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Analysis

Hematopoietic Stem Cell Transplantation in Nepal: International Partnership, Implementation Steps, and Clinical Outcomes

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A B S T R A C T

Blood and marrow transplantation (BMT) is rarely available in many low- to middle-income countries (LMICs). In 2012, Civil Service Hospital, a government hospital in Kathmandu, partnered with the University of Illinois at Chicago to consult on the establishment of BMT in their hospital, train staff, and promote educational activities. The implementation of BMT occurred in 3 phases over 4 years and included regular onsite visits, training of personnel in Chicago, continuous remote communication, and co-organization of educational events in Kathmandu. The Nepalese government funded the construction of a state-of-the art BMT unit and stem cell laboratory inside Civil Hospital. Autologous (auto) hematopoietic stem cell transplantation (HSCT) was started in 2016, and allogeneic (allo) HSCT from matched related donors (MRDs) or haploidentical (haplo) donors was initiated in 2017. The cost of transplantation was $5200 for auto-HSCT, $10,000 for MRD HSCT, and $13,300 for haplo HSCT. The major socioeconomic determinants reported by Nepalese BMT providers were the cost of transplantation, loss of revenue of the patient and/or caregiver, and cost of transportation. All patients (n = 66) received peripheral blood stem cell grafts, and all allo-HSCT recipients were given post-transplantation cyclophosphamide as graft-versus-host disease (GVHD) prophylaxis. Among recipients of auto-HSCT (n = 30), with a median follow-up of 1029 days (range, 130 to 1653 days), 87% were alive, and transplantation-related mortality (TRM) was 10%. Among allo-HSCT recipients (n = 36), all patients engrafted, and at a median follow-up of 204 days (range, 12 to 1131 days), 75% of them were alive (MRD, 71%; haplo, 83%), with a TRM of 19%. Only 3 of 36 patients developed acute GVHD grade II-IV. The median overall survival in auto-HSCT recipients was 1610 days and was not reached in allo-HSCT recipients. The long-lasting partnership with University of Illinois at Chicago helped build capacity and allowed the Civil Service Hospital team to establish a BMT program in Nepal that has high quality standards at an affordable cost for the majority of patients.

INTRODUCTION

Transplantation of hematopoietic stem cells (HSCs) is an expensive procedure that has been developed extensively in high-income countries (HIC) but remains limited in low- to middle-income countries (LMICs). In fact, although the rate of HSC transplantation (HSCT) in 2016 was 560 per 10 million population in North America and 438 in Europe, it was only 53.6 in Southeast Asia/Western Pacific and 27.8 in Africa/East Mediterranean [1]. The gap between the need and healthcare capacity in countries accounting for the majority of the world's population is enormous owing to various political, socioeconomic and cultural factors, as well as to the scarcity of training programs in many of these countries. Among the LMIC countries without HSCT is Nepal, a relatively small country between China and India with approximately 30 million people, a gross national income per capita that before the recent pandemic

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had increased to $1230 [2], and with extensive mountainous areas (the Himalayas). The healthcare system of Nepal is limited mostly to urban areas [3–6], and care delivery is based largely on self-pay [7,8]. In addition, Nepal has a high rate of blood cancers, such as acute leukemias and lymphomas, which are associated with mortality of approximately 90% [9], as opposed to <50% in high-income countries (HICs). This is likely because postdoctoral training in hematology historically was not included in the Nepalese medical education system, and the care of patients with hematologic disorders was provided by physicians with internal medicine, medical oncology, or radiation oncology expertise. HSCT was initiated in the neighboring India in the 1980s and is now offered in multiple Indian cities, including New Delhi, which is relatively close to Nepal. However, only a small proportion of Nepalese patients had sufficient financial resources to undergo HSCT in India or other countries. Therefore, the majority of patients with severe blood disorders could not afford to seek treatment abroad, and high mortality was the result.

To address the urgent need for HSCT in Nepal and make it financially accessible to a large proportion of patients, in 2012 a Nepalese physician who previously trained in hematology and headed the Department of Hematology at a government hospital in Kathmandu (Civil Service Hospital) established a partnership with the University of Illinois at Chicago (UIC) for training and consulting on the development of a blood and marrow transplantation (BMT) program. Civil Service Hospital performed its first HSCT in 2016. Here we describe the implementation plan that led to this achievement, the tools and determinants identified in the process, as well as the clinical results of 66 HSCTs performed between 2016 and 2020.

