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A Hematopoietic Stem Cell Transplantation Startup in Iraqi Kurdistan: Results in Thalassemia Patients and Analysis of the Methodology

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A B S T R A C T

In hemoglobinopathy-prone regions, like the Middle East, thalassemia is the most prevalent noncommunicable life-threatening disorder of children and is highly curable by hematopoietic stem cell transplantation (HSCT). Moreover, transplantation is very cost-effective, and HSCT programs can be established directly in middle-income countries (MICs) at a reduced cost while maintaining quality standards and outcomes consistent with international ones. The aim of the present study was to review and verify the efficacy of the applied methodology through the analysis of 47 consecutive matched-related HSCTs in children with thalassemia. In 2016, the first HSCT unit for adults and children with both malignant and nonmalignant diseases was developed in Iraqi Kurdistan, thanks to a capacity building project funded by the Italian Agency for Development Cooperation. Data on clinical activity were obtained from a cohort of patients treated in the newly established HSCT unit. Primary endpoints were overall survival (OS) and thalassemia-free survival (TFS). Startup of the HSCT unit was completed over a 3-year period. Assessing and meeting minimum requirements were crucial for the startup; moreover, a team of international health care professionals (HCPs), all experts in the field of HSCT, conducted the education and training phase, involving all the clinical and nonclinical professionals in the program. At a median follow-up of 2.6 years, the 3-year TFS and OS were 82.8% (SE, 5.5%) and 87.1% (SE, 4.9%), respectively. TFS and graft-versus-host-disease-free composite survival was 80.6% (SE, 5.8%). At present, the HSCT service is completely autonomous, and more than 250 transplants have been done in both adults and children. The minimal essential requirements for an HSCT startup may be affordable in many MICs. Our results for thalassemia are comparable with international data. A twinning program with an international group of experts and a capacity-building approach is crucial for the success of the program, a strategy that allows for rapid development of HSCT units.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is curative for many diseases, including hematologic malignancies and nonmalignant disorders of the hematopoietic and immune systems. Hemoglobinopathies are the most prevalent noncommunicable potentially life-threatening pediatric disorders in the Middle East. Particularly for thalassemia, HSCT is highly cost-effective [1,2], providing a significant improvement in quality of life [3–5]. Among1,500 consecutive transplant registry cases reported to the European Society for Blood and Marrow Transplantation (EBMT) hemoglobinopathy database, the 2-year overall survival (OS) and event-free-survival (EFS) rates were 88% and 81%, respectively [6].

As a result of advances in supportive care, the mortality of allogeneic HSCT has decreased significantly over the past few decades. Thus, HSCT activity continues to progressively expand worldwide. Although HSCT is potentially curative for many diseases, it is also a highly resource-intensive treatment modality. However, HSCT services can be established at a reduced cost in middle-income countries (MICs). These programs should comply with adequate safety standards while

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ensuring appropriate patient access, cost containment, and sustainability [7–9].

In 2016, the first HSCT unit for adults and children with both oncologic and nononcologic diseases was opened in Iraqi Kurdistan at the Hiwa Cancer Hospital of Sulaymaniyah, thanks to a capacity-building project funded by the Italian Agency for Cooperation and Development [10,11]. Here we the data on 47 pediatric patients with thalassemia who underwent HSCT from a matched related donor (MRD) between October 2016 and July 2021 as part of a twinning program between Italian and Kurdish institutions, based on intensive onsite training.

METHODS

The aim of the project was to set up an autonomous and sustainable HSCT activity through the definition of a transplantation pathway including early and late patient follow-up; identification of a donor selection process, including HLA typing and stem cell collection, processing, and storage; training of clinical staff (MDs and Registered Nurses [RNs]) in specific HSCT patient care; and the overall optimization of the diagnosis and treatment pathway of hemato-oncologic diseases and thalassemia in pediatric patients, the focus of this report.

Risk Classification and Management of Thalassemia Patients

Low- and intermediate-risk patients were considered those age ≤10 years with both ferritin level <2000 ng/dL and liver <2 cm from the costal margin on palpation, and patients age ≤17 years with Pesaro risk class I or II. High-risk patients were considered those with Pesaro risk class III and all patients age >10 years with no available liver biopsy data.

