Haematopoietic Stem Cell Transplantation: A Single Center Experience of Four Years in Bangladesh

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Abstract:

Background: *Haematopoietic stem cell transplantation (HSCT) is the standard consolidation therapy for a variety of malignant and non-malignant diseases in children and adults. Our experience of HSCT in 26 patients with various indications is shared in this article. Materials and Methods: This was a retrospective analysis of first 26 patients who had undergone autologous and allogeneic transplant at our center, with M:F=2.7:1. The mean age for autologous transplant was 45 years (range 23-57 years). The median follow-up period was 23 months 25 days (range 3to 47 months).The data was obtained carefully from medical records of the BMT center. Indications for autologous HSCT were Multiple Myeloma (12 patients), Non- Hodgkin's lymphoma (7 patients), Hodgkin's lymphoma (4 patients). Allogeneic HSCT were for Acute Myeloid Leukaemia (3 patients). Results: The mean time for WBC engraftment was 12 days (range: 9-19 days) and for platelet engraftment was 16 days (range: 11-35 days) in our autologous transplant cases and for allogeneic transplant mean time for WBC engraftment was12 days (range: 11-15 days) and for platelet engraftment was 14 days (range: 12-17 days). Irradiated blood components were given in the pre, peri and post-transplant period to maintain Hb>8 gm/dl and platelet count >20X10^9/L. Mean single-donor platelet requirement was 4 units (range 1-7), and mean packed red cell requirement was 1.5 units (range 1-6). The post-transplant complications encountered were mucositis, infections and diarrhoea. Oral mucositis was the most common complications. Twenty three (88.46 %) out of our 26 HSCT patients had developed mucositis , among them grade 1 in 5 patients, grade 2 in 11 patients, and grade 3 in 7 patients. There were 21(80.76%) cases of febrile neutropenia. Out of 26 patients 13 (50.0%) bacterial infection were documented with culture positivity. One (3.84%) case of viral infection was documented. Major bacterial infections were culture positive with* **Pseudomonas, Escherichia coli** *and* **Klebsiella** *followed by other species like* **acinatobacter, burkholderia and coagulase negative staphylococcus.** *One case of* **Cytomegalovirus** *was noted with significant viral copies that required Ganciclovir. Average duration of hospital stay after autologous HSCT was 23 days (range of 14-54 days) and allogeneic HSCT was 35 days (range of 30-57 days). 19 out of our 23 autologous transplant patients were in complete remission and all 03 cases of allogeneic HSCT were in remission. Conclusion: We believe our center has made a remarkable progress within short period of time to develop both autologous and allogeneic HSCT and is comparable with nationally and internationally renowned HSCT centers in terms of standard, quality and safety of care, and the ultimate outcomes.*

Keywords: *Haemopoietic stem cell transplantation, Conditioning regimen, Engraftment.*

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Introduction:

Stem cell transplantation is a procedure that can restore marrow function for patients who have had severe marrow injury or abnormalities of the immune system. Marrow injury can occur because of primary marrow failure, destruction or replacement of marrow by disease, or intensive chemical or radiation exposure. HSCT has become the standard of care for many patients with

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defined congenital or acquired disorders of the hematopoietic system or with chemo- radio- or, immuno-sensitive malignancies.[1,2,3] The first ever successful transplant was performed by Dr. E. Donnall Thomas in late1950s for which he was awarded Nobel Prize of Physiology or Medicine in 1990.[4] In our country, the first successful bone marrow transplant was done in March 2014 on a case of Multiple myeloma in Dhaka Medical College.[5] Presently few haematopoietic stem cell transplant centers have been established in our country. Combined Military Hospital (CMH), Dhaka is a tertiary care hospital playing the key role in health sector in our country. In CMH Dhaka, Bone marrow center was inaugurated in May 05, 2015 by the Honourable Prime Minister. First case (Multiple myeloma) of autologous stem cell transplantation was done in our center on Nov 22, 2016.

