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Autologous Hematopoietic Stem Cell Transplantation —10 Years of Data From a Developing Country

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Key Words. Autologous transplant • Lymphoma • Multiple myeloma

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ABSTRACT

Intensive chemotherapy followed by autologous stem cell transplantation is the treatment of choice for patients with hematological malignancies. The objective of the present study was to evaluate the outcomes of patients with mainly lymphoma and multiple myeloma after autologous stem cell transplant. The pretransplant workup consisted of the complete blood count, an evaluation of the liver, kidney, lung, and infectious profile, chest radiographs, and a dental review. For lymphoma, all patients who achieved at least a 25% reduction in the disease after salvage therapy were included in the study. Mobilization was done with cyclophosphamide, followed by granulocyte colony-stimulating factor, 300 µg twice daily. The conditioning regimens included BEAM (carmustine, etoposide, cytarabine, melphalan) and high-dose melphalan. A total of 206 transplants were performed from April 2004 to December 2014. Of these, 137 were allogeneic transplants and 69 were autologous. Of the patients receiving an autologous transplant, 49 were male and 20 were female. Of the 69 patients, 26 underwent transplantation for Hodgkin's lymphoma, 23 for non-Hodgkin's lymphoma, and 15 for multiple myeloma and 4 and 1 for Ewing's sarcoma and neuroblastoma, respectively. The median age ± SD was 34 ± 13.1 years (range, 4–64). A mean of $4.7 \times 10^8 \pm 1.7$ mononuclear cells per kilogram were infused. The median time to white blood cell recovery was 18.2 ± 5.34 days. Transplant-related mortality occurred in 10 patients. After a median follow-up period of 104 months, the overall survival rate was 86%. High-dose chemotherapy, followed by autologous stem cell transplant, is an effective treatment option for patients with hematological malignancies, allowing further consolidation of response. STEM CELLS TRANSLATIONAL MEDICINE 2015;4:873–877

SIGNIFICANCE

This report presents the results of autologous stem cell transplant in hematological malignancies from a developing country. This is a large cohort from Pakistan, with overall survival comparable to that from international data.

INTRODUCTION

Autologous stem cell transplantation (ASCT) is an alternative treatment modality for lymphomas, multiple myeloma, and a few solid tumors [1]. In the 1970s, it was postulated that stem cell mobilization was possible after a high level of progenitor cells were observed in the blood of patients who had received cyclophosphamide chemotherapy [2]. In 1984, the CD34 marker was identified on hematopoietic stem cells. This second discovery led to a swift increase in the understanding and manipulation of ASCT, which resulted in its significant growth [3].

Autologous hematopoietic stem cell transplantation (HSCT) is used to bridge hematopoietic failure during high-dose chemotherapy for the treatment of tumors of the hematopoietic system that are adequately sensitive to this treatment. In this sense, autologous stem cell support is not a

“transplant”; however, the term “autologous HSCT” is commonly used. This procedure was initially developed for patients with leukemia without a sibling donor for allogeneic transplant. Later, it became the standard of care for patients with lymphoma, myeloma, and some childhood neoplasms [4].

More than one half of the stem cell transplants performed in Europe are autologous. The European Bone Marrow Transplant (EBMT) annual activity survey for 2011 reported a 58% rate of autologous stem cell transplants. Most of these ASCTs were performed for lymphoid malignancies (plasma cell disorders, 46%; non-Hodgkin's lymphoma, 30%; Hodgkin's disease, 11%). The focus from marrow to peripheral blood as a source of stem cells occurred in the early 1990s for ASCT. Recent data now suggest that 99% of all autologous transplant procedures use peripheral blood as the source [5].

The 2011 Center for International Blood and Bone Marrow Transplant Research (CIBMTR) data

showed that 12,047 autologous transplants were performed, for which multiple myeloma and lymphomas were the most common indications [6].

The standard treatment for B-cell non-Hodgkin's lymphoma (NHL) includes chemotherapy with rituximab.