A downstaging protocol for intermediate-risk patients was applied 4 to 5 months before HSCT with hydroxyurea, started at 20 to 25 mg/kg/day and increased up to 50 mg/kg/day depending on weekly blood counts (to maintain an absolute neutrophil count of 1000 to 1500/μL and platelet count of 100,000 to 150,000/μL). If ferritin level was >1000 ng/mL, chelation therapy was started with deferoxamine 40 mg/kg for 5 days/week or deferasirox 20 to 25 mg/kg/day. High-risk patients received azathioprine 2 to 3 mg/kg and a hypertransfusion regimen to maintain hemoglobin (Hb) at 12 to 14 g/dL starting on day -45. Chimerism monitoring was established onsite starting in 2019, before which it was outsourced on a case-by-case basis.

Conditioning Regimen and Graft-versus-Host Disease Prophylaxis

All low- and intermediate-risk patients received a conditioning regimen with i.v. busulfan every 6 hours based on body weight (<9 kg, 1 mg/kg/dose; 9 to 16 kg, 1.2 mg/kg/dose; 16 to 23 kg, 1.1 mg/kg/dose; 23 to 34 kg, .95 mg/kg/dose; >34 kg, .8 mg/kg/dose) over 4 days and cyclophosphamide 50 mg/kg/day over 4 days (total dose, 200 mg/kg). High-risk patients received busulfan according to body weight as above, along with cyclophosphamide (total dose, 160 mg) and fludarabine 20 mg/m^2/day from day -17 to day -13 (total dose, 100 mg/m^2).

All patients received early (day -12 to day -10) low-dose antithymocyte globulin (ATG; Thymoglobulin; total 3.75 mg/kg), low-dose prednisone (.5 mg/kg/day) for the first 45 days, short-course methotrexate (10 mg/m^2 for 4 doses), and cyclosporine for at least 6 months post-transplantation.

Anti-Infective Regimens

Fluconazole was used for antifungal prophylaxis. No antibacterial prophylaxis was planned. Antiviral prophylaxis with acyclovir was provided for the first 30 days, and anti-*Pneumocystis jirovecii* one during cyclosporine prophylaxis. Preemptive treatment for cytomegalovirus (CMV) reactivation included primarily ganciclovir and foscarnet as a second step. Piperacillin-tazobactam plus amikacin was used for empirical treatment of fever and neutropenia, and voriconazole or liposomal amphotericin B was used for suspected fungal infection.

Endpoints

The primary study endpoints were OS and TFS; secondary endpoints were a composite outcome of thalassemia-free and graft-versus-host-disease (GVHD)-free survival (TGFS), incidence rates of acute GVHD (aGVHD) and chronic GVHD (cGVHD), and hematopoietic recovery. Neutrophil recovery was defined as the first of 3 consecutive days with an absolute neutrophil count >.5 × 10^9/L. Platelet recovery was defined as a platelet count ≥20 × 10^9/L unsupported for 7 days. Graft rejection was defined as >95% residual host cell chimerism as evaluated by DNA analysis in peripheral blood. aGVHD was defined using Mount Sinai Acute GVHD International Consortium criteria [12], and cGVHD was defined using 2014 National Institutes of Health criteria [13].

Statistical Analysis

TFS was defined as the time from HSCT to first failure, either death or rejection. The Kaplan-Meier method was used to estimate probabilities of OS, TFS, and TGFS; comparisons of medians were done using the Wilcoxon test, and mean values were compared using the *t* test. All statistical analyses were performed with SAS 9.4 (SAS Institute).

RESULTS

Analysis of the Methodology

The HSCT unit startup was completed over a 3-year period (Table 1). Meeting the following minimum requirements was crucial for the startup:

- Well-sealed (eg, around windows and electrical outlets) single-patient rooms with adequate ventilation (HEPA [high-efficiency particulate air] filters capable of removing particles >.3 μm in diameter with >99% efficiency are not

Table 1
HSCT Unit Startup Schedule over a 3-Year Period.