METHODS

Partnership

In 2012, UIC and Civil Service Hospital signed a memorandum of understanding to support the establishment of an HSCT program. At that time, the Binaytrara Foundation (Seattle, WA) also agreed to support the project. Civil Service Hospital is a 130-bed public multispecialty government hospital in Kathmandu and is the sole institution in Nepal with a dedicated hematology department, run by the lone certified hematologist in the country, according to the Nepal Medical Council.

Each partner contributed to the development of a plan that included training Nepalese staff at UIC, providing Continuous Medical Education on hematologic malignancies and BMT in Kathmandu, and monitoring the initial phases in establishing the clinical program. For the last 5 years, UIC and Civil Service Hospital have maintained an ongoing collaboration including biannual onsite visits, frequent remote communication, and research studies.

Implementation Plan

A 3-phase implementation plan was designed based on direct engagement of Nepalese medical and administrative teams (stakeholders) during onsite visits and ongoing remote communication via email and WhatsApp messaging. Phase 1 was aimed at reaching an agreement with hospital administration to build a BMT unit based on UIC standard requirements; initial training of 1 hematologist, 1 pathologist, and 1 nurse at the UIC BMT program in Chicago for 3 months; and exchanging technical information on equipment and logistic requirements. Regular visits of UIC's BMT Director to Kathmandu were scheduled twice yearly to meet with doctors, nurses, lab staff and administrators, and these visits continued throughout all 3 phases. Phase 2 included the construction of the BMT unit with a high-efficiency particulate air (HEPA)-filtered space, including 2 patient rooms with positive laminar airflow, a clinical stem cell lab with a flow cytometer, and an automated cell cryopreservation system, as well as a -80 °C freezer for direct short-term (up to 6 months) stem cell cryopreservation, and a donor room in which peripheral blood stem cells (PBSCs) from patients or donors are collected with a Spectra Optia apheresis system (Terumo BCT; Manganam Kottayam, Kerala, India).

On completion of the foregoing tasks, phase 3 included multiple meetings with staff to share guidelines and policies and address questions, quality validation of BMT unit HEPA filters by local engineers, and validation of hematopoietic stem cell (HSC) collection by purchasing commercial mobilized HSC products to run flow cytometry analysis of $CD34^+$ cells, assess the cryopreservation system, and evaluate cell viability on thawing. These latter validations were carried out with the support of the UIC stem cell lab team in Chicago. After quality validation, the plan was for the BMT unit to perform autologous (auto) HSCTs for 1 year and with 10 patients, before initiating allogeneic (allo) HSCT.

Patients and Methods

The first auto-HSCT was performed in August 2016, and the first allo-HSCT was performed in August 2017. A retrospective study by chart review was approved by the Civil Service Hospital Ethical Committee to analyze the results of BMT in all the patients transplanted from August 2016 to December 2020. A total of 66 consecutive cases were analyzed. Eligibility criteria for auto- and allo-BMT included age >3 and <65 years, standard indication criteria to HSCT for patients with hematologic malignancies or severe blood disorders, and standard eligibility criteria determined by adequate organ function assessed before transplantation. For allo-HSCT, patients received grafts from either an HLA-matched related donor (MRD) or a haploidentical (haplo) (>2 HLA antigen-mismatched) related donor.

Transplantation

Donor selection was based on high-resolution molecular HLA-A, -B, -C, -DRB1, and -DQB1 typing (Histogenetics, New York, NY) and donor-specific antibodies (DSA) titer <5000 in haplo-HSCT. In both auto- and allo-BMT, the HSC source was mobilized PBSCs. Patients or donors received filgrastim (granulocyte colony-stimulating factor) at 10 to 12 μg/kg/day s.c. for 5 days. If they had >20 circulating $CD34^+$ cells/μL, measured by standard flow cytometry CD34 cell assay (BD Stem Cell Enumeration Kit; BD India, New Delhi, India), they then underwent leukapheresis to collect $>2 \times 10^6$ $CD34^+$ cells/kg of the recipient. After collection, PBSC products were moved inside the cell processing lab in a close HEPA-filtered space, analyzed for microbial sterility, RBC contamination, and total number of $CD34^+$ cells, followed by cryopreservation via either a controlled-rate freezer with liquid nitrogen or a dump freezing technique and storage in a -80 °C mechanical freezer.

