole, acyclovir, cyclosporine A, omeprazole, and magnesium. For autologous outpatient follow-up,

visits took place twice a month during the first 2 months. Requested laboratories were CBC and liver panel, and no medications were prescribed.

Definitions and End Points

The demographic variables were: age, sex, socioeconomic level, educational attainment, marital status, occupation, health insurance, residence, and living area. Real patient out-of-pocket expense was considered as the real payment made by patients to our institution according to their socioeconomic classification plus chemotherapy, immunosuppressive, and other expensive medications (not provided by our institution). Subsidies from Unidos exclusively included costs of chemotherapy, immunosuppressive, and other expensive medications not provided by our institution. Non-relapse mortality (NRM) was defined as death related to the conditioning regimen, infections during aplasia or under immunosuppressive treatment, or associated with the development of GVHD, without relapse/progression and excluding causes due to underlying disease. Relapse- and progression-free survival was established as the length of time from transplantation until relapse or progression of the underlying disease. OS was defined as time from transplantation until death from any cause.

Cost Calculation

At our institution, hospitalization (inpatient days, supportive therapy such as blood products and nutritional support, laboratories, imaging, antibiotics, and some medications such as antimicrobial therapy) and further outpatient consultation expenses (visits and laboratories) vary according to socioeconomic classification assigned to our patients by the Department of Social Work, ranging from 1 to 6, which correspond to a payment of 4%, 16%, 36%, 47%, 77%, and 100% of the total cost (ie, if a patient was classified as 3, they will pay 36% of the total cost, and our institution through the Health Ministry will pay the remaining 64%). This classification is based on the patient's income, living area, occupation, and other social and economic factors.

Therefore, percentages of expenses subsidized by Unidos were calculated by considering previously published overall costs for allogeneic and autologous HSCT at our center (considering socioeconomic level 6, full payment without institutional subsidy)[7] and by considering the real patient out-of-pocket expenses. The currency charged by our institution is Mexican pesos, and conversions to 2016 US dollars (USD) were made for this study.

Statistical Analysis

Continuous variables were described by the median and interquartile range using the frequency analysis. Categorical variables were described by frequencies and percentiles. The OS for all patients was calculated using the Kaplan-Meier estimator. Cumulative incidence estimates were calculated for other end points (NRM, relapse, GVHD) to account for competing risks. SPSS v.21 (IBM, Chicago, IL) was used.

RESULTS

Demographics

One hundred forty-six patients underwent an HSCT from March 2003 to June 2016. Most patients underwent HSCT from 2010 to 2016 (n = 86; 59%). Seventy-five HSCTs were autologous (51%), and 71 were allogeneic (49%). Median age was 30 years (15 to 64 years). Patient demographics are shown in Table 1. The following range of underlying diseases was presented: nonseminomatous germ cell tumor (n = 22; 15%), aplastic anemia (n = 19; 13%), non-Hodgkin lymphoma (n = 19; 13%), acute myeloid leukemia (n = 16; 11%), myelodysplastic syndrome (n = 15; 10%), Hodgkin lymphoma (n = 14; 9.5%), acute lymphoblastic leukemia (n = 13; 9%), multiple myeloma (n = 11; 7.5%), chronic myeloid leukemia (n = 5; 3%), and others (n = 12; 8%; three paroxysmal nocturnal hemoglobinuria, two Fanconi anemia, two myelofibrosis, one erythropoietic protoporphyria, one Crow-Fukase syndrome, one adrenoleukodystrophy, one primitive neuroectodermal tumor, and one myeloproliferative neoplasm). Conditioning regimens for all HSCTs were: reduced BUCY2 (n = 52; 36%), BEAM (n = 29; 20%), MEL-200 (n = 9; 6%), carboplatin plus etoposide (n = 18; 12%), BUCY2 (n = 8; 5%), and RIC (n = 30; 20%).

Table 1. Patient Demographics and Clinical Characteristics

Characteristic or Demographic	No. (%)
Sex	
Male	94 (64)
Female	52 (36)
Median age (range)	30 (15-64)
Type of transplant	
Autologous	75 (51)
Allogeneic	71 (49)
Period of HSCT	
2003-2009	60 (41)
2010-2016	86 (59)
Underlying disease	
AA	19 (13)
ALL	13 (9)
AML	16 (11)
CML	5 (3)
HL	14 (9)
MDS	15 (10)
MM	11 (8)
NHL	19 (13)
NSGCT	22 (15)
Others	12 (9)
Socioeconomic level	
I-II	115 (79)
III	20 (14)
≥ IV	11 (7)
Educational attainment	
None	1 (1)
Elementary to high school	80 (55)
Bachelor or higher	32 (22)
Unknown	33 (22)
Healthcare insurance	
Yes	0 (0)
No	146 (100)
Marital status	
Married	47 (32)
Other	99 (68)
Occupation	
Employed	110 (75)
Unemployed/student	36 (25)
Living region in Mexico	
Mexico City	53 (36)
North	12 (8)
Center	72 (49)
South	9 (7)
Living area	
Urban	128 (88)
Rural	18 (12)

(Continued in next column)

Table 1. Patient Demographics and Clinical Characteristics (Continued)

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; HSCT, hematopoietic stem-cell transplantation; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NSGCT, nonseminomatous germ cell tumor.