A Cochrane analysis published in 2013 evaluated 2 randomized control trials ($n = 157$) of relapsed Hodgkin's lymphoma (HL) patients that included 2 treatment arms: high-dose chemotherapy (HDCT) plus autologous stem cell transplantation versus conventional chemotherapy without autologous stem cell transplantation. The difference in progression-free survival was statistically significant for patients treated with HDCT followed by ASCT compared with patients treated with conventional chemotherapy alone (hazard ratio [HR], 0.55; 95% confidence interval [CI] 0.35–0.86; $p = .009$) [7].

Two systematic reviews assessed the efficacy of high-dose chemotherapy with single ASCT versus conventional chemotherapy in patients with multiple myeloma. The pooled results have shown a statistically nonsignificant difference in survival between high-dose chemotherapy plus stem cell rescue (HR, 0.92; 95% CI, 0.74–1.13; $p = .40$) versus chemotherapy. For the outcome of progression-free survival, a statistically significant benefit was associated with high-dose chemotherapy plus stem cell rescue (HR, 0.75; 95% CI, 0.59–0.96; $p = .02$) [8].

Kumar et al. [9] in a study from India in 2010 reported a median overall and event-free survival of 78 and 28 months, respectively, for patients undergoing autologous stem cell transplant for Hodgkin's and non-Hodgkin's lymphoma.

In Pakistan, use of the hematopoietic stem cell transplant procedure started in 1995. Because of the burden of non-malignant diseases such as β -thalassemia major and aplastic anemia, the number of allogeneic transplants have outnumbered the number of autologous transplant procedures. Nevertheless, we have a significant burden of lymphoid malignancies in young patients for whom autologous hematopoietic transplantation is the only curative option. In the present report, we present our initial data on the frequency and outcomes of autologous stem cell transplants performed in our center from 2004 to 2014.

MATERIALS AND METHODS

We retrospectively analyzed the data from all patients who underwent autologous stem cell transplant from April 2004 to December 2014. The patients were considered to have chemosensitive disease if they had had a complete response (CR) or partial remission at ASCT. These included patients with HL, NHL, and multiple myeloma. Patients with a minimal response (25%–50% response), progressive, or refractory disease were considered to have chemoresistant disease.

Our institute is a tertiary care, private hospital with 29 beds dedicated to cancer patients. In addition, 54 beds are available in a day care center exclusively for hematology/oncology patients for chemotherapy administration and blood and/or blood product transfusion. The transplant unit was established in 2004 and was initially a 2-bed facility that was upgraded to 4 beds later. Pakistan's gross domestic product in 2013 was reported to be \$232.3 billion. The average household income ranges from \$1,200 to \$1,500 annually. Therefore, affording an expensive procedure such as stem cell transplant is very challenging. Nevertheless, the cost of the procedure is met by the patients themselves,

philanthropists, and medical insurance. Patients are referred for transplant from all over the country. All patients are initially assessed at outpatient clinics. The patients and their family members are counseled about the procedure and the potential risks and benefits. Post-transplant patients are followed up initially monthly for 3 months, every 3 months for 1 year, and every 6 months thereafter. Some of our patients come from outside the city or country. These patients are followed up locally by the referring oncologist or hematologist. If required, communication was maintained through electronic mail and telephone.

The pretransplant evaluation included the complete blood count, liver and kidney function tests, infectious disease profile (i.e., hepatitis B surface antigen, hepatitis C antibody, HIV antibody, cytomegalovirus, Mantoux test, and chest radiography), blood group determination and coagulation testing, pulmonary function tests, echocardiography, and a dental evaluation. A central line (Hickman's catheter) was inserted in all patients. All the patients were admitted to a single room, and reverse barrier nursing was practiced. The patients provided written informed consent for chemotherapy, blood product administration, and transplantation.

Mobilized peripheral blood stem cells (PBSCs) were harvested from all the patients. For mobilization, the patients received cyclophosphamide 1.5 g/m^2 followed by granulocyte colony-stimulating factor (G-CSF) $5 \mu\text{g/kg}$ twice daily subcutaneously for 6 days. The stem cells were harvested on days 5 to 7 using either the Cobe Spectra AutoPBSC or COMTEC (Fresenius Kabi, Bad Homburg, Germany, <https://www.terumobct.com>) system and the default software configuration recommended by the manufacturer. The mononuclear cells were counted manually.

