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ABSTRACT

Background: Bone marrow transplant (BMT) is an integral part of managing various blood disorders; however, establishing a new transplant unit is a significant undertaking. Resource constraints in underdeveloped countries like Pakistan compound the process further. This study reviews the challenges and initial outcomes of our newly established transplant unit.

Methodology: The transplant unit's activity over the past two years, since its inauguration, was reviewed. Data was collected from meeting minutes, regulatory approval documents, and patient records.

Results: The unit was established with a 4-room setup, designed to accommodate up to 40 transplants per year. Each room was equipped with portable HEPA filters, achieving ISO 8-level cleanroom air quality. During the first year, efforts focused on developing SOPs, optimizing conditions for neutropenic patients, establishing a drug formulary, obtaining regulatory approvals, and recruiting trained staff. Admission delays occurred on three occasions due to shortages of qualified nurses and chemotherapy drugs. Thirteen transplants have been performed, with a median follow-up of 274 days and an overall survival (OS) rate of 92.3%. Febrile neutropenia was observed in 61.5% of cases, primarily caused by central venous-line infections (n=8). Gut-toxicity affected 75% of autografts (n=6/8), along with complications such as mucositis, cyclosporin-induced hypertension and toxicity, and platelet refractoriness requiring frequent transfusions. All five allografts achieved complete donor chimerism at both 1 and 3 months, while one developed mixed chimerism at 6 months, which remained stable, with no relapses reported in the autografts to date. One patient succumbed on day +201 post-allogeneic BMT due to septic shock secondary to poor graft function.

Conclusion: BMT improves survival and quality of life for patients with bone marrow failure, hemoglobinopathies, and diverse malignancies in regions with high prevalence. However, establishing competitive units in countries like Pakistan requires substantial investment, advanced infrastructure, and coordinated efforts from healthcare professionals, policymakers, and global partners.

Keywords: Resource-limited settings, Transplant unit establishment, low-and middle-income countries.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a life-saving therapy for a wide range of hematological disorders, including hematological malignancies, bone marrow failure syndromes, and genetic blood disorders. While this life-saving therapy is widely available in high-income countries, access remains limited in many low- and middle-income countries (LMICs) like Pakistan. Establishing a transplant program in such settings is often complex and resource-intensive, requiring not only adequate infrastructure but also skilled personnel, effective infection control protocols, reliable drug availability, and adherence to regulatory compliance. The Worldwide Network for Blood and Marrow Transplantation (WBMT) has offered detailed recommendations to help guide countries with limited resources through this process, focusing on practical, step-by-step strategies to develop safe and sustainable transplant services[1,2,3].

Pakistan carries a high burden of hematologic diseases such as thalassemia, aplastic anemia, leukemias, lymphomas, and multiple myelomas, yet the availability of BMT services remains limited. Many patients travel long distances or seek care abroad, which is often unaffordable[4]. Against this backdrop, the establishment of a new transplant unit comes with significant challenges but also great promise. Studies from other LMICs have echoed these concerns and emphasize the importance of tailoring transplant programs to local realities, focusing on achievable infection control measures, locally sourced protocols, and collaborative training models[5,6,7]. Furthermore, global initiatives such as the WHO's framework for essential cancer care also recognize the importance of integrating complex treatments like BMT into national health systems, even in constrained settings[8].

This article describes our early experience in establishing and operating a new BMT unit in Pakistan over two years. We reflect on the initial challenges we faced, from infrastructure development to patient care complications, and share clinical outcomes from the first cohort of transplant recipients. By aligning our approach with the WBMT framework and adapting it to our local context, we aim to provide a practical model for other centers in similar settings that are working toward expanding access to this critical treatment.

Methodology

This study is a retrospective review of the activities of the BMT unit since its inception in a resource-limited setting over two years. It outlines a phased approach that includes infrastructure development, staff hiring and training, protocol creation, and clinical operations. Patients with hematological disorders eligible for hematopoietic stem cell transplantation were enrolled consecutively. Clinical information, including demographics, diagnoses, transplant procedures, complications, and outcomes, was systematically gathered from patient records, meeting minutes, and regulatory documents.

Descriptive statistics were used to summarize patient characteristics, transplant procedures (autologous and allogeneic), conditioning regimens, complications, and clinical outcomes. The study aimed to evaluate the feasibility, safety, and early efficacy of the newly established BMT unit. Ethical approval was obtained from the institutional review board (PKLI-IRB/AP/00712024), and all patients provided informed consent in accordance with ethical guidelines.