Outcomes

One hundred twenty-four patients (84%) presented toxicity to the chemotherapy regimen; however, only 25% presented grades III to IIV. Most frequent toxicity was upper mucositis (n = 81; 55%), followed by hepatic effects (n = 58, 40%).

The incidence of GVHD in allogeneic HSCT was as follows: acute GVHD in 19% (14 of 71), mostly grade II (57%). Chronic GVHD presented in 24 patients (34%), mostly limited (75%). Thirty-day NRM was 1% for autologous and 12% for allogeneic transplantation, and 100-day NRM was 1% and 17% for autologous and allogeneic transplantation, respectively. For allo-HSCT, 1- and 3-year NRM was 22% and 25%, respectively.

At the last follow-up, 96 patients (66%) were alive. Fifty patients were dead (n = 22; 44% and n = 28; 56%, autologous and allogeneic, respectively). Most frequent causes of mortality were relapse and infections, 90% and 10% for autologous and 54% and 25% for allogeneic, respectively. GVHD was the cause of death in seven (21%) patients undergoing allo-HSCT.

Five- and 10-year relapse was observed in 45% and 33%, in autologous and allogeneic HSCT, respectively (Fig 1). As shown in Figure 2, 5- and 10-year OS were 70% and 65% for autologous and 59% for allogeneic, respectively. Analysis by time intervals (2003 to 2009 and 2010 to 2016) did not provide accurate information regarding relapse and survival because of major heterogeneity in underlying diseases (results not shown).

Costs

According to previously published costs,[7] subsidies from Unidos (chemotherapy and other medications, including granulocyte-colony stimulating factor for harvesting and immunosuppressive

treatment) are listed in Table 2, corresponding to 42% and 40% of the cost (socioeconomic level 6, no institutional subsidy) in autologous and allo-HSCT, respectively. However, according to the real patient out-of-pocket expense (by socioeconomic level ≤ 5, institutional subsidy 23% to 96%, plus medications not provided by our institution), the subsidy from Unidos corresponded to 88% and 72% in autologous and allo-HSCT, respectively (Table 2).

DISCUSSION

HSCT is a relatively complex medical procedure, and seeking sustainable funding is part of the main practical guidelines when establishing an HSCT program. Costs are always a main issue for low- and middle-income countries, especially because this procedure is one of the most expensive medical interventions.[8] Also, it prompts ethical dilemmas because of its morbidity and mortality. HSCT is an economically viable treatment of hematologic diseases in well-resourced countries, and recently it has become feasible to perform this procedure in developing countries.[7,9-11]

Currently, updated HSCT statistics in Mexico have not been published; a recent study performed in Latin America[11] reported a transplantation rate of 127 and 97 allogeneic and autologous transplantations in 2012, respectively. Our institution and the National Cancer Institute, along with other governmental centers, are the primary tertiary/referral hospitals to perform HSCT, and at the moment, approximately 20% of HSCT in Mexico is performed at our institution. On the other hand, allo-HSCT is not performed by all centers in Mexico; thus, we perform approximately 30% of this type of procedure.

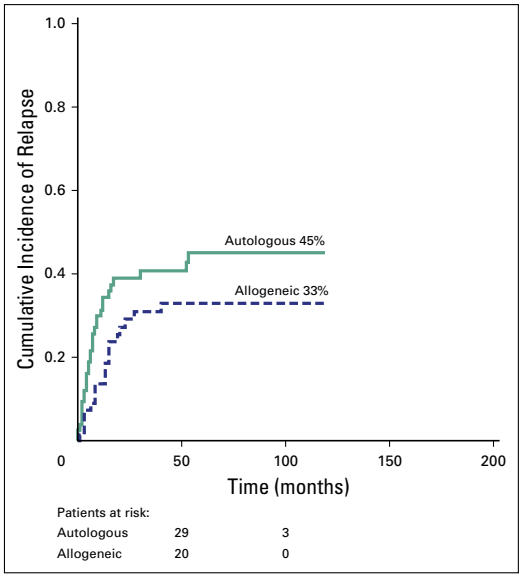

Fig 1. Relapse/progression in autologous and allogeneic hematopoietic stem-cell transplantation.

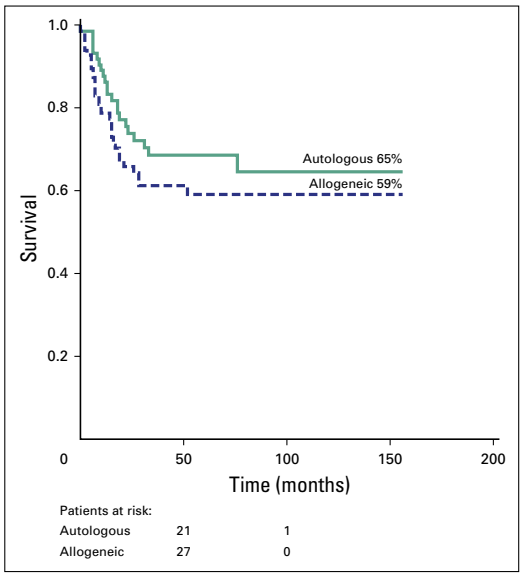

Fig 2. Overall survival in autologous and allogeneic hematopoietic stem-cell transplantation.

