International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319 – 6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 6; Issue 7; July 2017; Page No. 4830-4833
DOI: http://dx.doi.org/10.24327/ijcar.2017.4833.0592

Research Article

"AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT: A SINGLE CENTER EXPERIENCE"

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A R T I C L E I N F O

Article History:

Received 18th April, 2017
Received in revised form 14th May, 2017
Accepted 20th June, 2017
Published online 28th July, 2017

Key words:

Autologous HSCT, haematological and non-hematological diseases

A B S T R A C T

In this modern era, haemopoietic stem cell transplant is becoming the treatment of choice in various haematological and non-hematological diseases. Our experience of autologous HSCT in 39 patients with various indications is shared in this article.

Material and methods: This is a retrospective analysis of first nineteen patients who undergone autologous transplant at our institute, with M: F = 13: 6 and mean age 49 years (range 5-70 years). The median follow-up was 21 months with range from 1 to 84 months. The data was obtained carefully from case sheets, medical records of the hospital.

Indications for autologous HSCT were Multiple Myeloma (12 patients), Non-Hodgkin's lymphoma (3 patients), Hodgkin lymphoma (1 patient), Seminoma (1 patient), Multiple Sclerosis (1 patient) and Neuroblastoma (1 patient).

Results: The mean time for WBC engraftment was 11 days (range: 7-18 days) and for platelet engraftment was 15 days (range: 8-34 days). Mean single-donor platelet requirement was 4 (range 1-17), and mean packed red cell requirement was 1.5 (range 0-6). The post-transplant complications encountered were mucositis, infections and diarrhoea. There were 19 incidences of febrile neutropenia, out of which in 7 (36%) infection was documented with culture positivity. Major infections were bacterial followed by fungal (5.2 %) and viral (5.2%) causes. Major bacterial infections were by Escherichia coli and Enterobacter followed by other species like Pseudomonas. One incidence of Cytomegalovirus was noted with significant viral copies that required Ganciclovir and one incidence of hepatic candidiasis was noted. Major sites of culture positivity were stool and blood. Average duration of hospital stay after autologous HSCT is 23 days with a range of 14-54 days. The mortality at our center for autologous HSCT is zero. Sixteen out of our 19 patients are in complete remission.

Conclusion: Autologous HSCT is a curable treatment option with results comparable to national and international hematopoietic stem-cell transplantation centres in terms of complications, outcomes of treatment, and cost effectiveness with an excellent safety profile.

INTRODUCTION

In this modern era, haemopoietic stem cell transplant is becoming the treatment of choice in various haematological and non-hematological diseases. The first ever successful transplant was performed by Dr. E.Donnall Thomas in late 1950s for which he was awarded Nobel Prizeof Physiology or Medicine in 1990.[1] In our country, India; the first successful bone marrow transplant was done in March 1983 on a nine year old girl with acute myeloid leukemia.[2]

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Though presently many hematopoietic stem-cell transplant centers (HSCT) have been established across India, the numbers of centres which are performing regular HSCT are less as required infrastructure and expertise are lacking and also the cost of HSCT is higher further limiting accessibility and feasibility in this developing country. Radha Krishan Birla Cancer Center (RKBCC) is a tertiary care cancer center in Rajasthan with hemato-oncology department. This center has the facilities of chemotherapy and surgical oncology for the treatment of hematological disorders and solid tumors. It is a referral center for hemato–oncology and BMT patients. We started our Bone Marrow and Stem Cell Transplant

programme for first time in Rajasthan in 2009, and upgraded our unit in 2012 with a mission to minimize the cost to make the middle and lower-middle class of the society avail the transplant facility. Patients of myeloma, lymphoma, leukemia, thalassemia and aplastic anemia are the main patient pools for transplant and we are regularly doing all types of stem cell transplants including autologous, allogenic, half matched allogenic stem cell transplants. In this article, our experience of autologous HSCT in 39 patients with various indications will be shared.

MATERIALS AND METHODS

This is a retrospective analysis of first nineteen patients who undergone autologous transplant at our institute, with M: F = 13: 6. The median follow-up was 21 months with range from 1 to 84 months. Out of total 19 patients, the first case was taken from 2009 while remaining cases were taken from 2012 to 2016. The data was obtained carefully from case sheets, medical records of the hospital. Total 19 patients underwent autologous BMT with mean age 49 years (range 5-70 years), male: female ratio of 13: 6 and median follow-up of 21 months (range 1-84 months).

Indications

Indications for autologous HSCT were Multiple Myeloma (12 patients), Non-Hodgkin's lymphoma (3 patients), Hodgkin lymphoma (1 patient), Seminoma (1 patient), Multiple Sclerosis (1 patient) and Neuroblastoma (1 patient).