Year	Main Activities
1	• Assessment and achievement of minimum criteria (structural, organizational, and educational) • Local human resources implementation (considering staffing and responsibilities, roles, coverage) • Educational and training program • Structuring and implementation of quality service (JACIE model: protocol handbook; SOPs) • Analysis of data on patients and planning a staggered approach leading to the transplantation list • Start of clinical activity
2	• Bedside activity • Completion of nonessential training (ie, high-resolution HLA typing, chimerism, apheresis, total body irradiation) • Educational and training activities in the field • Continuous medical education
3	• Remote follow-up and continuous remote monitoring • Education and training both locally, from remote and abroad • Research and results dissemination

considered an absolute requirement for low-risk transplantation activity [14]. A positive pressure differential [>2.5 Pa] between rooms and hallway, >12 air exchanges/hour, and point-of-use HEPA filters should be recommended if activities include more complicated transplantations. Rooms should have directed airflow so that air enters one side of the room and is exhausted on the opposite side. HEPA-filtered, well-sealed rooms with positive pressure are the standard on the unit.)
- The opportunity to perform low-intermediate HLA typing with the availability of both parents for study
- Availability of irradiated blood products
- Availability of essential drugs for conditioning regimens (busulfan, fludarabine, thiotepa, melphalan), GVHD prophylaxis and treatment (cyclosporine, mycophenolate, antithymocyte globulin, rituximab), and infection prevention (broad-spectrum antibiotics, acyclovir, ganciclovir, antifungal drugs)
- Laboratory testing for cyclosporine level and CMV DNA copies
- Trained local clinical staff working alongside an external expert supervisor onsite.

This preliminary evaluation and the process of meeting the criteria were performed by a team of Italian experts in the field of HSCT, together with the hospital administration and local clinicians. Various areas needed to be implemented.

Staffing

An organizational chart according to the JACIE model [14] was developed, and a recruitment process was implemented. Nursing staff already employed by the institution were selected based on previous experience in pediatric or oncologic care, interest in the field, and English language skills. Four positions of responsibility were identified: director of the HSCT program; person responsible for stem cell collection, processing, and storage; HSCT pediatric hematologist, and HSCT head nurse.

Education and training

A team of international health care professionals with expertise in the field of HSCT ran the education and training phase, involving all the clinical and nonclinical professionals in the program, including MDs, RNs, assistant nurses, laboratory technicians, and biologists. This phase included a classroom-based educational course, followed by intensive on-the-job training. This enabled the acquisition of a set of skills and knowledge deemed essential for program startup: bedside management of patients; stem cell collection, processing, and storage; CD34 cell count and HLA typing; and determination of minimal residual disease and chimerism. Among the essential skills to be acquired before the start of clinical activity is bone marrow harvesting. The local staff, after coaching, achieved autonomy in executing this procedure.

During the first 6 to 8 months, local staff was continuously supported in the field by an experienced supervisor. Later, several visits were organized, tailored to the specific needs identified by the multidisciplinary team members. Various experts augmented the local team to help reinforce acquired skills and knowledge and implement new areas of expertise (eg, nurses expert in the positioning of peripherally inserted venous catheters, surgeons for centrally inserted catheters). In addition, training sessions were carried out in Italy for local staff in specific fields of interest (eg, apheresis, nursing, pediatric HSCT). Periods abroad were funded by charities, trainee institutions, scholarships provided by scientific societies, and international grants by relevant institutions (eg, European Union).

Quality assurance program

This area was developed through the early identification of the issues to be covered. Staff were involved in writing documentation (procedures, protocols, clinical documentation forms). More than 100 protocols were included in the HSCT protocol handbook.

Clinical activity

Patient management was planned and initiated according to a stepwise approach tailored to the population of interest, selected based on disease type, indication for transplantation, and complexity of the procedure. Thus, the program initially involved children with nonmalignant diseases undergoing allogeneic HSCT from a matched sibling donor, then patients with an oncologic disease and an MRD, and finally, recipients of allogeneic HSCT from a mismatched family donors were included.

This intensive local training process enabled a rapid transition from the theoretical to the hands-on phase. In fact, the first HSCT in an adult patient was performed only 3 months after implementation of the educational course, and the first pediatric HSCT was performed 3 months later.

Outcomes

A total of 286 HSCTs were performed in adult and pediatric patients in the transplantation program during the study period for the following indications: multiple myeloma (n = 76), Hodgkin lymphoma (n = 58), transfusion-dependent thalassemia (n = 57), acute myeloid leukemia (n = 35), non-Hodgkin lymphoma (n = 19), acute lymphoblastic leukemia (n = 16), neuroblastoma (n = 11), Fanconi anemia (n = 7), severe aplastic anemia (n = 6), and Diamond-Blackfan anemia (n = 1).