Conditioning regimens used in auto-BMT included a standard BEAM regimen [10] for patients with lymphoma, high-dose melphalan [11] in patients with multiple myeloma (MM), and a standard myeloablative busulfan/cyclophosphamide (BuCy) regimen [12] in patients with myeloid malignancies. In allo-HSCT from MRDs, conditioning regimens included myeloablative fludarabine/i.v. busulfan for 4 days or reduced-intensity fludarabine/melphalan [13] in hematologic malignancies and fludarabine/cyclophosphamide [14] in severe aplastic anemia (SAA). Recipients of allo-HSCT from a related haplo donor were given a standard nonmyeloablative regimen with fludarabine/cyclophosphamide/total body irradiation at 2 Gy [15]. In all types of allo-HSCT, GVHD prophylaxis consisted of post-transplantation high-dose cyclophosphamide (PTCy) on days 3 and 4 along with mycophenolate mofetil for 35 days and tacrolimus [15]. Acute and chronic GVHD were graded according to standard criteria [16,17].

Neutrophil engraftment was defined as an absolute neutrophil count $>0.5 \times 10^9$/L for 3 consecutive days. Platelet engraftment was defined as a platelet count $>20 \times 10^9$/L without transfusion for 7 days. Analysis of donor cell chimerism in peripheral blood mononuclear cells was done on days 30, 60, 180 and 365 or in the event of unexplained cytopenia.

Supportive Care

All patients received standard institutional prophylaxis with levofloxacin during neutropenia. Antifungal prophylaxis was performed with fluconazole in auto-HSCT and with voriconazole in allo-HSCT until neutrophil engraftment. Patients also received post-transplantation prophylaxis with penicillin, acyclovir, and trimethoprim/sulfamethoxazole until day 180. Routine RT-PCR monitoring of cytomegalovirus (CMV) serostatus was performed weekly for 2 months in recipients of allo-HSCT.

Socioeconomic Determinants

To assess the financial burden that patients and families are asked to face, the Civil Service Hospital physicians analyzed the average charges for auto-HSCT, MRD-HSCT, and haplo-HSCT. In addition, they reported what patients and caregivers consider the major financial barriers to transplantation and post-transplantation supportive therapies, such as the costs of drugs and transportation. Finally, caregivers of transplantation recipients were asked whether they had to leave their job or drop out of school during the time in the hospital with the patient.

Statistical Analysis

Overall survival in each group of patients was calculated using the Kaplan-Meier method. All analyses were performed using GraphPad Prism 7 (GraphPad Software, San Diego, CA).

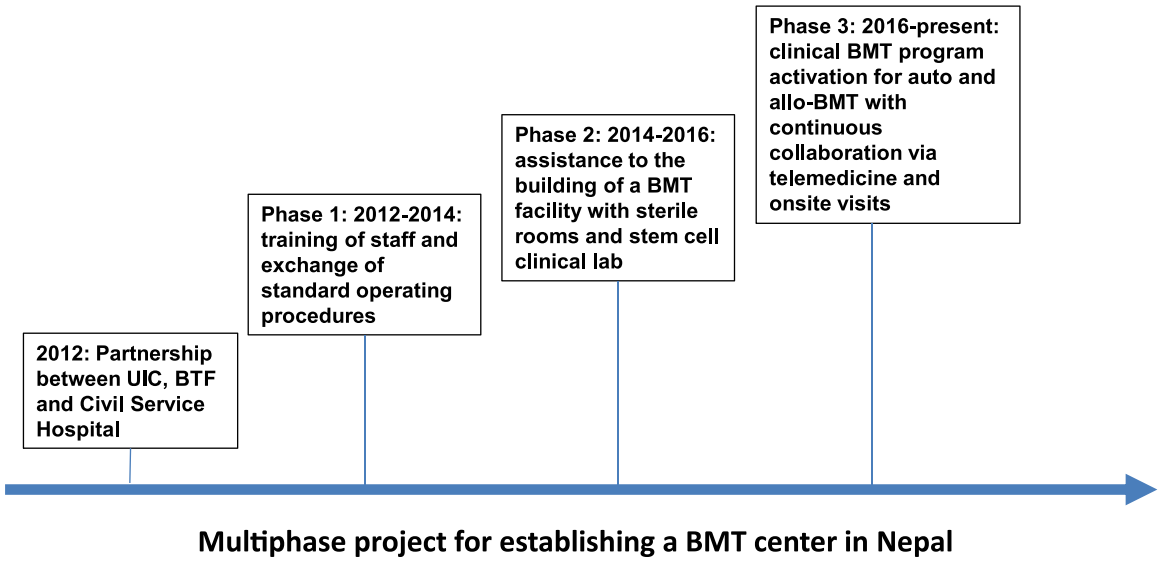

Figure 1. Multistep implementation plan developed by the UIC and Civil Hospital partnership to establish a BMT center at Civil Service Hospital in Kathmandu. The plan included 4 phases that started in 2012 and continued until 2016.

