Original Article

Outcome of Patients Treated with Hematopoietic Stem Cell Transplantation: Results from A Single Center

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ABSTRACT

Objective: Hematopoietic stem cell transplantation (HSCT) is known as one of the most advanced and modern treatments in the world for various diseases which do not respond well to other therapies. Evaluating outcomes of these patients, especially in newly developed centers, can crucially help in developing and improving the quality of these centers. **Methods:** In a retrospective analytical cohort study, we statistically analyzed all patients treated with HSCT in the Bone Marrow Transplant Unit of the Ali-Asghar Pediatric Hospital affiliated to Iran University of Medical Sciences. The demographic information as well as all information concerning each patient's transplant process was extracted and statistically analyzed using SPSS Version 23. **Results:** The mean neutrophilic and platelet engraftment days were, respectively, 16 (range = 12–21) and 22 (range = 15–34) days after HSCT, while the neutrophilic engraftment occurred significantly earlier in allogeneic transplants compared to the autologous ones (P = 0.020). The total event-free survival (EFS) rate of the patients based on the median follow-up of 12 months was 11.50% ± 53.60%. Based on the total follow-up period, the estimated total EFS rate of the patients was calculated as 35.20% ± 13.50%. The estimated EFS rate was found to be better in patients who had undergone allogeneic transplantation than those who received an autologous transplant (P = 0.780). **Conclusions:** The HSCT results at our center are comparable to those at other centers in Iran. We argue that the facility can provide adequate therapy to patients requiring HSCT, on the proviso that some organizational limitations are addressed.

Key words: Bone marrow transplant, hematopoietic stem cell transplantation, modern treatments

Introduction

Hematopoietic stem cell transplantation (HSCT) is currently the best treatment option for a variety of malignant and nonmalignant diseases, as well as genetic diseases, in achieving a complete cure or for long-term survival.[1-3] Since bone marrow was the only source from which these cells could be obtained previously, the procedure to obtain these cells was referred to as a bone marrow transplant. However, with the growing ability to extract cells from other more readily available sources, the name of the procedure was changed to hematopoietic stem cell transplant.[4]

Hematopoietic stem cells are now easily extracted from the peripheral blood.[5] On the other hand, cord blood stem cells are widely used as an available rich source of immature stem cells.[6,7] Yet, the transplants from matched-unrelated

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donors have been received abundantly during the past two decades, due to the lack of matched-related donors.[8,9] As some diseases do not permit sufficient time to find an appropriate donor, an alternative procedure has had to be established. The haploidentical transplantation has arisen recently, which is now widely used in prestigious centers around the world. In this type of transplant, hematopoietic stem cells are taken from the first-degree relatives of the patient.[10] Despite the significant side effects of HSCT (such as drug side effects, graft versus host disease [GVHD], veno-occlusive disease [VOD], and infection), it still seems to be the only treatment of choice for many malignancies and some nonmalignant diseases.[11]

The first bone marrow transplant center in Iran was started operating in 1992 at Shariati Hospital in Tehran, Iran. This center had some significant advances in bone marrow transplantation. However, given the country's population and the possible need for at least 1400 new patients a year who can be treated with HSCT, bone marrow-transplant sections were launched in other centers to accommodate this need.[11]

The Bone Marrow Transplant Unit of Ali-Asghar Children Hospital is a level 3 center affiliated with the Iran University of Medical Sciences. It also commenced work in this field, with a standard HSCT room of class 1000. Despite many physical, administrative, and financial constraints, the center managed to perform several types of HSCT for various diseases.

This research aimed to evaluate the results of performed transplants. Furthermore, we wished to understand the capacity and capability of the center to be able to provide service in this area at the highest possible level.