Results

Establishment and Infrastructure Development

With support from the provincial government, the Bone Marrow Transplant (BMT) unit was set up as the first public sector facility of its kind. It offers modern transplantation services to both adult and pediatric patients and is part of the Pakistan Kidney and Liver Institute and Research Center (PKLI&RC). This center is the province's leading transplant center, pioneering advances in the field of transplantation.

The transplant unit was structured initially with four dedicated rooms, each equipped with portable HEPA filtration units to maintain ISO Class 8 cleanroom air standards. This setup was designed to support approximately 40 transplants per year. Key achievements during the establishment phase included:

- Development and enforcement of Standard Operating Procedures (SOPs) covering the entire transplant process
- Formulation of a dedicated transplant medication list
- Coordination with regulatory authorities to ensure compliance and obtain necessary accreditations
- Recruitment and specialized training of clinical and nursing teams in transplant protocols
- Implementation of infection control strategies designed explicitly for neutropenic patient care.

A strong focus was placed on enhancing supportive care due to the high susceptibility of patients to infections and transplant-related complications in this setting.

Operational Challenges

Despite thorough planning, several operational and systemic challenges were encountered:

Human Resource Limitations: There were three separate

instances where patient admissions were delayed due to a shortage of trained nurses for bone marrow transplants (BMT). Our team developed a structured training program to educate registered general nurses in the field of bone marrow transplantation. The program combined classroom lessons, hands-on clinical practice, competency-based evaluations, and teamwork with experienced transplant centers. The main topics covered included preventing infections, nursing protocols for transplant patients, managing symptoms, and providing psychosocial support. The nursing staff still faced challenges, such as high turnover rates, heavy workloads, and the technical complexity of bone marrow transplant nursing; to address these issues, we implemented regular refresher courses, ongoing professional development, and interdisciplinary team workshops across various disciplines to boost capacity. Despite these efforts, maintaining a stable, skilled nursing workforce remained a challenge, which aligns with broader trends in low- and middle-income countries. In these settings, nursing shortages, low social status, cultural barriers, and inadequate leadership and management support all hinder retention and ongoing training.

Medication Supply Issues: Intermittent unavailability of essential chemotherapy and antifungal agents occurred, primarily due to procurement delays, financial limitations, and global supply chain disruptions. Senior management was alerted to concerns about occasional shortages of chemotherapy, essential medications, and other supplies. In response, we started holding bi-monthly inventory reviews with the Pharmacy and Materials and Management Department (MMD). These departments now collaborate closely with Finance and Procurement to prioritize bids for the BMT program. We also explored sustainability through a blended funding approach that includes public funding, patient contributions, philanthropic donations, and in-house cost-cutting measures.

Laboratory Constraints: Establishing a robust laboratory infrastructure is crucial to the success of a bone marrow transplant program. Our services encompass critical areas such as hematology, biochemistry, transfusion medicine, Human Leukocyte antigen (HLA) typing, stem cell processing, and molecular chimerism monitoring. Despite this, we encountered technical challenges. The absence of real-time therapeutic drug monitoring, particularly for agents like Busulfan, necessitated the use of weight-based dosing approximations (e.g., <9 kg: 2 mg/kg; 9 to <16 kg: 2.4 mg/kg; 16–23 kg: 2.2 mg/kg; >23 to 34 kg: 1.9 mg/kg; >34 kg: 1.6 mg/kg). While not ideal, these estimations were clinically acceptable and effectively utilized during the initial phase of practice[9]. These constraints necessitated dynamic coordination between clinical, pharmacy, and administrative teams to prevent delays and mitigate patient risk.

Clinical Outcomes

During the study period, a total of 13 patients underwent stem cell transplantation, with 8 (61.5%) receiving autologous transplants and 5 (38.5%) undergoing allogeneic procedures. The average age of patients in the autologous group was significantly higher at 37.2 ± 17.8 years compared to 9.8 ± 9.3 years in the allogeneic group. The youngest patient was a 2-year-old with beta thalassemia major, while the oldest was a 58-year-old female diagnosed with multiple myeloma.

Males predominated in both groups, representing 87.5% of autologous and 100% of allogeneic recipients. In the autologous group (n=8), the majority were treated for multiple myeloma (n=5), with two patients having Hodgkin's lymphoma, and one patient diagnosed with plasma cell leukemia. Conditioning regimens mainly involved melphalan-based treatments for multiple myeloma and plasma cell leukemia, and the BEAM protocol for Hodgkin lymphoma. The allogeneic cohort (n = 5) consisted of patients with beta thalassemia major (n = 4) and aplastic anemia (n = 1). Conditioning regimens for thalassemia patients consisted of fludarabine, busulfan, cyclophosphamide, and anti-thymocyte globulin (ATG), with three patients receiving pre-transplant immunosuppression with fludarabine and dexamethasone. Blood level monitoring of intravenous busulfan was not available; therefore, fixed doses based on body weight were used without apparent detriment **(Table 1)**.