RESULTS

Tools and Determinants Impacting the Implementation of HSCT

The primary goal of the partnership between UIC and Civil Service Hospital was to address the needs of Nepal, a low-income country in South Asia with approximately 30 million inhabitants, to implement its first HSCT program and make the treatment affordable to the majority of Nepalese patients with hematologic malignancies or severe blood disorders.

A 3-stage implementation plan was developed, as shown in Figure 1. The 2 main implementation tools that were adopted throughout the process were active engagement of all the stakeholders and continuous remote communication between UIC and Civil Service Hospital. During each phase, stakeholders such as hospital administrators, healthcare providers, and laboratory staff were involved at multiple levels and were instrumental in the decision making related to space, policies, or deadlines. A meaningful example of this occurred during construction of the 2 sterile rooms in the transplantation unit. While standard guidelines related to room design and air filtration were shared by UIC with the partner institution in Nepal, the local construction consultants and hospital administrators suggested installing metal walls in the rooms to limit the growth of mold, which was frequently detected in other areas of the hospital and is potentially dangerous to immunocompromised patients. Images of different stages of the construction of the transplantation rooms are shown in Figure 2A-C. Similarly, an ad hoc location was found for a centralized HEPA filter on the building's roof to allow its use in both the patient rooms and the cell processing laboratory (Figure 2D). Finally, owing to the lack of capacity to irradiate blood products by Nepalese blood banks, the hospital administration decided to purchase a dedicated device to irradiate purified cell products (Figure 2E) and to equip the stem cell lab with a liquid nitrogen supply for long-term stem cell cryopreservation, in addition to a -80 °C mechanical freezer.

Multiple determinants affected the implementation of HSCT. One of these was a cultural gap in Nepalese oncologists in the up-to-date treatment of hematologic cancers, as well as indications for HSCT. To partly address this, 4 conferences with local and international speakers were organized in Kathmandu between 2014 and 2019, with Nepalese private oncologists invited to discuss the possible challenges of transplantation in LMICs [18]. In addition, during the initial phase of implementation, the Civil Service Hospital BMT program director, lead BMT nurse, and pathologist in charge of the stem cell lab were trained for 3 months at UIC.

Multiple socioeconomic determinants have been described previously in Nepalese patients with cancer [7]. Here we identified 3 major determinants that were reported by patients or their families to their providers during the time of HSCT (Table 1). A limitation of this study was that this information was not collected with an established standard tool but rather was based on direct questions that the Nepalese providers asked the patients and their caregivers to document specific factors affecting the affordability of transplantation. The cost of HSCT is the main obstacle to accessing HSCT in any LMIC. The choice of low-cost drugs for conditioning regimens and low charges for the procedure assessed by the hospital resulted in a total cost of $5200 for auto-HSCT, $10,200 for MRD-HSCT, and $13,300 for haplo-HSCT. In addition to the cost of the transplantation procedure, the drugs associated with the greatest increase in the cost of post-transplantation care were gancyclovir and valgancyclovir (cost per day: $60 and $32, respectively), used preemptively in patients experiencing reactivation of CMV viremia.

Patients and their families often experience a significant loss of household income when the patient and/or caregiver stop(s) supporting the family financially. Of 46 caregivers who answered a question related to their job, 43 were adults who stopped working to assist their relative, and 3 younger caregivers dropped out of high school. Third, given the geography of Nepal, with large mountain areas surrounding a few large cities and poor road conditions, the travel time to reach the hospital for patients in rural areas can range from hours to days by means of overcrowded public buses or private motorcycles. The median distance from home to Civil Service Hospital for the 66 patients analyzed here was 160 km (range, 6 to 683 km), which meant that the majority of them spent several weeks after transplantation in a hotel or had to face a long commute to the hospital in case of complications or even to

Figure 2. Building the BMT unit in phase 2 of the project. Intervention of local engineers during the construction of the BMT unit addressed the high risk of mold infection from the external walls of the old hospital (A) by reinforcing the wall structure (B) and applying metal internal panels in the patient rooms (C) and positioning the HEPA filter on the roof of the hospital above the BMT unit (D). During phase 2 of the project, the lack of irradiated blood products in Nepal was addressed by purchasing a dedicated irradiator (E) that was positioned inside the BMT unit. The same space included a separate cell processing laboratory with liquid nitrogen automated stem cell cryopreservation system (F), as well as a -80 °C freezer (not shown).