Methods

Using a retrospective analytical study, we statistically analyzed all patients treated with HSCT at the Ali-Asghar Children Hospital affiliated to the Iran University of Medical Sciences, since the opening of the Bone Marrow Transplantation Unit to date. Demographic information including patient age at transplantation, gender, underlying diseases, as well as how to perform the HSCT and its consequences for each patient was extracted from case files and computerized data recorded in the hospital medical records. Engraftment is most defined as the first of 3 consecutive days of achieving a sustained peripheral blood neutrophil count >500 × 10^6/L.[12] Platelet engraftment is usually defined as an independence from platelet transfusion for at least 7 days with a platelet count >20 × 10^9/L.[13] Poor graft function criterion was diagnosed in patients with two or three cytopenic lines (hemoglobin 100 g/L, neutrophil count <1.0 × 10^9/L, and platelet count <30 × 10^9/L) at day 30 posttransplant, with transfusion requirements associated with hypoplastic aplastic bone marrow, in the presence of a complete donor chimerism and in the absence of severe GVHD and relapse.[14]

Statistical analysis

All enrolled patients, diagnosed and treated in the bone marrow transplant unit of Ali-Asghar Children Hospital, were analyzed for clinical and pathological data and event-free survival (EFS) rates. The EFS was calculated using the follow-up duration from the date of transplantation to either the date of relapse or death for any cause (each occurred earlier).

The Kaplan–Meier test was used to determine the EFS. The log-rank method was used to measure the survival rate and a $P < 0.05$ was considered statistically significant. Based on the median follow-up (12 months, range = 1.5–92 months), the estimated EFS values were determined for patients.

Results

There were 20 cases of HSCT performed in the Bone Marrow Transplant Unit of the Ali-Asghar Pediatric Hospital in Tehran, one of the educational hospitals affiliated to the Iran University of Medical Sciences. The number of allogeneic and autologous transplant cases was relatively equal, including male ($n = 11$) and female ($n = 8$) patients. The proportion of diseases treated with autologous transplantation were as follows: Hodgkin's disease (30%), neuroblastoma (50%), Wilms' tumor (nephroblastoma, 10%), and an acquired aplastic anemia (Iran's first autologous cord transplant and the fifth done in the world at the time of the transplantation). The allogeneic transplant was used for the following pathologies: acute lymphoblastic leukemia (ALL, 30%), hemophagocytic lymphohistiocytosis (HLH, 20%), acquired aplastic anemia (20%), Fanconi anemia (10%), lymphocyte adhesion deficiency syndrome type 1 (LADS1) (10%), and a case of malignant infantile osteopetrosis (MIOP).

Hematopoietic stem cells were extracted and used for 18 patients from the peripheral blood. In two patients, the cord blood stem cells were injected. Out of 18 patients who underwent peripheral blood HSCT, only two patients received mononuclear cell levels lower than 5 × 10^8/kg, while all patients received sufficient levels of $CD34^+$ cells [Tables 1-3]. As expected, the levels of MNC, $CD34^+$, and CD3 injected into patients undergoing allogeneic transplantation were significantly higher than patients undergoing autologous transplantation [Table 4]. The neutrophil engraftment in allogeneic transplants also occurred earlier than the autologous transplant, which was statistically significant [Table 5].

Only three patients developed acute Grade 3 GVHD, all of which recovered. Three patients who underwent allogeneic

Table 1: Data of all enrolled patients treated by autologous hematopoietic stem cell transplantation

Patient number	Gender	Age (yr)	Diagnosis	Stem cell harvesting	MNC ($\times 10^8$/kg)	$CD34^+$ ($\times 10^6$/kg)	CD3 ($\times 10^8$/kg)	Conditioning regimen	PMN engraftment (d)	Platelet engraftment (d)	Outcome	Dead	Dead cause	Follow-up duration (mon)
1	Male	10	HD	PB	6.65	6.31	2.19	CEAM	19	23	CR	No	-	92
2	Male	17	HD	PB	4.66	4.28	1.16	CEAM	21	26	R	No	-	23
3	Female	4	NB	PB	4.23	3.80	1.90	CEM	21	25	R	No	-	8
4	Female	5	NB	PB	4.50	4.50	1.80	Bu/Mel	17	21	R	Yes	DR	5
5	Male	15	NB	PB	4.64	4.25	2.10	CEM	13	24	R	No	-	43
6	Female	2	NB	PB	4.16	11.70	2.00	Bu/Mel	14	19	R	Yes	DR	13
7	Male	5	AA	CB	2.52 ($\times 10^7$/kg)	3.43 ($\times 10^5$/kg)	-	ATG	19	30	CR	No	-	57
8	Male	1.6	NB	PB	3.00	2.80	1.24	Bu/Mel	15	19	CR	No	-	24
9	Male	11.6	HD	PB	7.80	7.41	2.65	CEAM	18	23	CR	No	-	10
10	Female	6	WT	PB	4.55	4.55	1.27	Bu/Mel	18	21	R	Yes	DR	6