Patients

Patient, disease, and transplantation characteristics are summarized in Table 2. Data were updated in November 2021, at a median follow-up of 2.6 years. The mean age at transplantation was 6.6 years (range, 2.4 to 14.8 years). The mean total nucleated cell (TNC) dose was 17.35 $\times$ 10^8/kg (range, 5.95 to 32.6 $\times$ 10^8/kg), and the mean volume of bone marrow collected was 472 mL. Forty-three patients were classified as low to intermediate risk, and 4 patients were classified as high risk. Twenty patients were matched for sex and 44 were matched for CMV positivity; 3 patients were CMV-positive with a negative donor.

All donors were low-resolution fully matched siblings except for 2 phenotypically identical parents. The median age at donation was 12 years; 30 donors had thalassemia minor, and 17 had normal Hb electrophoresis. They all received granulocyte colony-stimulating factor-primed bone marrow, with the aim of promoting faster neutrophil engraftment, reducing the risk of infection without increasing the incidence of both aGVHD and cGVHD [15,16].

Hematopoietic recovery

Hematopoietic recovery was obtained in all patients. The median time to engraftment of neutrophils >500 $\times$ 10^9/L was 17 days (range, 12 to 25 days), and that of platelets >50 $\times$ 10^9/L was 19 days (range, 13 to 104 days).

Table 2
Patient, Disease, and Transplantation Characteristics.

Characteristic	n (%)
No. of patients	47 (100)
Age at transplantation	
≤10 yr	42 (89)
>10 yr	5 (11)
Total serum bilirubin before conditioning	
<3.5 mg/dL	44 (93)
>3.5 mg/dL	3 (7)
Presence of fibrosis on liver biopsy	
Absent	9 (19)
Present	32 (68)
Not reported	6 (13)
Liver size	
>2 cm below costal margin	6 (13)
<2 cm below costal margin	41 (87)
Iron chelation therapy	
Inadequate	20 (42.5)
Adequate	27 (57.5)
Not reported	0 (0)
Pesaro risk class	
I	5 (11)
II	32 (68)
III	4 (8)
Not reported	6 (13)
Serum ferritin level before conditioning	
<2000 μg/L	36 (76.5)
>2000 μg/L	11 (23.5)
Not reported	0 (0)

GVHD

Ten of the 47 patients (21%) had grade III-IV aGVHD, and 14 (30%) had moderate/severe cGVHD. The median counts of both TNCs and WBC in bone marrow were compared in patients with and without grade III-IV aGVHD (P = .74 and .84, respectively). This comparison also was done for WBCs in donor peripheral blood at the time of donation (P = .98) and for $CD3^+$ cells infused with the marrow (P = .81).

The same analysis (ie, median counts of TNCs and WBCs in the marrow and in donor peripheral blood at the time of donation, $CD3^+$ cells infused with the marrow) was done in patients with and without moderate/severe cGVHD (P = .59, .55, .82, and .57, respectively).

Finally, mean values of plasma cyclosporine levels at weeks 1, 2, 3, 4, 8, 12, 16, and 20 before the onset of the GVHD were analyzed in patients with grade III-IV aGVHD (P = .44) and moderate/severe cGVHD (P = .59).

Early complications

Six patients met the EBMT diagnostic criteria for pediatric EBMT veno-occlusive disease (VOD), including 2 with a moderate and 4 with a severe severity score [17]. All 6 had hepatomegaly, 3 with upper right abdominal pain, and 5 had bilirubin >2 mg/dL. All 6 also had ascites and >5% weight gain; 3 had also platelet refractoriness. All patients were treated with supportive care, and 4 received methylprednisolone 2 mg/kg/day owing to the high cost of defibrotide. All but 1 of the patients (male, age 14 years) responded to drug treatment. Causes of death were recorded as VOD, along with Coronavirus disease 2019 infection and resistant aGVHD (gut and skin).

Thirteen patients were diagnosed with suspected transplantation-associated thrombotic microangiopathy. Twelve patients had a decrease in Hb level to below baseline, 11 had an increased reticulocyte count, 11 had a decrease in platelet count above baseline, 7 had >5% schistocytes at blood smear, 11 had an increased lactate dehydrogenase level (7 patients with >600 U/L, 4 with >300 U/L), and 4 had a doubling of their creatinine level above baseline. All patients temporarily stopped cyclosporine with a gradual response except 2, in whom steroids and immunoglobulin were added. Cyclosporine was introduced again in all patients, but for those with laboratory signs of microangiopathy relapse, methylprednisolone alone was maintained alone until day +180, then tapered gradually in patients who remained GVHD-free.