Table 1
Major Socioeconomic Determinants and Effects on HSCT Recipients and Their Families at Civil Service Hospital in Kathmandu

Determinants	Findings	Socio-economic effects
Charges for inpatient HSCT	$5,200: Auto-HSCT $10,200: MRD-HSCT $13,300: Haplo-HSCT	More affordable than going to other countries, but additional burden on the family.
Loss of income of patient and/or family caregiver	93% caregivers were adults and stopped working, while 7% were high school students and dropped school to assist their relative.	When the patient or the caregiver are the main source of income in the family, other family members may not receive support for healthcare or school expenses.
Distance and cost of transportation	Median distance from home to hospital for HSCT patients in the study: 160 km (range: 6-683 km).	Need for patient and caregiver to stay in an hotel for a few weeks upon discharge. Expensive commute for follow-up visits or blood transfusions.

receive blood transfusions, thereby increasing the financial burden of transplantation significantly.

Two major contextual barriers to the implementation design described above also occurred. In May 2015, a devastating earthquake hit Nepal, causing massive destruction and many casualties. Almost the entire healthcare workforce of Nepal was deployed to support the victims, especially in the mountainous areas, where entire villages

Table 2
Characteristics of 66 Consecutive Recipients of Auto- or Allo-HSCT at Civil Service Hospital, August 2016 to December 2020

Characteristic	Value
No. of patients	66
Males/females, n	44/22
Auto-HSCT, n	30
Allo-HSCT, n	36 (MRD, 24; Haplo, 12)
Auto-HSCT recipient age, yr, median (range)	54 (15-63)
Allo-HSCT recipient age, yr, median (range)	20 (8-38)
Diagnosis, n	
Auto-HSCT	23
MM	3
Non-Hodgkin lymphoma	1
Hodgkin disease	1
Acute promyelocytic leukemia	2
Myeloid chloroma	
Allo-HSCT	5
Acute lymphoblastic leukemia	18
Acute myelogenous leukemia	1
Myelodysplastic syndrome	11
SAA	1
Fanconi anemia	
PBSC dose, $\times 10^6$/kg, median (range)	
Auto-HSCT	4.9 (2-36)
Allo-HSCT	8.0 (3.5-22)

disappeared. Later in the same year, a political crisis between Nepal and India resulted in an embargo on medical supplies, medical instruments, and construction materials, in addition to gasoline, electric power, and food for several months. Because of these events, procurement of materials and instruments was greatly delayed during phase 2 of the implementation plan.

Transplantation Outcomes

The first auto-HSCT was performed at Civil Service Hospital in August 2016, followed by allo-HSCT 1 year later. The characteristics of the first 66 consecutive auto-HSCT (n = 30) and allo-HSCT (n = 36; 24 MRD, 12 haplo) are shown in Table 2. The cohort had a male preponderance (44 versus 22 females). The median age was 54 years (range, 15 to 63 years) for the auto-HSCT cohort and younger (median, 20 years; range, 8 to 38 years) in the allo-HSCT cohort, despite the fact that patients up to age 65 years were eligible. A possible interpretation is that in Nepal, acute leukemia is more commonly treated in young patients, whereas an older leukemia patient often may be reluctant to take on a financial burden that would put the whole family at risk, especially with the uncertain outcome. On the other hand, older patients with lymphoma or MM who can be treated for some time as an outpatient at lower cost enter into the system more frequently and become available for transplantation.

In the auto-HSCT group, all patients were able to mobilize PBSCs and receive $\geq 2 \times 10^6$ $CD34^+$ cells/kg (median, 4.9×10^6 cells/kg; range, 2 to 36×10^6 cells/kg). As expected, allo-HSCT recipients received adequate numbers of stem cells obtained from healthy donors (median dose, 8.0×10^6 $CD34^+$ cells/kg; range, 3.5 to 22×10^6 $CD34^+$ cells/kg). These patients were predominantly females (21 versus 15 males), with a median age of 22 years (range, 11 to 48 years). Data on engraftment and survival in 30 auto-HSCT recipients are shown in Table 3. At a median follow-up of 1029 days (range, 130 to 1653 days), 87% of patients were alive, 1 patient died of disease progression, and 3 MM patients (10%) died, 1 of H1N1 viral infection on day 426 and 2 of COVID-19 viral infection on days 855 and 1590. The median survival was 1610 days in the auto-HSCT group, and the overall survival curve is shown in Figure 3A.