In autologous transplants, peripheral blood stem cells were exclusively used. Conversely, bone marrow was the primary source in 80% of allogeneic cases, with the remaining 20% receiving a combination of bone marrow and peripheral blood stem cells. Among allogeneic transplants, major ABO blood group incompatibility and gender mismatches were noted in 20% (n=1) and 40% (n=2) of cases, respectively. Only HLA-matched sibling donors were selected for allogenic bone marrow transplant[10].

In the allogeneic group, neutrophil and platelet engraftment occurred at a mean of 14 ± 1.87 days and 21 ± 7.89 days post-transplant, respectively. In contrast, patients who underwent autologous stem cell transplantation achieved neutrophil and platelet engraftment earlier, at an average of 10.37 ± 0.74 days and 11 ± 1.77 days, correspondingly. There were no cases of primary graft failure in either group. Stem cell infusion-related adverse reactions were observed in 40% of patients undergoing allogeneic transplantation, whereas none were reported in the autologous cohort.

Mucositis (grade 1-2) and febrile neutropenia were the most common complications, both affecting 62.5% (n=5/8) of autologous recipients and 80% (n=4/5) and 60%

Autologous BMT			
Sr. No	Patient Details	Disease	Transplant Details
1	58 Y, Male	Multiple Myeloma	Conditioning: Melphalan 140mg/m2
2	54 Y, Male	Multiple Myeloma	Conditioning: Melphalan 200mg/m2
3	27 Y, Female	Plasma Cell Leukemia	Conditioning: Melphalan 200mg/m2
4	51 Y, Male	Multiple Myeloma	Conditioning: Melphalan 200mg/m2
5	13 Y, Male	Hodgkin's Lymphoma	Conditioning: BEAM
6	37 Y, Male	Multiple Myeloma	Conditioning: Melphalan 200mg/m2
7	58 Y, Female	Multiple Myeloma	Conditioning: Melphalan 200mg/m2
8	14 Y, Male	Hodgkin's Lymphoma	Conditioning: BEAM
Allogeneic BMT			
1	2 Y, Male	Beta Thalassemia Major	Conditioning: Flu-Bu-Cy-ATG
2	26 Y, Male	Aplastic Anemia	Conditioning: Flu-Cy-ATG
3	6 Y, Male	Beta Thalassemia Major	Conditioning: Flu-Bu-Cy-ATG with PTIS
4	7 Y, Male	Beta Thalassemia Major	Conditioning: Flu-Bu-Cy-ATG with PTIS
5	7 Y, Male	Beta Thalassemia Major	Conditioning: Flu-Bu-Cy-ATG with PTIS

Table 1 Patient Demographics and Transplant Details: *ATG=rabbit Anti-thymocyte Globulin (Grafolon), Bu = Busulfan, Cy = Cyclophosphamide, Flu = fludarabine, BEAM = BCNU, Etoposide, Cytarabine, and Melphalan. PTIS: Pre-transplant immunosuppression with Fludarabine (30mg/m2) and dexamethasone 20mg/m2 each for 4 days from day -45 to -42.*

(n=3/5) of allogeneic patients, respectively. Fungal infections were documented in 25% (n = 2/8) of autologous recipients. Unique to the allogeneic group were complications such as neutropenic colitis, hemorrhagic cystitis, upper gastrointestinal bleeding, platelet refractoriness, and serositis. Gastrointestinal toxicity (grade 1 -3) related to melphalan was reported in 75% (n=6/8) of autologous patients.

Additionally, cyclosporine-induced hypertension occurred in 60% of allogeneic recipients, alongside acute graft-versus-host disease in 20%. One allogeneic patient developed poor graft function and died from sepsis on day +201 post-transplant. None of the patients experienced sinusoidal obstruction syndrome (SOS), Posterior Reversible Encephalopathy Syndrome (PRES), or chronic graft-versus-host disease (chronic GVHD). At a median follow-up of 274 days (range, 107 -582 days), the overall survival (OS) of the cohort was 92.3% (n = 12/13). OS was 100% for autologous and 80% (n = 4/5) for the allogeneic recipients. All five allografts achieved complete donor chimerism at both 1 and 3 months. One allograft developed mixed chimerism at 6 months, which remained stable at 12 months, with no relapses reported in the autografts to date **(Table 2)**.

Discussion

The successful establishment of a bone marrow transplant (BMT) unit in a low-resource setting, as described in this study, highlights both the opportunities and the persistent challenges inherent in delivering advanced hematopoietic stem cell transplantation (HSCT) services in such environments. The phased approach to infrastructure development, including the use of portable HEPA filtration to achieve ISO Class-8 cleanroom standards, aligns with international recommendations for infection prevention in immunocompromised patients. This strategy enabled the unit to provide a safe environment for transplantation despite resource constraints[11,12].