Materials and Methods:

This was a retrospective study. The data was obtained carefully from medical case records from the BMT center. The statistical analysis was done using SPSS version 21. In this study, 26 patients had undergone autologous and allogeneic stem cell transplantion with M: F=2.7:1. The first case was taken from November 2016 while last one from August 2020. Out of 26 patients, 23 patients underwent autologous stem cell transplant with mean age 45 years (range 23-57 years), M:F ratio of 3.6:1. Allogeneic stem cell transplant was done in 03 cases. All cases were Acute Myeloid Leukaemia (AML) with M:F ratio = 1:2. The youngest patient was 23 years and eldest one was 40 years old. It is to be mentioned here that in our country the first allogeneic HSCT was done successfully in our center. The median follow-up period was 23 months 25 days with range from 3 to 47 months.

Indications

Indications for autologous HSCT were Multiple Myeloma (12 patients), Non-Hodgkin lymphoma (07 patients), Hodgkin lymphoma (04 patients). Allogeneic HSCT was done in patients with Acute Myeloid Leukaemia (AML), out of which one was AML with FLT-3 positive (high risk), another one Relapsed AML and the 3rd one was AML with intermediate risk cytogenetics.

Stem cells Collection

Stem cells were collected from peripheral blood after mobilization therapy either with G-CSF alone or G-CSF with Plerixafor. Stem cells were taken in range from 3.34 to 6.24x10^6/kg CD34+ counts.

Conditioning regimens

All patients with Multiple Myeloma received High dose Melphalan as conditioning regimen, while BEAM and R-BEAM regimen were used for patient with lymphoma. Reduced intensity conditioning (RIC) Regimen Flu-Mel was used in patient with AML-intermediate risk and the other two received Flu-Bu as myeloablative conditioning regimen.

Post-transplant care

Patients were nourished by special and sterilized food and special diet according to each patient characteristics and needs. They were observed closely for complications. All patients were treated in completely isolated rooms during the pre-, peri- and post-transplant period. These were conventional High-Efficiency Particulate-Air (HEPA) filtered rooms.

Results

Engraftment

By definition, WBC engraftment is, when absolute neutrophil count>500/cumm for three consecutive days and the platelet engraftment is the platelet count >20,000/cumm for three consecutive days without any external transfusion support. The mean time for WBC engraftment was 12 days (range: 9-19 days) and for platelet engraftment was 16 days (range: 11-35 days) in our autologous transplant cases and for allogeneic transplant mean time for WBC engraftment was12 days (range: 11-15 days) and for platelet engraftment was 14 days (range: 12-17 days).

Table-I

Sex distribution (n=26)

Sex	Number	Percentage
Male	19	73
Female	7	27

Table-II

Summary of transplant performed by type (Allo HSCT vs Auto HSCT) (n=26)

Type of transplant	Number	Percentage
Auto HSCT	23	88
Allo HSCT	3	12

Table-III

Indications of Auto HSCT (n=23)

Indications of Auto HSCT	Number	Percentage
Multiple myeloma	12	52
Non-Hodgkin lymphoma	7	30
Hodgkin lymphoma	4	17

Table-IV

Baseline characteristics of Autologous HSCT (n=23)

Total Number	23
Age (median)	45 years
Gender (M:F)	3.6:1
Indication:	
Multiple Myeloma	12
Non-Hodgkin Lymphoma	07
Hodgkin Lymphoma	04

Table-V

Baseline characteristics of Allogeneic HSCT (n=03)

Total Number	03
Age (median)	30 years
Gender (M:F)	1:2
Indication:	
Acute Myeloid Leukaemia-Intermediate risk	01
Acute Myeloid Leukaemia-Relapsed	01
Acute Myeloid Leukaemia-FLT3,ITD Positive (High risk)	01

Table-VI

Outcome of Autologous HSCT (n=23)