Table 3
Results for 30 Consecutive Recipients of Auto-HSCT at Civil Service Hospital, August 2016 to December 2020

Outcome	Value
Day of neutrophil engraftment, ANC $\geq 0.5 \times 10^9$/L, median (range)	12 (10-27)
Day of platelet engraftment, $\geq 20 \times 10^9$/L, median (range)	13 (10-34)
Patients alive, n/N (%)	26/30 (87)
Transplantation-related mortality, n/N (%)	3/30 (10)
Relapse/progression-related mortality, n/N (%)	1/30 (10)
Follow-up, d, median (range)	1029 (130-1653)

ANC indicates absolute neutrophil count.

In the allo-HSCT group, both MRD HSCT and haplo HSCT recipients engrafted within 3 weeks (Table 4). At a median follow-up of 204 days (range, 12 to 1131 days), 27 of 36 (75%) allo-HSCT recipients were alive. However, 3 patients were lost to follow-up early after transplantation, on days 67, 67, and 140. Seventeen of the 24 MRD HSCT recipients (71%) were alive, compared with 10 of 12 haplo-HSCT recipients (83%). Acute GVHD of any grade occurred in 8 of 36 patients, but it was grade II-III in only 3 (8%) and grade IV in none. All these patients responded to treatment with corticosteroids. Only 3 patients developed mild chronic GVHD, 2 of the mouth and 1 of the skin. Of 36 patients, 2 patients, both with B cell acute lymphoblastic leukemia, died of disease relapse, whereas 7 (19%) died of complications, including cytomegalovirus (CMV) infection (n = 1; B cell acute lymphoblastic leukemia on day 260), CMV followed by graft failure (n = 2, SAA on days 78 and 45), thrombotic thrombocytopenic purpura (n = 1; acute myelogenous leukemia on day 160), veno-occlusive disease (n = 2; myelodysplastic syndrome on day 45 and SAA on day 12), and COVID-19 (n = 1; SAA on day 214). Median survival has not yet been reached in the 36 allo-HSCT recipients (Figure 3B) or in each of the MRD HSCT and haplo HSCT groups. It is interesting to observe that despite the relatively short follow-up, the survival curve for MRD HSCT has already reached a stable plateau.

DISCUSSION

The partnership between Civil Service Hospital and UIC, along with the initial collaboration with BTF, was instrumental in the initiation of an HSCT program in Nepal. In August 2016, Civil Service Hospital performed the first auto-HSCT in Nepal, followed 1 year later by the first allo-HSCT. By the end of 2020, 66 patients had undergone auto-HSCT or allo-HSCT (from an MRD or a haplo donor), with very encouraging clinical outcome.

The HSCT global activity reported in a study by the Worldwide Network for Blood and Marrow Transplantation in 2010 [19] showed rates of transplantation ranging between 0 and 50 per 10 million people in large parts of Africa, Asia, and South America, compared with >300 per 10 million people reported in North America, Western Europe, Japan, Australia, and New Zealand. In the subsequent years, encouraging data have been published from increasing numbers of transplantation centers in the Eastern Mediterranean region [20], Latin America [21], and the Asia-Pacific region [22,23]. In particular,