HD: Hodgkin's disease; NB: Neuroblastoma; AA: Aplastic anemia; WT: Wilms' tumor; PB: Peripheral blood; CB: Cord blood, CEAM: CCNU, etoposide, cytarabine, melphalan; CEM: Carboplatin, etoposide, melphalan; BU/Mel: Busilvex and melphalan; ATG: Antithymocyte globulin; CR: Complete remission; R: Relapse; DR: Disease related, MNC: Mononuclear cell; PMN: Polymorphic mononuclear cell

Table 2: Data of all enrolled patients treated by allogenic HSCT

No.	Gender	Age (yr)	Diagnosis	Stem cell	Donor type	Donor Sex	MNC ($\times 10^8$/kg)	$CD34^+$ ($\times 10^6$/kg)	CD3 ($\times 10^8$/kg)	Conditioning Regimen	GVHD prophylaxis
1	F	8	FA	PB	MSD	f	10.20	12.00	1.83	Flu/Cy/ATG	Cyclosporine
2	F	5.5	HLH	PB	MSD	m	10.55	9.50	3.69	Flu/Mel/ATG	Cyclosporine + MTX
3	M	0.75	HLH	PB	MRD	f	7.22	10.83	1.73	Flu/Mel/ATG	Cyclosporine + MTX
4	M	18	ALL	PB	MSD	m	8.50	7.22	2.67	Flu/Bu/VP16	Cyclosporine
5	F	0.8	MIOP	PB	MRD	f	10.60	10.60	6.04	Flu/Bu/ATG	Cyclosporine
6	F	7	AA	PB	MSD	f	6.10	7.70	2.26	CY/ATG	Cyclosporine + MTX
7	M	0.25	LADS1	PB	MRD	f	8.50	7.65	5.69	Flu/Bu/ATG	Cyclosporine
8	F	4.75	ALL	CB	MSD	m	3.66 ($\times 10^7$/kg)	3.10 ($\times 10^5$/kg)	-	Flu/Bu/VP16	Cyclosporine
9	M	13.5	AA	PB	MSD	f	4.20	4.37	1.97	CY/ATG	Cyclosporine + MTX
10	F	15.5	ALL	PB	MSD	f	5.52	3.68	2.19	Flu/Bu/VP16	Cyclosporine

f: Female; M: Male; FA: Fanconi anemia; HLH: Hemophagocytic lymphohistiocytosis; ALL: Acute lymphoblastic leukemia; MIOP: Malignant infantile lymphohistiocytosis; AA: Aplastic anemia; LADS 1: Leukocyte adhesion deficiency type 1; MTX: Methotrexatel; ; MNC: Mononuclear cell; GVHD: Graft versus host disease; HSCT: Hematopoietic stem cell transplantation

Table 3: Outcome of all enrolled patients treated by allogenic HSCT

Patient No.	GVHD grade	GVHD grade	Chimerism (%)	PMN E. (d)	Platelet E. (d)	Outcome	Dead	Dead cause	Follow-up (mon)
1	1	-	97	19	24	CR	No	-	12.0
2	2	-	100	12	19	CR	No	-	27.0
3	3	1	100	13	19	CR	No	-	43.0
4	2	-	99	15	18	R	Yes	DR	12.0
5	-	-	95	14	20	D	Yes	Infection	2.5
6	1	-	95	15	24	D	Yes	Infection	3.0
7	3	-	100	16	-	D	Yes	Infection	1.5
8	1	-	100	14	15	R	Yes	DR	4.0
9	3	2	92	16	34	CR	No	-	31.0
10	2	-	98	14	19	CR	No	-	14.0

E.: Engraftment; GVHD: Graft versus host disease; PMN: Polymorphic mononuclear cell; HSCT: Hematopoietic stem cell transplantation; CR: Complete remission; R: Relapse; DR: Disease related

transplantation died due to infection. A patient with MIOP developed an unknown viral infection after HSCT and unfortunately died. A patient with LADS1 developed severe parainfluenza Type 3 pneumonia following HSCT from his mother. He died despite treatment with ribavirin nebulizer. Another patient with acquired aplastic anemia died of fever of unknown origin, and two patients with ALL died from recurrence after transplantation [Table 3]. Two patients with neuroblastoma and one with Wilms' tumor died of a recurrence after autologous transplantation [Table 1].