For multiple myeloma, the patients received high-dose melphalan (200 mg/m^2). For patients with HL and NHL, carmustine (BCNU; 300 mg/m^2), etoposide (200 mg/m^2), cytarabine (ara-C; 200 mg/m^2), and melphalan (140 mg/m^2) were used.

Patients were admitted to a single room with a high-efficiency particulate air (HEPA) filter. Standard prophylaxis with ciprofloxacin (500 mg twice daily or $20\text{--}30 \text{ mg/kg}$ in 2 divided doses), fluconazole (200 mg once daily or 6 mg/kg per day), and valaciclovir (500 mg twice daily or 10 mg/kg twice daily) was started in all patients on day -5 . All patients were provided a neutropenic diet. The autologous stem cells were reinfused on day 0 through the central venous catheter and preceded by i.v. pheniramine maleate (50 mg). G-CSF, $5 \mu\text{g/kg}$, was started on day +1. All patients received irradiated blood products. All packed red blood cell transfusions were performed with a leukocyte filter, and febrile neutropenia evaluations and treatment were performed in accordance with the standard guidelines.

Engraftment was defined as achievement of an absolute neutrophil count of $\geq 0.5 \times 10^9$ per liter for 3 consecutive days. Platelet engraftment was defined as a count of $\geq 20 \times 10^9$ per liter with transfusion independence. Patients were evaluated for response using the World Health Organization criteria at 4 weeks after transplant at the outpatient clinic with subsequent follow-up examinations. In patients with multiple myeloma, the response was assessed and monitored using serial immunoglobulin levels.

Patients with Ewing's sarcoma or neuroblastoma were excluded from the analysis because of insufficient patient numbers. The remaining patients were evaluable for the response and survival analyses. Overall survival was defined as that from the date of transplant until death or the date of the last follow-up visit. The curve for overall survival was plotted according to Kaplan and Meier. Statistical analysis was performed using SPSS software,

version 19.0 (IBM Corp., Armonk, NY, <http://www-01.ibm.com/software/analytics/spss/>).

RESULTS

In the study period, a total of 206 hematopoietic stem cell transplants were performed at our center. Of these, 69 were autologous transplants. Of the patients with lymphoma, 2 underwent the procedure in the first CR. All others achieved more than a 50% response to salvage chemotherapy and underwent the procedure in the second CR. Hodgkin's disease was the most common indication ($n = 26$, 38%) followed by non-Hodgkin's lymphoma ($n = 23$, 33%), multiple myeloma ($n = 15$, 22%), Ewing's sarcoma ($n = 4$, 6%), and neuroblastoma ($n = 1$). Owing to the small numbers, the patients with Ewing's sarcoma and neuroblastoma were excluded from the analysis. Before transplantation, all patients had chemosensitive disease. The salvage regimens for the patients with lymphoma included dexamethasone, Ara-C, and cisplatin in 29 patients, ifosfamide, carboplatin, and etoposide in 16 patients, and etoposide, methylprednisolone, cytarabine, and cisplatin in 4 patients. All 15 patients with multiple myeloma underwent the procedure in the plateau phase. The median age \pm SD was 34 ± 13.1 years (range, 4–64). Of the 69 patients, 5 were in the pediatric age group and the rest were adults (49 men and 20 women).