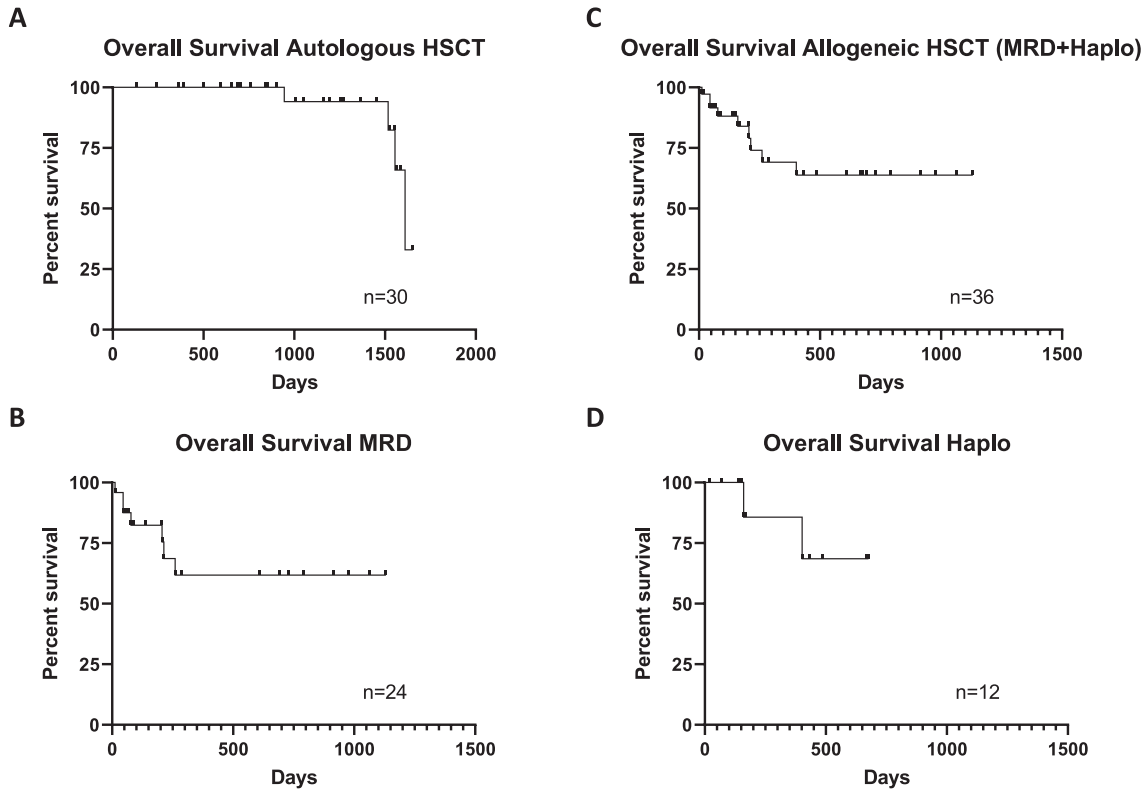

Figure 3. Overall survival (OS) of the first 66 recipients of auto-HSCT or allo-HSCT at Civil Service Hospital in Kathmandu. The median OS was 1610 days for auto-HSCT recipients (n = 30) (A) but was not reached for all allo-HSCT recipients (MRD and haplo donor) (n = 36) (B), only MRD allo-HSCT recipients (n = 24) (C), or only haplo-HSCT recipients (n = 12) (D).

the number of transplants is increasing rapidly in China and India [1]. However, considering that these countries have >1 billion inhabitants, their HSCT capacity is still very low compared with that of North America and Western Europe.

Although Nepal had multiple medical schools and cancer hospitals, it did not offer any specific training in hematology or HSCT. As a result, only a small fraction of hematologic patients could afford to travel abroad, mostly to India, to undergo transplantation, with the majority of patients receiving standard chemotherapy. The goals of the Civil Service Hospital-UIC partnership were to build capacity, provide medical education, and provide continuous support to clinical development and research. An important lesson learned was that accomplishment of these goals required local administrators and providers to successfully lead the implementation plan in collaboration with US partners, based on mutual trust that was built primarily through regular visits on the ground and an always fully transparent agenda. Similar to the experience in Nepal described here, other partnerships between LMIC and HIC institutions have proven effective in allowing LMICs in the Middle East and Asia to build capacity and start performing transplantations, especially auto-HSCT to treat relapsed/refractory lymphomas or MM and initial experiences with allo-HSCT [24–26].

Table 4
Results for 36 Consecutive Recipients of MRD or Haplo Related Donor Allo-HSCT at Civil Service Hospital, August 2017 to December 2020

Outcome	Value
Day of neutrophil engraftment, ANC ≥0.5 × 10^9/L, median (range)	13 (10-19)
Day of platelet engraftment, ≥20 × 10^9/L, median (range)	14 (10-22)
Patients alive, n/N (%)	27/36 (75)
MRD HSCT, n/N (%)	17/24 (71)
Haplo HSCT, n/N (%)	10/12 (83)
aGVHD any grade, n	8
aGVHD grade II-III, n	3
Transplantation-related mortality, n/N (%)	7/36 (19)
Relapse/progression-related mortality, n	2/36
Follow-up, d, median (range)	204 (12-1131)