Median engraftment day	WBC : 12 days Platelets : 16 days
Median post-transplant hospital stay	23 days (14-54 days)
Total Patient	23
Complete remission	19
Death during peri-transplant period	01
Post-transplant death	02
Relapse but alive	01
Overall survival (median 2 years)	95.65%
Transplant related mortality (TRM)	4.34%

Table-VII

Outcome of Allogeneic HSCT (n=03)

Median engraftment day	WBC: 12 days Platelets: 13 days
Median post-transplant hospital stay	35 days (30-57 days)
Complete remission	03
Overall survival 100%	100%

Table-VIII

Conditioning regimen used for Autologous HSCT

Conditioningregimen	Indications	Protocol
BEAM& R-BEAM regimen	Hodgkin Lymphoma Non-Hodgkin Lymphoma	Day-7: Rituximab 375 mg/m^2 Day-6: Carmustine (BCNU)(300 mg/m^2), Days -5, -4, -3, -2:Etoposide (200 mg/m^2) and Cytarabine (Ara-C) (400 mg/m^2), Day -1: Melphalan (140 mg/m^2/dose) Day 0: Stem cell transplant
Melphalan regimen	Multiple Myeloma	Day -1: Melphalan 200 mg/m^2 Day 0: Stem cell transplant

Table-IX

Conditioning regimen used for Allogeneic HSCT

Coditioning regimen	Indication	Protocol
Reduced intensity (Flu- Mel)	Acute Myeloid Leukaemia- (Intermediate risk) Remission after induction chemo	Days -6, -5, -4 , -3, -2: Fludarabine 30 mg/m^2 Day -1: Melphalan 140 mg/m^2 Day 0: Stem cell transplant
Myeloablative (Flu-Bu)	AML- Relapsed	Fludarabin 30 mg/m^2 D-5 toD-2 Busulfan 3.2 mg/kg/day in divided dose D-5 to D-2
Myeloablative(Flu-Bu)	AML- FLT3, ITD (High risk)	Fludarabin30 mg/m^2 D-5 toD-2 Busulfan 3.2 mg/kg/day in divided dose D-5 to D-2

Table-X

Antimicrobial prophylaxis used for Autologous HSCT

Antibiotics	Dose	Duration
Cap Cefixime	400 mg daily	After removal of CV line
Inj Fluconazole followed byTab Fluconazol	200 mg daily	Starts on day 0 tillD+28
Inj Acyclovir followed by oralTab	400 mg thrice daily	Starts on day 0 tillD+90
Tab Phenoxymethyl penicillin	500 mg twice daily	Starts D+29 to D+90

Table-XI

Antimicrobial prophylaxis used for Allogeneic HSCT

Antibiotics	Dose	Duration
Cap Cefixime	400 mg daily	After removal of CV line
Syp Posaconazol	200 mg three times a day	Starts on day 6 to day 14
Tab Fluconazole	200 mg daily	Starts on day 15 tillD+28
Tab Acyclovir	400mg twice daily	Starts on day 0 tillD+90
Tab Phenoxymethyl penicillin	500 mg twice daily	Starts D+29 to D+90

Table-XII

GVHD Prophylaxis for Allogeneic SCT

Drugs	Dose	Duration
Inj Cyclosporin	2.5 mg/kg /dose	From D-1 till oral
Cap Cyclosporin	200 mg /day	After injectable form
Inj MTX	10 mg/m^2 and 7 mg/m^2	D+1, D+3 ,D+6 ,D+11

Table-XIII

Pattern of infection

Type of Infection	*Organisms*	Sample	Number
Bacterial (13)	*Pseudomonas aeruginosa*	From bloodC/S	04 patients
	Escherichia coli	From urine C/S	02 patients
	Klebsiellaspp	From throatswab C/S	02 patients
	Coagulase negative *Staphylococcus spp*	From bloodC/S	01 patient
	BurkholderiaCepacia	From bloodC/S	02 patients
	Acinetobacterspp	From throatswab C/S	02 patients
Viral (01)	Cytomegalovirus	From blood	01 patient