The peripheral blood stem cells were infused in 67 patients, and 2 patients received both peripheral and bone marrow progenitor stem cells. A mean of $4.7 \times 10^8 \pm 1.7$ mononuclear cells per kilogram (range, 2.2–10) were infused. Of the 69 patients, 64 achieved engraftment (93%), and 5 had primary graft failure, mainly because of sepsis. The median time to white blood cell recovery was 18.2 ± 5.34 days (range, 12.9–23.5). The median time to platelet transfusion independence was 15 days (range, 12–40). The median duration of antibiotic therapy secondary to febrile neutropenia was 13 days. The hospital stay was ranged from 11 to 52 days (median \pm SD, 28 ± 8). A total of 149 febrile episodes were documented in 41 patients. Central line-associated bloodstream infections were present in 12 patients. The common organisms were *Staphylococcus* species and *Escherichia coli*. Ten patients developed bloodstream infections (BSIs). The most common organism was *E. coli* (Fig. 1). During the hospital stay, 13 patients (19%) required intensive care unit admission. In 1 patient, the sputum culture and sensitivity testing was positive for *Aspergillus flavus*. The computed tomography scan of the chest showed a fungal ball that was subsequently removed surgically. Transplant-related mortality for all evaluable patients was 15%. The cause of death for transplant-related mortality was mainly sepsis (Table 1). After a median follow-up of 104 months, the overall survival rate was 86% (Fig. 2). One transplant-related mortality (TRM) occurred in a patient with multiple myeloma, and the overall survival was 93%. For patients with non-Hodgkin's lymphoma, the TRM rate was 25% and the overall survival rate was approximately 70%. The TRM for patients with Hodgkin's disease was 12%. The overall survival for these patients was 71%. The overall survival according to the diagnosis is shown in Figure 3.

DISCUSSION

The rationale of the present study was to compile data on the frequency, complications, and overall survival after autologous transplant performed in the past decade at our center. The two main indications were lymphoma and multiple myeloma, in accordance with the frequency reported from the CIBMTR, EBMT, and India [10]. The use of PBSCs for autologous and allogeneic transplantation has increased significantly in recent years. According to the

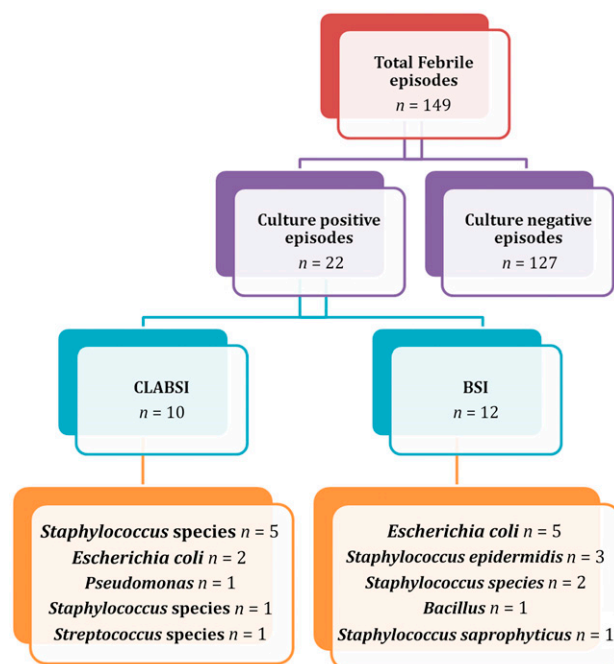


Figure 1. Frequency of CLABSI and BSI organisms. Abbreviations: BSI, bloodstream infection; CLABSI, central line-associated bloodstream infection.

Table 1. Causes of transplantation-related mortality

Pt. No.	Age (yr)	Diagnosis	Toxicity
1	62	NHL	Sepsis, NSTEMI, cardiogenic shock, graft failure
2	35	HL	Sepsis
3	49	HL	Sepsis, ARDS, cardiomyopathy
4	52	NHL	Acute renal and liver failure, graft failure
5	59	HL	Sepsis
6	42	NHL	Sepsis, MOF
7	45	NHL	Sepsis, ARF
8	20	NHL	Pneumonia, respiratory failure, graft failure
9	39	MM	Sepsis, graft failure
10	24	HL	Sepsis, graft failure

Abbreviations: ARDS, acute respiratory distress syndrome; ARF, acute renal failure; HD, Hodgkin's lymphoma; MM, multiple myeloma; MOF, multiorgan failure; NHL, non-Hodgkin's lymphoma; NSTEMI, non-ST-segment elevation myocardial infarction; Pt. No., patient number.

CIBMTR, in more than 95% of autologous stem cell transplants, mobilized PBSC are used. The advantages of using PBSCs include a shorter engraftment time, fewer transfusions, a shorter hospital stay, the convenience of stem cell collection, and rapid restoration of the immune system [11]. In 97% of our patients, PBSCs were used. In the 2 patients who had received bone marrow stem cells, no difference was found in the engraftment time or hospital stay. The relatively late engraftment resulted from the late presentation and pretreatment with high doses of cytotoxic chemotherapy in these patients. Five patients experienced primary graft failure and multiple organ failure, which contributed to the overall mortality. Most of these deaths were in the initial years of the transplant program.