A key factor in the unit's operationalization was the implementation of comprehensive Standard Operating Procedures (SOPs), dedicated medication lists, and targeted

Characteristic	Autologous (n=8)	%	Allogenic (n=5)	%
Mean Age (years + SD)	37.2+17.83	-	9.8+9.3	-
Gender				
Male	7	87.50%	5	100%
Female	1	12.50%	0	0%
Source of Stem Cells				
Bone marrow	0	0%	4	80%
Peripheral blood	8	100%	0	0%
Both	0	0%	1	20%
Day of Neutrophil Engraftment (mean ± SD)	10.37 ± 0.74	-	14 ± 1.87	-
Day of Platelet Engraftment (mean ± SD)	-	-	21 ± 7.8	-
Adverse Effects of Stem Cell Infusion	0	0	2	40%
Post-Transplant Complications				
Mucositis	5	62.50%	4	80%
Febrile Neutropenia	5	62.50%	3	60%
Fungal infection	2	25%	0	0%
Neutropenic Colitis	0	0%	1	20%
Melphalan induced Gut toxicity	6	75%	-	-
CSA-induced Hypertension	-	-	3	60%
Hematuria	0	0%	3	60%
Hemorrhagic Cystitis	0	0%	1	20%
Upper GI Bleed	0	0%	2	40%
Platelet refractoriness	0	0%	3	60%
Serositis	0	0%	1	20%
Acute GVHD	-	-	1	20%
Chronic GVHD	-	-	0	0%
Poor Graft Function	-	-	1	20%

Table 2 *Clinical Characteristics and Outcomes by Transplant Type*

staff training. Previous studies have emphasized the importance of standardized protocols and continuous professional development in enhancing transplant outcomes and ensuring patient safety, particularly in resource-constrained settings[11,12,13,14]. The focus on infection control strategies was especially pertinent, given the heightened vulnerability of BMT patients to infectious complications[15,16].

Despite these achievements, the unit encountered several systemic challenges. Human resource shortages, particularly among specialized nursing staff, have led to delays in patient admissions, a challenge commonly reported in similar settings. Addressing workforce shortages through ongoing training and retention initiatives is crucial to sustaining and scaling transplant programs in low- and middle-income countries (LMICs)[17,18].

Medication supply interruptions, stemming from procurement delays and financial limitations, intermittently affected the availability of essential chemotherapy and antifungal agents. Such disruptions can compromise patient care and have been identified as a significant barrier to the effective delivery of HSCT in LMICs. Strengthening supply chain management and securing consistent funding are therefore vital for the reliability of transplant services[12,17].

Laboratory constraints, including the absence of real-time therapeutic drug monitoring for agents like Busulfan, necessitated reliance on weight-based dosing regimens. Although not ideal, such adaptations are clinically acceptable in the early phases of program development, provided there is close coordination among clinical, pharmacy, and laboratory teams[11,17,19].

The clinical outcomes observed in this cohort reflect both the achievements and limitations of hematopoietic stem cell transplantation (HSCT) in resource-constrained environments, consistent with global HSCT data. Our patient distribution (61.5% autologous, 38.5% allogeneic) mirrors patterns seen in emerging transplant programs, with engraftment success rates aligning with international standards for neutrophil and platelet recovery[18].

Disease-specific variability persists; hematologic malignancies demonstrate treatment success rates of 60–70%, while non-malignant disorders, such as thalassemia, exhibit graft failure rates of 5–18%, depending on the conditioning regimens and donor compatibility[19]. Our cohort experienced expected complications, including mucositis, infections, and delayed engraftment, complications well-documented in both transplant modalities[20].

This experience highlights that effective bone marrow transplant (BMT) services can be established in resource-limited settings through thoughtful planning, strong institutional support, and flexible problem-solving approaches. Sustained efforts in workforce training, strengthening supply chains, and enhancing laboratory infrastructure, combined with supportive health policies and global partnerships, will be critical to improving clinical outcomes and broadening access to this life-saving therapy for underserved communities.

Conclusion

Setting up a functional and efficient Bone Marrow Transplant (BMT) unit in a resource-constrained environment is undoubtedly challenging, yet achievable. Our experience demonstrates that with deliberate strategic planning, robust institutional support, and phased infrastructure development, safe and effective transplant services can be successfully delivered. Sustained investment, ongoing staff training, enabling policies, and collaboration with international partners are crucial to expanding access to life-saving hematopoietic stem cell transplantation for underserved populations.

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