Table-XIV

Antimicrobials used to treat infection for our patients

Name	Dose
Inj Ceftriaxone	1 gm 12 hourly
Inj Metronidazol	500 mg 8 hourly
Inj Piperacilline+Tazobactum	4.5 gm 6 hourly
Inj Meropenem	1 gm 8 hourly
Inj Amikacin	500 mg 12 hourly
Inj Teicoplanin	200 mg/day
In Tegecycline	100 mg-1st day then 50 mg/daily
Inj Vancomycin	1 gm/day
Inj Colistin	1 Million IU/day
Inj Ganciclovir	5 mg/kg/dose-12 hourly

Transfusion support

Irradiated blood products were given in the post-transplant period to maintain Hb>8 gm/dl and platelet count >20X10^9/L. Mean single-donor platelet requirement was 4 (range 1-17), and mean packed red cell requirement was 1.5 (range 0-6).

Post-transplant Complications

The post-transplant complications encountered were mainly mucositis, infections and diarrhoea.

Oral Mucositis

Oral mucositis was the most common complications. 23 (88.46%) out of our26 HSCT transplant patients had developed mucositis , among them grade 1 in 5 patients, grade 2 in 11 patients, and grade 3 in 7patients. Grade 2 mucositis patients were managed with dietary modification, analgesics, Sodi-bi-carb mouth wash and oral care. Patients with grade 3 mucositis required some interventions like parental nutrition.

Infection

There were 21 (80.76%) cases of febrile neutropenia. Out of 26 patients 13 (50.0%) bacterial infection cases were documented with culture positivity. One viral (3.84%) case was documented. Major bacterial infections were by*Pseudomonas*,*Escherichia coli* and *Klebsiella*followed by other specieslike *acinatobacter, burkholderiaandcoagulase negative staphylococcus.* One incidence of *Cytomegalovirus* wasnoted with significant viral copies that requiredintravenous Ganciclovir.

Gastrointestinal Complications

These were 10 (38.46%) incidences of diarrhoea and 01 (3.84%) incidence of oral bleeding.

Duration of hospital stay after transplant

Average duration of hospital stay after autologous HSCT was 23 days with a range of 14-54 daysand allogeneic HSCT was 35 days with a range of 30-57 days.

Outcomes

One patient who was a case of relapsed Diffuse Large B-cell lymphoma (DLBCL) with spinal mass and heavily pre-treated, died during Transplant procedure. He developed typhilitis and septicaemia and we could not revive him and ultimately died. The rest of all cases of both autologous and allogeneic HSCT came out with successfully in the course of pre and peri-transplant periods as well as during transplant procedure. Two patients died after transplantation, one was a case of Plasma cell leukaemia who died after 08 months of transplantation due to relapse and another one was Non-Hodgkin Lymphoma (NHL)-DLBCL died after 10 months of transplantation due to respiratory tract infection (Pneumonia), he reported lately to hospital, otherwise he could have been saved. 19 out of our 23 autologous transplant patients were in complete remission. One of the autologous transplant patients had disease relapse and in good response with salvage chemotherapy. All 03 cases of allogeneic HSCT were in remission state. 1st case is now without any drugs and other two are getting tapering dose of GVHD prophylaxis and clinically stable.

Discussion:

Stem cells have different proliferative properties and functions depending on their physical location or tissue compartment. Hematopoietic stem cells (HSCs) are characterized by the ability to self-renew and differentiate into all mature blood lineages.[6,7] Hematopoiesis is a continuous developmental process in which HSCs make specific cell fate decisions, producing the various blood lineages.[8] Though HSCT has many side effects and consequences, like drug toxicities, graft-versus-host disease (GVHD) and complications of immunosuppressive drugs, it is still the only curative option for many malignant hematologic (i.e. Refractory/relapsed leukaemia and lymphoma), non-malignant hematologic (i.e. severe aplastic anaemia, thalassaemia major), solid organ malignancies (i.e. seminoma, neuroblastoma) and genetic diseases (i.e. congenital immunodeficiency disease, inherited metabolic disorder).[9,10,11] HSCs for transplantation can be collected from bone marrow or peripheral blood. Instead of bone marrow aspiration and biopsy which are invasive procedures, peripheral blood is a feasible and easily available source now-a- days.[12] Because of using this new source of stem cells other than bone alone, "Hematopoietic stem cell transplantation" term has completely replaced the term "Bone MarrowTransplantation".[13] Our bone marrow/stem-cell transplant center is a new set-up compared to some other set-ups in this sub- continent and across the world. The first successful autologous transplant was performed on November 22, 2016 in a patient with Multiple myeloma and the first was performed on August 27, 2018 on a twenty-three year-old male with Acute Myeloid Leukaemia allogeneic transplant. Within 4 years period, a total of 26 patients had undergone HSCT at our center. Out of which, autologous HSCT was done in 23 patients and allogeneic HSCT in 03 patients. Haemopoietic stem cells were collected from peripheral blood following G-CSF and/or Plerixafor mobilization. The median age of autologous HSCT was 45 years in our study with range of 23 -57 years, whereas in the study of Mukhopadhyay A *et al*. the median age of the patients was 19.6 years, with a range of 5 years 8 months to 52 years.[14] In Chirag AS *et al.* study the median age of autologous patients was 50 years.[15] Mean duration of neutrophil engraftment was 12 days (9 -19 days) and platelet engraftment was 16 days (11-35 days) days in our patients for autologous HSCT which is consistent with the literature.[16] For Allogeneic HSCT mean duration of neutrophlils engraftment was 12 days (11-15 days) and platelet engraftment was 14 days (12-17 days) which is comparable to other series.[16] In our center febrile neutropenia developed in 21(80.76%) patients. Out of 26 patients, bacterial infection documented in 13 (50.0%) patients and viral infection in 01 (3.84%) patient. Infection rates were similar to other centers of this subcontinent but much higher than western studies where bacterial infection rate of 5%, viral infection rate of 7%, and fungal infection rate of 12%.[14] The possible risk factors of infections in our center might be aggressive myeloablative conditioning regimens leading to prolonged neutropenia during pre-engraftment period. Environmental factors may also contribute to infection. Major complications during HSCT were infections, mucositis, disease-related complications, chemotherapy-induced complications and complications related to

other co-morbidities. Major causes of mortality in our autologous HSCT patients were infections (66.66%) and disease relapse/progression (33.33%). Overall survival of our autologous HSCT patients was 95.65%. After a median follow up of 24 months (3-49 months) 82% of our autologous patients were in complete remission. Similar findings were noted in the study of Jasuja SK where overall survival of autologous transplant patients was 100% and after a median follow up of 24 months (4-84 months), 84% of autologous patients were in complete remission.[17]All three allogeneic HSCT cases were in remission state and overall survival is 100% in our study. By definition, complete remission means disappearance of all signs of cancer in response to treatment and does not always mean that the cancer has been cured.[18] In a developing country like Bangladesh, there are very few centers which perform regular HSCT. This study will help in sharing its outcomes with other haematology/oncology practitioners and will encourage other centers to start stem-cell transplantation as standard of care for many otherwise incurable haemopoietic diseases.

Conclusion:

HSCT has become the treatment of choice in various haematological and non-haematological diseases. Now-a-days HSCT is an accepted standard therapeutic option with different conditions and needs are increasing worldwide despite evolving targeted and immune therapies. Availability of resources, a network of specialists from all fields, good infrastructure, governmental support and access for patients to a transplant team is necessary for successful outcome of HSCT. Our center has made a remarkable progress pertaining to HSCT and is able to produce similar results and outcomes with nationally and internationally renowned HSCT centers in terms of quality of care, safety, and HSCT outcomes and we believe this will help us getting international accreditations such as JACIE EBMT.

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