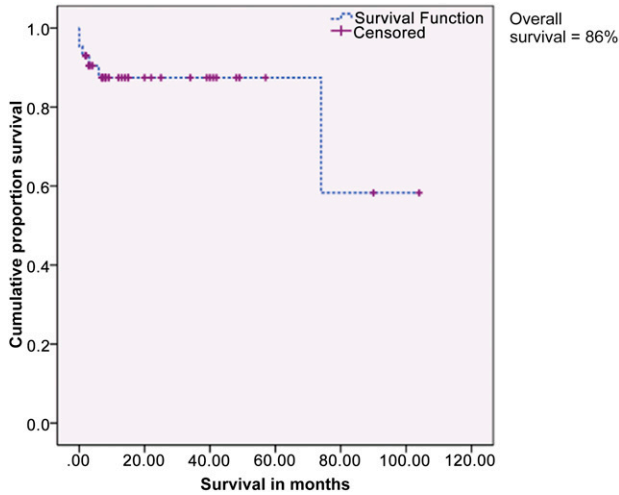


Figure 2. Overall survival.

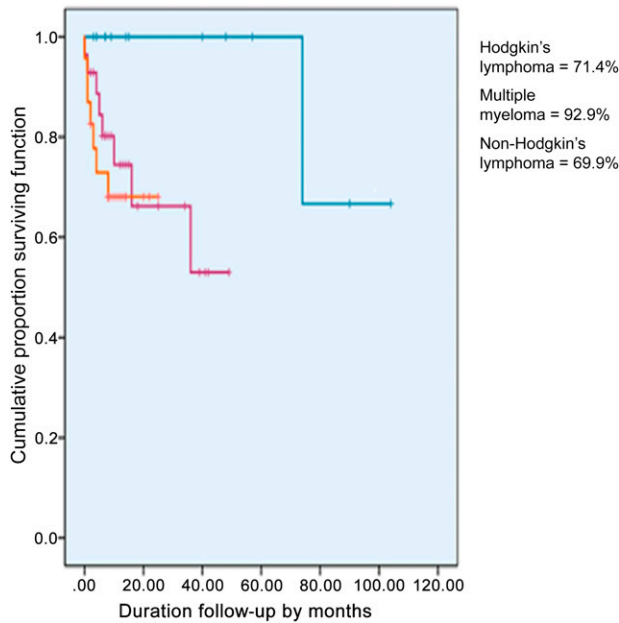


Figure 3. Overall survival according to diagnosis.

Once the learning curve had been completed, the mortality rate decreased from 21% in 2004–2009 to 8% in 2010–2014. The median \pm SD age was 34 ± 13.1 years. Studies reported from the region have shown the median age to be 45 years, in particular, for NHL [12]. Our study reported a much younger age of presentation. This younger age group preponderance has been reported previously in other hematological and nonhematological malignancies [13–15] from our region, consolidating that cancer, in our population, has a predilection for a younger population.

The major gastrointestinal toxicities observed were grade III to IV nausea/vomiting, diarrhea, and mucositis. These toxicities were higher in patients with multiple myeloma owing to the high-dose melphalan conditioning therapy. The incidence of organ toxicities (e.g., renal dysfunction [16], veno-occlusive disease [17], and pulmonary [18], cardiac [19], and central nervous system toxicity [20]) was similar to that reported in published studies and did not differ according to the type of conditioning therapy used.