Stem cells Collection

Stem cells were collected from peripheral blood after mobilization therapy consisted of G-CSF alone or GCSF with plerixafor. Stem cells were taken in range from 1.5 to $7x10^6$/kg CD4 counts.

Conditioning regimens

All patients were given myeloablative conditioning chemotherapy without the use of total body irradiation (TBI). We have not used nonmyeloablative or reduced intensity regimens. Chemotherapy was given through central lines in all patients. BEAM regimen was used for lymphomas. Melphalan was used for myelomas according to standard protocols. BEAM plus ATG was used for multiple sclerosis. Carboplatin, Etoposide and Cyclophoshamide regimen was used for seminoma.

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 and their treatment. All patients were treated in completely isolated rooms during the pre and post-transplantation period. They were conventional, private and High-Efficiency Particulate-Arresting (HEPA) filtered rooms.

RESULTS

Engraftment

By definition, WBC engraftment is absolute neutrophil count >500 for three consecutive days and the platelet engraftment is the platelet count >20,000 for three consecutive days without any external transfusion support. The mean time for WBC engraftment was 11 days (range: 7-18 days) and for platelet engraftment was 15 days (range: 8-34 days) in our patient population.

Table No. 1 Baseline characteristics of Autologous HSCT patients

Total numbers (*N*)	**19**
Age (median)	49 years
Gender (M:F)	13:6
Indications	Multiple myeloma: 12 Non-Hodgkin lymphoma: 3 Hodgkin lymphoma: 1 Seminoma :1 Neuroblastoma : 1 Multiple sclerosis: 1
Stem-cell source	peripheral blood
Stem-cell dose (median cell dose)	1.5 to $7x10^6$ cells/kg body weight

Table No. 2 Outcome of Autologous HSCT

Median engraftment day (Range)	**11 days (7–18 days)**
Median posttransplant hospital stay (range)	23 days (14–54 days)
Mortality	*N* =0
Current disease status	
Complete remission:	*N* = 16
Relapse but alive:	*N* = 03
Overall survival (median 2years)	100% (*N* = 19)
Transplant related mortality (TRM)	0
Non-TRM	0

Table No. 3 Conditioning regimen used in Autologous HSCT

Conditioning regimen	**Indications**	**Protocol**
BEAM regimen	Hodgkin's lymphoma Non-Hodgkin's lymphoma	Day −6: Carmustine (BCNU) (300mg/m2) Days −5, −4, −3, −2: Etoposide (200mg/m2) And Cytarabine (ara-c) (400mg/m2) Day −1: Melphalan (140mg/m2/dose) Day 0: stem-cell transplant
Melphalan regimen	Multiple myeloma	Day −1:Melphalan 140mg/m2 Day 0: stem-cell transplant
BEAM +ATG regimen	Multiple Sclerosis	Day −6: Carmustine (BCNU) (300mg/m2)Days -5, −4, −3, −2: Etoposide (200mg/m2) And Cytarabine (ara-c) (400mg/m2) Day −1: Melphalan (140mg/m2/dose) Day 0: stem-cell transplant Day +1,+2: ATG (2.5 mg/kg)
CEC regimen	Seminoma	Day −6, −5, −4: Etoposide (800 mg/m^{2}perday) and carboplatin (667 mg/m^2 per day) Day −3, −2: Cyclophosphamide (60 mg/kgper day) Day 0: stem-cell transplant
BU- MEL regimen	Neuroblatoma	Day -5,-4,-3, -2: Busulfan (4mg/kg/d)Day -1:melphalan (140 mg/m^2) Day 0: stem-cell transplant

Transfusion support

Irradiated blood products were given in the post-transplant period for our transplant patients to maintain Hb >8 gm/dl and platelet count >20000/dl. Mean single-donor platelet requirement was 4 (range 1-17), and mean packed red cell requirement was 1.5 (range 0-6).