OS and TFS

At a median follow-up of 2.6 years, the 3 year TFS and OS were 82.8% (SE, 5.5%) and 87.1% (SE, 4.9%), respectively (Fig. 1), and TGFS was 80.6% (SE, 5.8%) (Fig. 2). Treatment-related mortality was 12.9% (SE, 4.9%); causes of death were sepsis in 2 patients, pneumonia in 1 patient, and SarsCov2 infection in 3 patients (who developed infection at 6.3, 7.6, and 1.7 months post-transplantation).

Chimerism analysis revealed 1 persistent mixed chimerism and 1 transient mixed chimerism level 3 (in both cases with transfusion-independence) and 2 rejections; all other patients had complete chimerism. All patients were transfusion-independent and had an Hb >9 mg/dL. Only those with post-transplantation iron overload underwent regular phlebotomy. Even the 2 patients presenting with persistent mixed chimerism had an Hb >9 mg/dL with no transfusion requirement.

DISCUSSION

This study reports the 3-year outcomes (with a median follow-up of 2.6 years) of a homogeneous group of pediatric thalassemia patients who underwent transplantation in a startup HSCT center in Iraqi Kurdistan, the first in that region. Thalassemia has a very high prevalence in the Middle East region, with carrier rates in Kurdistan ranging from 3.7% to 6.9% [18,19]. In Iraqi Kurdistan, prenatal screening, transfusion regimens, and chelation treatment are guaranteed by the government for the entire population.

HSCT is the sole established highly successful and cost-effective cure for severe thalassemia syndromes [2,20,21]. In a cost-effectiveness analysis, John et al. [2] compared HSCT with transfusion and chelation (TC) for thalassemia major patients in India, estimating the lifetime costs and effects of HSCT and TC and evaluating the incremental cost per life-year and per quality-adjusted life-year gained with both MRD and matched unrelated donor (MUD) HSCT compared with TC. Lifetime treatment costs per patient associated with TC, MRD, and MUD were (in USD) $19,978, $28,191, and $43,649. The incremental cost per life-year gained was $916 for MRD HSCT compared to TC and $2,250 for MUD HSCT compared to TC. When considering quality-adjusted life-year instead of life-year as a measure for the effects of the treatments, the ICER (the incremental cost associated with the health gain deriving from implementing one intervention) for HSCT compared to TC remained low: around $986 for MRD—only one-half of the Indian per capita GDP. Thus, considering the aforementioned thresholds, HSCT is highly cost-effective for patients with thalassemia major compared with TC.

The largest experience of transplant in thalassemia was reported in Pesaro, Italy, where a pretransplantation risk assessment was developed that identifies 3 risk classes based