In the present study, 7% of patients died of regimen-related toxicity. The CIBMTR data reported 12% mortality from regimen-related toxicity in their series [21]. Infections due to myelosuppression remain the major cause of morbidity and mortality until day 100. Management of febrile neutropenia was in accordance with institutional guidelines. First-line i.v. antibiotic therapy consisted of piperacillin/tazobactam and amikacin. If a patient remained febrile after 48–72 hours, the regimen was changed to imipenem/cilastatin, vancomycin, and amphotericin B (conventional). For afebrile patients, the initial antibiotic regimen was continued until the resolution of neutropenia. Our patients mainly developed *E. coli* bloodstream infections (isolated from blood culture). Similar results were reported previously in HSCT recipients in a retrospective study that investigated the effect of BSI on the outcome of 246 allogeneic transplant recipients [22]. Gram-negative rods constituted 54% of the bacterial isolates. Hospital-acquired infections mainly due to *Acinetobacter baumannii* [23] and carbapenem-resistant *E. coli* are an issue at our center. All our transplants are performed in single rooms with HEPA filters. Because of the increased frequency of possible fungal infections, the hospital policy is to start amphotericin B early if the fever does not resolve or if radiological signs suggestive of fungal infection are present. Debilitating fungal infection was observed in 1 patient only at our center and required surgical removal. *Mycobacterium tuberculosis* infection has been reported occasionally in both autologous and allogeneic transplant recipients, possibly due to reactivation after the myelosuppression caused by conditioning therapy [24]. Only 1 patient developed *M. tuberculosis* in our series.

Several observational and clinical trials have been conducted of patients with NHL and HL. The 5-year survival after transplant in these patients is approximately 50%–60% [25, 26]. The most common cause of treatment failure is relapse or disease progression. This predominantly occurs in the first 2 years after the procedure. Our cohort of patients with NHL and HL showed that after a median \pm SE follow-up of 23.4 ± 4.3 months (range, 14.8–32), the overall survival was 70% and 71.4%, respectively. Most of our patients with NHL had diffuse large B-cell lymphoma (DLBCL) in second remission. The role of ASCT during first remission as consolidative therapy in patients with DLBCL remains controversial and should not be performed outside the clinical trial setting [27]. Bolwell et al. [28] in 2002 reported a 5-year overall survival rate of 43% in patients with NHL and high-grade histologic findings. Our results are comparable to their data. Philip et al., in a multicenter, prospective randomized trial, also compared autologous HSCT and nontransplant salvage therapy and showed that autologous HSCT is the standard of care for patients younger than 60 years old with chemotherapy-sensitive relapsed or primary refractory aggressive NHL [29].

High-dose therapy with melphalan (200 mg/m^2), followed by ASCT in combination with novel agents is considered the standard of care for patients with newly diagnosed multiple myeloma. In our cohort of patients with MM, all were younger than 65 years old. The median age \pm SD was 48 ± 7.5 years (range, 32–55). A recent, open-label, randomized phase 3 trial comparing high-dose melphalan followed by ASCT and melphalan, prednisolone, and lenalidomide showed significantly longer progression-free and overall survival [30]. Other studies of younger patients have shown overall survival rates ranging from 48.3% to 66% [31, 32]. Compared with this, our patients did relatively better, with an overall survival of approximately 93%. All these patients were receiving maintenance therapy with either thalidomide or lenalidomide at the last follow-up visit.

In a retrospective analysis, the median cost of autologous transplant at our institution was approximately \$20,000 (range, \$10,000–\$35,000). This cost includes the cost of chemotherapy, stem cell/bone marrow harvest, antibiotic usage, blood and/or blood product transfusion and growth factor support, the daily bed and investigation charges, and the consultation fees. The cost of clinic visits and subsequent admissions was omitted. Our data clearly show that the cost of stem cell transplant is less expensive in Pakistan than in developed countries with similar success rates. The major contributing factors to the cost and overall mortality include debilitating infections and regimen-related toxicities that prolonged the hospital stay.

CONCLUSION

We observed survival rates similar to those in the international data for non-Hodgkin's and Hodgkin's lymphoma. Higher response rates and reduced morbidity and mortality in patients with multiple myeloma resulted from their younger age and proper case selection.

Overall, the results suggest that with improved management of infections and conditioning-related toxicities, it is possible to develop hematopoietic stem cell transplant programs in third-world countries and achieve outcomes comparable to those in the international data.

AUTHOR CONTRIBUTIONS

N.A.: collection and/or assembly of data, data analysis and interpretation, manuscript writing; S.N.A.: critical review of manuscript; M.U.S.: collection and/or assembly of data, critical review of manuscript.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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