After the restructuring of our program in 1998, a total of 146 patients have received an HSCT (mostly autologous; n = 75), obtaining financial support from Unidos. More than 10 transplantations have been performed annually, with an increase during the last 5 years (> 15/y), compared with 33 transplantations at the beginning of our program (1986 to 1997), before the restructuring. Also, we observed a remarkable improvement in outcomes: 100-day NRM for autologous and allogeneic HSCT substantially decreased (1% *v* 30% and 12% *v* 61%, respectively), along with acute GVHD in allo-HSCT (37% *v* 19%).

NGOs have become increasingly important players in global health and development, operating projects in low- and middle-income countries throughout the world.[12] Although NGOs in Mexico can be traced to the 19th century in the form of charities or voluntary organizations, it was not until the 1970s that many foundations were set up, and during the 1980s NGOs began to set up in large numbers. In 1995, the Mexican government began to develop policies on establishing collaborative agreements with civil society organizations.[13] According to the National Registry of NGOs, approximately 27,000 NGOs have

Table 2. Costs and Subsidies from Unidos (2016 USD)

Medication	Autologous Median Cost USD (range)	Allogeneic Median Cost USD (range)
Harvesting[7] G-CSF	612 (68 per injection, 9 total)	476 (68 per injection, 7 total)
Inpatient[7]	1,157 (106-15,551)	2,629 (1,349-7,513)
Antibiotics		
Immunosuppression		
Supportive therapy (blood products and nutritional support)		
Conditioning chemotherapy[7]	4,171 (309-5,463)	1,779 (126-7,318)
Outpatient[7]	N/A	1,200
Bactrim		
Acyclovir		
Cyclosporine A		
Magnesium		
Omeprazole		
Costs		
Published HSCT costs[7]	12,155	18,260
% subsidized by Unidos	42	40
HSCT real patient out-of-pocket expense	6,772 (5,616-12,155)	8,491 (6,185-18,260)
% subsidized by Unidos	88	72

Abbreviations: G-CSF, granulocyte-colony stimulating factor; HSCT, hematopoietic stem-cell transplantation; N/A, not applicable; USD, US dollars.

been registered in Mexico so far; however, they are engaged in a wide variety of activities. Only approximately 10% correspond to associations helping patients with cancer, of which only three, including Unidos, help patients undergoing an HSCT.

The contribution of NGOs to the HSCT field is not recognized; there are still few public agencies that collaborate with NGOs, and agreements are often limited to short-term financing of projects. The future of NGOs in Mexico will depend largely on their ability to obtain funding from within the country, and more effective mechanisms from the government are needed to generate resources for health care. In Latin America, governmental support to NGOs accounts for only 8%, compared with 85% of auto-generated resources. This is minimal compared with developed countries, where public support is approximately 35%.[14,15]

We performed a microcosting analysis at our institution describing the costs in Mexico: 12,155 USD for autologous and 18,260 USD for allogeneic transplantation,[7] highlighting an abysmal difference between these results and costs in developed countries.[4] Within the inpatient HSCT procedure, we demonstrated that hospitalization and conditioning regimens were associated with higher expenses, and the contribution of 2-month outpatient care to overall expenses in our experience was relatively small.[7] Expenses associated with health care in some developing countries might be lower, probably as a result of diminished costs in patient care and perhaps because some medications are more affordable; however, because of the socioeconomic characteristics of the total population in Mexico (> 50% live in vulnerability and poverty, earning a minimum average monthly salary of approximately 120 USD), HSCT remains unaffordable for the majority. Consequently, since its creation, Unidos has supported poor, underserved patients in need of an HSCT. This cohort included young patients, with a median age of 32 years, who did not obtain a bachelor degree (56%), had a socioeconomic level < 3 (79%), and were unemployed (75%). Twelve percent lived in rural areas, most of them lived in Mexico City or nearby states (85%), and none had public or private health coverage.

In summary, we demonstrated that undergoing an HSCT was feasible because of the subsidy of most medications and chemotherapy by Unidos, showing that this NGO helped patients undergoing autologous and allogeneic HSCT with 88% and 72% of real out-of-pocket expenses, respectively. An HSCT program at a public/governmental hospital in a developing country is feasible, but, most importantly, it is possible to obtain similar outcomes when compared with developed countries.[16] Because of budgeting restrictions in low- and middle-income regions, cost-effectiveness must be maximized. Although scientific information is available, sometimes it can be biased to the reality of developed countries; hence, experiences of centers in limited-resourced countries should be reported to learn from them and have a wide view of difficulties and clever solutions on common issues regarding HSCT. Our results highlight that creating NGOs in developing regions is important to provide complex medical procedures, such as HSCT, at limited-resource centers to vulnerable patients while obtaining good outcomes.

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Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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