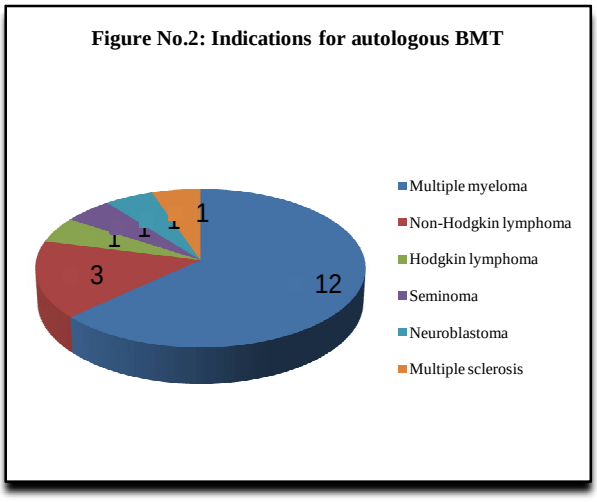
Post-transplant Complications

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

Table No. 4 Antimicrobial prophylaxis used for autologous BMT

Antibiotics	Dose	Duration
Trimethoprim-sulfamethoxazole single strength(double strength for adults)	1 tab. once daily	Stops on day -2 and is restarted after day 28 or engraftment and iscontinued for 6 months
Tab. of Fluconazole	200mg twice daily	Starts on day -7 till discharge
Tab. of Levofloxacin	500mg once daily	Starts on day -7 till discharge
Syp Posaconazole	200 mg thrice daily	Starts on day -7 till discharge
Tab.Acyclovir	500mg twice daily	Starts on day -2 till discharge

Figure No.1 Radha Krishan Birla Cancer Center, Sawai Man Singh medical College, Jaipur



Oral Mucositis

Oral mucositis was the most common complications. Seven (36%) of our autologous transplant patients had mucositis (grade 1 in 3 patients, grade 2 in 3 patients, and grade 3 in 1 patient). Grade 2 mucositis patients were managed with dietary modification, analgesics, and oral care. Patients with grade 3 required some interventions like parental nutrition and/or feeding tube insertion. Chemotherapy and HSCT were the probable causes of the mucositis.

Pattern of infection

Bacterial infection(5/7)	Escherichia coli	2 pts
	Enterobacter	2 pts
	Pseudomonas	1 pt
Viral infection (1/7)	CMV	1 pt
Fungal infection (1/7)	Hepatic Candidiasis	1 pt

Infection

There were 19 incidences of febrile neutropenia, out of which in 7 (36%) infection was documented with culture positivity. Major infections were bacterial followed by fungal (5.2 %) and viral (5.2%) causes. Major bacterial infections were by *Escherichia coli* and *Enterobacter* followed by other species like *Pseudomonas.* One incidence of *Cytomegalovirus* was noted with significant viral copies that required Ganciclovir and one incidence of hepatic candidiasis was noted. Major sites of culture positivity were stool and blood.

Gastrointestinal Complications

These were ten incidences of diarrhoea and one incidence of oral bleeding**.**

Duration of Hospital Stay after Transplant

Average duration of hospital stay after autologous HSCT is 23 days with a range of 14-54 days.

Outcomes

The mortality at our center for autologous HSCT is zero as none of our autologous transplant patients died in the course of follow-up either by transplant related mortality (TRM) or Non-TRM. Median follow up is 24 months (range 4months- 7 years). Sixteen out of our 19 patients are in complete remission. Three of the autologous transplant patients had disease relapse; out of whom one patient lost to follow up after 2 years follow-up and two patients are alive and have good response to second line treatment, however, not willing for second transplant.

DISCUSSION

Though Hematopoietic stem cell transplantation (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. Refactory/relapsed leukemia and lymphoma), non malignant hematologic (i.e. severe aplastic anemia, thalassemia major), solid organ malignancies (i.e. Seminoma, neuroblastoma) and genetic diseases (i.e. congenital immunodeficiency disease, inheried metabolic disorder).[3-5] Instead of bone marrow aspiration and biopsy which are invasive procedures, peripheral blood is a feasible and easily available source nowadays.[6] Because of using this new source of stem cells other than bone marrow alone, "Hematopoietic stem cell transplantation" term has completely replaced the term "Bone Marrow Transplantation".[7] Radha Krishan Birla Cancer Center at Sawai Man Singh medical College, Jaipur is one of the major bone marrow transplant centres of India. Our bone

marrow/stem-cell transplant center is a new set-up compared to some other set-ups in India and across the world. The first successful autologous transplant was performed on July 2009, in a patient of non hodgkin lymphoma and the first allogenic transplant was performed on 2012, on a twinty-nine-year-old female with aplastic anemia. Within 4 years period, a total of 39 patients were treated with stem-cell transplants at our center out of which 19 patients underwent autologous HSCT. Our HSC collections were done from peripheral blood after G-CSF mobilization. Though number of transplants performed at our center are not big enough and data are for shorter duration, still our data is comparable with some national and internationally published data. The median age of autologous HSCT was 49 years in our study with range of 5 - 70 years, which is comparable to other study.[8-9] HSCT has not been recommended as a standard of care for Multiple myeloma patients who are ⩾ 65 years of age inspite of this we did a successful transplant in a paitent of 70 years.[10] Mean duration of engraftment in our patients was 11days (7 -18 days) for autologous HSCT which is comparable to other standard international data (mean days 15 with range of 10-35 days).[11]