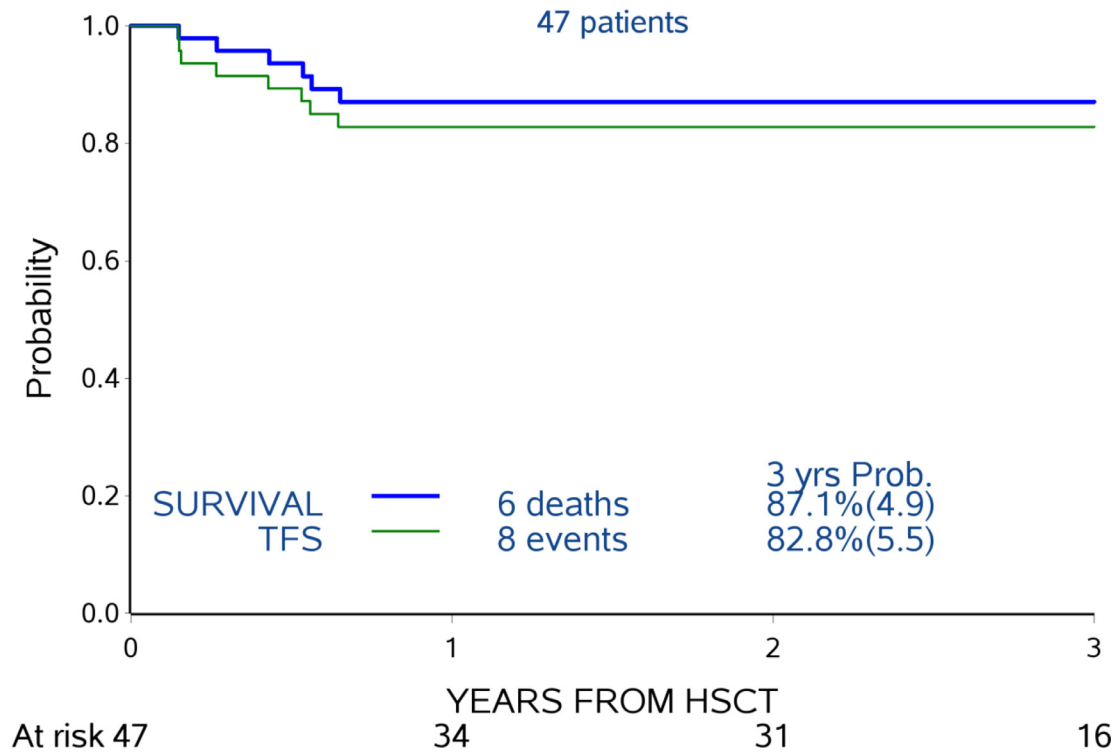

Fig. 1. With a median follow-up of 2.6 years, the 3-year OS and TFS in the 47 patients were 87.1% (SE, 4.9%) and 82.8% (SE, 5.5%), respectively.

on liver size, fibrosis by liver biopsy, and history of iron chelation [22]. More recently, Sabloff et al. [1] proposed a simplified risk score based on liver size and patient age; in their cohort, the 5-year probabilities of OS and EFS were 98% and 94%, respectively, in patients age <7 years at transplantation and without hepatomegaly, compared with 86% and 83% in older patients. We decided to apply a modified Sabloff criteria approach in our cohort. The downstaging protocol included hydroxyurea, chelation therapy, azathioprine, and a hypertransfusion regimen, taking risk category into account.

Low- and intermediate-risk patients received a busulfan and cyclophosphamide (200 mg/kg total dose) conditioning regimen, with the addition of fludarabine and a lower cyclophosphamide dose (160 mg total dose) in the 4 high-risk

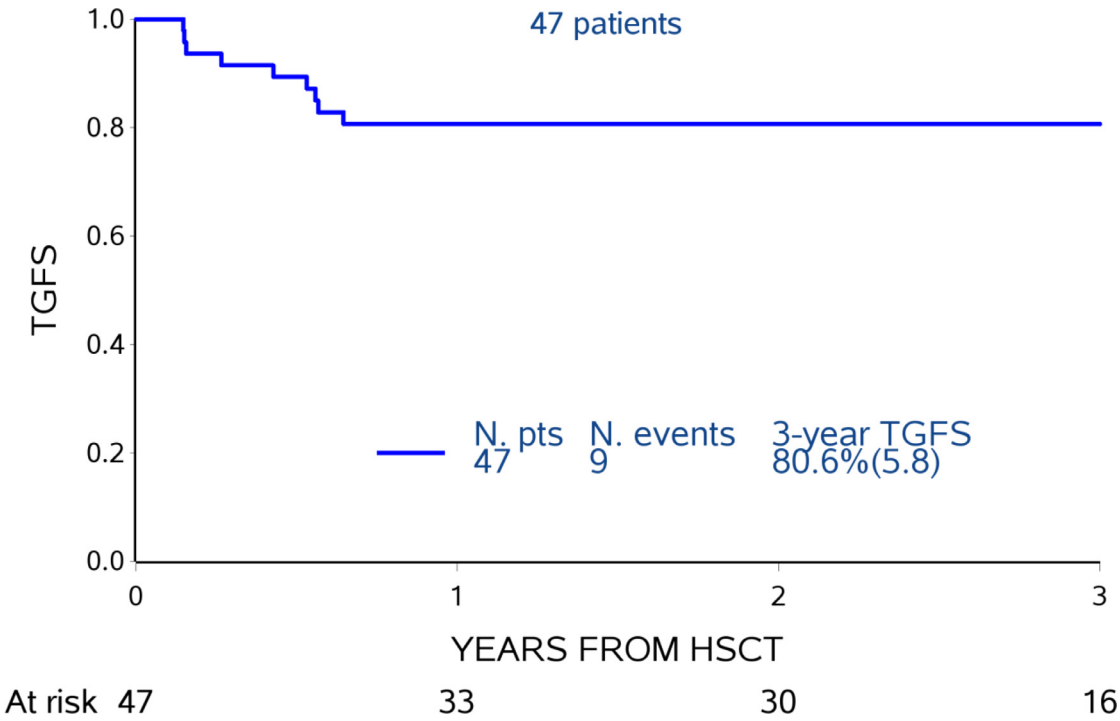

Fig. 2. With a median follow-up of 2.6 years, TGFS was 80.6% (SE, 5.8%).