The challenge for small LMIC institutions that rely on external support to start an HSCT program is to become completely independent, especially when performing allo-HSCT where HLA compatibility testing, immunosuppressive drug serum level monitoring, and management of clinical complications require multilevel capacity and hospital support. Overall, cancer care in LMICs is limited by factors that also apply to HSCT: (1) lack of infrastructure, (2) lack of understanding the burden of blood disorders in the country and its social and financial impact, (3) limited medical workforce and often poor training, (4) limited cancer screening or regular blood testing, and (5) limited access due to socioeconomic conditions [27,28]. In 2017, UIC and Civil Service Hospital organized a first “Global BMT” conference in Kathmandu with BMT leaders from India, Singapore, Sri Lanka, and Nepal who shared similar experiences in starting their programs [18], with special emphasis on the cost of drugs (often unregulated) and the financial burden that many patients and families cannot afford. A cross-sectional study done in Nepal analyzed the prevalence and factors associated with catastrophic health expenditures, defined as out-of-pocket expenditure per hospitalization >20% of annual

household income, and distress financing, defined as borrowing money from family/friends, taking loans from banks or other lenders, or selling assets to cope with out-of-pocket expenditures due to an illness [29]. For hospitalized patients, the prevalences of catastrophic health expenditures and distress finance recorded in the study were 13% and 42%, respectively. Independent factors associated with distress financing were age >45 years, underrepresented ethnicity (Janjatis/Dalits), distance >2 km from hospital, and hospitalization of >3 days. More recently, Civil Service Hospital completed a survey of 112 leukemia patients treated in their hospital, including some who would be candidates for HSCT, and reported astonishing data [30] on financial toxicity faced by these patients, who would need to request public charity (94%), take loans from friends or relatives (88%), or sell property, such as house, land, or livestock (87%). Extreme financial toxicity was experienced by 73% of patients who met all 3 parameters. Considering the long hospitalization time, the distance from home, and particularly the high out-of-pocket expenditure for chemotherapy, it is clear that socioeconomic determinants often affect the decision of many Nepalese families to have their relative with blood cancer treated or not, or to continue the treatment if complications occur, or to travel to India or another neighboring country if HSCT is needed. Because Civil Service Hospital was able to offer HSCT at approximately one-half the price of private hospitals in neighbor countries, more Nepalese patients could undergo a transplantation that otherwise would have been unaffordable. From a clinical perspective, it was important to select standard protocols that would combine a high level of efficacy, limited risk of complications, and affordability for the patients. This is the main difference with HSCT in HICs, where we can use the latest targeted therapy, or immunotherapy if covered by insurance, or achieve high levels of efficacy in clinical trials with experimental drugs, but rarely is an estimate of accessibility done. In LMICs, it is key to find cost-effective solutions among antimicrobials [31], to expand the list of essential medicines listed by the World Health Organization [32], or to select drugs or strategies that limit further complications, such as GVHD, and associated out-of-pocket expenditures without reducing the quality of treatment. This was why we chose to use PTCy as a strategy to limit the risk of GVHD in all allo-HSCTs, including those from an MRD, and to not perform matched unrelated donor transplantations, which are more expensive than haplo-HSCT. Although the number of patients is still low, and longer follow-up is needed, the survival reported so far in each group of patients (auto-HSCT, allo-HSCT [MRD and haplo]) is within standard ranges, although the relatively young age of patients in the allo-HSCT group must be taken into account. Importantly, we did not observe a learning curve effect, which in difficult procedures usually limits the initial results. We believe that this can be explained by having an experienced team of nurses and doctors who have treated high volumes of leukemia patients for years at Civil Service Hospital and have experience in management of infectious complications, the very low rates of acute and chronic GVHD due to PTCy, and the continuous open communication between Civil Service Hospital and UIC via the WhatsApp social media platform. A recent study of 257 haplo HSCTs performed over 10 years at a single center in India [33] and using PTCy similar to our approach, showed higher rates of acute GVHD grade II-IV, graft rejection, and severe infections compared with our study. Making comparisons is difficult, however, owing to the limited number of patients in our initial experience, mainly for malignant diseases, and also because over a 10-year period, changes in antibiotic and supportive therapy likely occurred in every center, and haplo HSCT began in Nepal only in 2017.

In conclusion, the partnership with Civil Service Hospital allowed the providers of this public hospital to establish a stem cell transplantation program in Nepal, with the capacity to also perform haplo HSCT at a cost affordable to patients in LMICs. We believe that the partnership between UIC and Civil Service Hospital has highlighted some successful experiences that could be of help to future LMIC sites embarking on initiating transplant centers: development of a step-by-step process with ongoing quality assessment/validation of each step (laboratory, logistic implementation, clinical), active and continuous communication with experienced partners, and development of trained leadership with transparent accountability within the local institution, the national health system and the international transplantation community. Importantly, a continuous dialog between global partners results in mutual knowledge growth and research opportunities. Because socioeconomic barriers often limit patients with hematologic malignancies or severe blood disorders from accessing high levels of care, particularly HSCT, more studies that focus on the efficiency of HSCT are needed, in which efficiency can be measured as the best affordable efficacy for the largest number of patients.

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