Infection rates are comparable to other Indian centres but much higher than western studies, which report bacterial infection rate of 5%, viral infection rate of 7%, and fungal infection rate of 12%.[8] In a study at Apollo hospital, Gandhinagar[9], bacterial infection rate was 50%, Fungal 14% and viral was 4% while in a study at CMC Vellore[12], it was 34.9%, 15.9% and 42.9% respectively. Bacterial infection rate in a study at NCRI, Kolkata[8] was 52%, viral in 24% and fungal in 12% cases. The possible risk factors of infections in our studies are aggressive myeloablative conditioning regimens leading to prolonged neutropenia during pre-engraftment period and possible environmental factors in India.[13] Major complications during the auto transplant were infections, mucositis, disease related complications, chemotherapy induced complications and complications related to other comorbidities. Major causes of mortality in auto HSCT patients were disease relapse/progression (94%) and infections (6%).[14] Overall survival of our autologous HSCT transplant patients was 100%. After a median follow-up of 24 months (4-84 months), 84% of our autologous patients are in complete remission phase. 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.[15] In a developing country like India, there are very few centres, which perform regular HSCT due to various reasons including lack of infrastructure and expertise, lack of knowledge of safety, efficacy, and cost of the procedure both in general population and in medical fraternity. This study will help in sharing its outcomes with other haematology/oncology practitioners and will encourage other centres to start performing stem-cell transplantations or refer eligible patients for this important treatment option available.

CONCLUSION

We had no mortality in autologous HSCT with results comparable to national and international hematopoietic stem-cell transplantation centres in terms of complications, outcomes of treatment, and cost effectiveness with an excellent safety profile.

References

1. History of Transplantation," Fred Hutchison Cancer ResearchCenter, 2013, http://www.fredhutch.org /en/treatment/longterm-followup/FAQs/transplantation.html.
2. M. Chandy, "Stem cell transplantation in India," Bone MarrowTransplantation. 2008; (42): S81-S84
3. Gratwohl A, Baldomero H, Passweg J, Frassoni F, NiederwieserD,Schmitz N, *et al*. Hematopoietic stem cell transplantation for hematological malignancies in Europe. *Leukemia*.2003; 17(5):941-59.
4. Ogawa K, Noji H, Furukawa M, Harada-Shirado K, MashimoY,Takahashi H, *et al*. Hematopoietic stem cell transplantation in the Department of Hematology, Fukushima Medical University. *Fukushima J Med Sci*.2010; 56(2):107-14.
5. Gratwohl A, Baldomero H, Aljurf M, Pasquini MC, Bouzas LF, Yoshimi A, *et al*. Hematopoietic stem cell transplantation: A Global Perspective. *JAMA* 2010; 303(16):1617-24.
6. Suárez-Álvarez B, López-Vázquez A, López-Larrea C. Mobilization and Homing of Hematopoietic Stem Cells. *Stem Cell Transplantation.* 2012;741:152-170
7. Sánchez-Guijo FM, Orfao A, Del Cañizo MC. Bone marrow transplantation extends its scope. Adv Exp Med Biol. 2012;741:121-34
8. A.Mukhopadhyay, P.Gupta, J. Basak *et al*., "Stemcelltransplant: an experience from Eastern India," *Indian Journal of Medicaland Paediatric Oncology. 2012;*33(4):203-209
9. Chirag A. Shah, Arun Karanwal, Maharshi Desai, Munjal Pandya, Ravish Shah, and Rutvij Shah. Hematopoietic Stem-Cell Transplantation in the Developing World: Experience from a Center in Western India. *J Oncol*. 2015; 2015: 710543.
10. le Blanc K., Remberger M., Uzunel M., Mattsson J., Barkholt L., Ringdén O. A comparison of nonmyeloablative and reduced-intensity conditioning for allogeneic stem-cell transplantation. *Transplantation*. 2004;78(7):1014-20
11. Be The Match. (n.d.), Engraftment: 0-30 days, http://bethematch.org/For-Patients-and-Families/ Getting-a-transplant/Engraftment–Days-0-30/
12. Chandy M., Srivastava A., Dennison D., Mathews V., George B. Allogeneic bone marrow transplantation in the developing world: experience from a center in India. *Bone Marrow Transplantation*. 2001;27(8):785-790
13. Chawla R. Infections after One Marrow Transplantation. 2013. http://emedicine.medscape. com/article/1013470-overview.
14. A. D. Schimmer, "Allogeneic or autologous bonemarrow transplantation (BMT) for non-Hodgkin's lymphoma (NHL): results of a provincial strategy," *Bone Marrow Transplantation*, vol. 26, no. 8, pp. 859-864, 2000.].
15. NCI Dictionary of Cancer Terms. (n.d.) http://www.cancer.gov/dictionary?cdrid=45651