patients. It was not possible to determine busulfan levels to determine and to administer defibrotide to treat VOD owing to its prohibitive cost.

In our cohort, TFS and OS were 82.8% and 87.1%, respectively, comparable with more recent international data from the EBMT group [6]. We note that 3 out of 6 deaths were related to SarsCov2 infection, with a significant impact on the overall outcome. In our previous analysis of 35 patients with a median follow-up of 12 months, TFS and OS were 87% and 92%, respectively.

We found a high incidence of cGVHD (30%), whereas the incidence of aGVHD was more in line with international data (21%). The incidence of both aGVHD and cGVHD was not correlated to donor marrow WBC and $CD3^+$ cell count or peripheral WBC count at the time of donation or recipient mean cyclosporine levels. However, GVHD resolved in all but 1 patient, who were then free of any immunosuppression. The actuarial 3-year TGFS was 80.6% (SE, 5.8%). A possible point to consider is that low-resolution HLA typing may miss clinically relevant mismatches, particularly in populations with a high consanguinity rate [22].

Other experiences in implementing low-risk HSCT services for pediatric patients with thalassemia directly in MICs have been described previously [23]. However, this is the first reported experience of a twinning program on a broader transplantation program in an MIC dedicated to both adults and children with both malignant and nonmalignant diseases.

We believe that the field-based training model is quite effective and promotes flexibility among learners and the capacity to work as a team [24]. Our experience suggests that the field-based training offered by experts in the field tutoring local staff is crucial to empower them by offering clinical routine guidance. Side-by-side training in the field has enabled both the acquisition of basic skills to care for transplantation recipients and the development of advanced skills, such as peripherally inserted central venous catheter nursing.

On completion of the “shadowing of the supervisor” intensive phase, tutoring and supervision were guaranteed by visits of professionals for training in transplantation, apheresis, nursing, and laboratory tests. Some of the health care professionals involved in the HSCT program had the opportunity to receive tailored training in an experienced European hosting institution. Interestingly, this also had an influence from an organizational perspective, helping local staff organize such services as the outpatient clinic and ensure the quality and safety of the work environment.

A remote follow-up program has been implemented with good results when considering the medical team and the lab staff; in fact, the local institution has provided good technological support and guaranteed the opportunity to connect with expert teams and discuss clinical cases, sharing decisions and priorities. This process is ongoing as supervisors are available to discuss cases and challenging issues. The local team has demonstrated self-reliance in organizing the list of transplant recipients and managing them until discharge and follow-up. Nonetheless, new models of remote follow-up need to be constantly identified and developed to keep the nursing staff updated. In our experience, nursing care, provided largely at the bedside, might not be amenable to the same training models used for physicians and laboratory personnel.

We believe that one of the most important aspects of continued fieldwork alongside local staff has been the development of soft skills useful in achieving autonomy and team functioning: implementation of communication processes, identification of priorities, development of problem solving skills, and provision of comprehensive patient care with not only health, but also psychosocial, assessments. In addition, it is important to develop parallel but preparatory aspects of clinical activity: the collection and analysis of clinical data, development of a quality system, and dissemination of results and their publication in scientific media.

CONCLUSIONS

This was our first experience with an HSCT startup capacity building project in adults and children for both oncologic and nononcologic indications. Focusing on the thalassemia patient population, our results are comparable with international data. Minimal essential requirements for an HSCT startup activity may be affordable in many MICs. The described methodology allows a reasonably quick development of HSCT units. A twinning program with an international group of experts is crucial [24–29]. The success of any startup HSCT program in MISs depends on the availability of clinical experts to spend time locally, adequate funds for training, and the appropriate focus on priorities to correctly assess and support the development of this highly specialized activity.

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