The total EFS rate of the patients based on the median follow-up of 12 months was 53.60% ± 11.50%. In addition, the estimated total EFS rate of the patients was 35.20% ± 13.50% based on the whole follow-up period [Figure 1].

The estimated EFS rate in allogeneic-transplant patients was greater than the autologous ones (53.00% ± 15.80% vs. 31.10% ± 16.80%). However, this difference was not statistically significant (P = 0.780) [Figure 2]. A patient with neuroblastoma, who had undergone allogeneic transplantation with busilvex and melphalan conditioning regimen, developed severe VOD. Fortunately, the patient recovered completely by receiving a standard dose of injective defibrotide for 21 days. A patient with severe aplastic anemia developed Epstein-Barr virus infection after an allogeneic transplant from her sister and subsequent EVANS syndrome. The patient improved following 4 weeks of receiving 375 mg/kg rituximab intravenously. This patient experienced a decrease in the percentage of chimerism during the posttransplant period and achieved the full chimerism by receiving the donor lymphocyte infusion. This patient, unfortunately, developed extensive GVHD with a drug-resistant extensive manifestation of scleroderma and was treated with ibrutinib. Overall, the nonrelapse mortality (NRM) rate was about 15% [Figure 3].

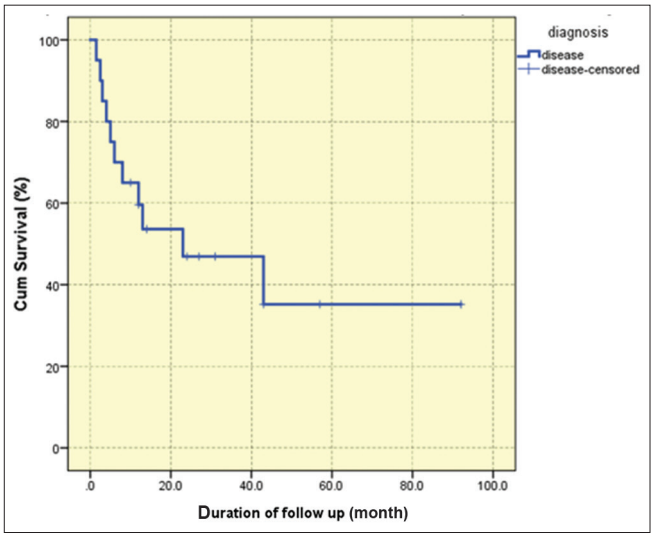

Figure 1: Estimated event-free survival of all enrolled patients treated by hematopoietic stem cell transplantation

Table 4: Comparison between allogeneic and autologous hematopoietic stem cell transplantation cases

Variables	Transplant type	*n*	Mean	SD	SEM	*P*
Age at transplant (mont)	Autologous	10	93.750	64.612	20.432	0.830
	Allogeneic	10	87.150	78.255	24.746	
MNC ($\times 10^8$/kg)	Autologous	9	4.643	1.287	0.429	0.003
	Allogeneic	9	7.932	2.328	0.776	
CD34 + ($\times 10^6$/kg)	Autologous	9	4.974	2.977	0.992	0.034
	Allogeneic	9	8.172	2.860	0.953	
CD3 ($\times 10^8$/kg)	Autologous	9	1.812	0.502	0.167	0.049
	Allogeneic	9	3.119	1.665	0.555	
PMN engraftment (d)	Autologous	10	17.500	2.759	0.872	0.020
	Allogeneic	10	14.800	1.932	0.611	
Platelet engraftment (d)	Autologous	9	23.100	3.381	1.069	0.400
	Allogeneic	9	21.330	5.523	1.841	

SEM: Standard error of mean; SD: Standard deviation; MNC: Mononuclear cell; PMN: Polymorphic mononuclear cell

Discussion

The HSCT Unit started its work with the establishment of a standard positive pressure room (1000 class), which has managed to perform 20 hematopoietic stem cell transplantation procedures to date. The diversity of transplanted diseases as well as the variety of transplants performed, including autologous, allogeneic from the peripheral blood cell specimens and the cord, indicates the acceptable capability of the transplant team at this center. None of the patients died of known HSCT complications such as GVHD and VOD, and the NRM rate of our center is comparable to other valid centers. However, 30% of the patients who underwent allogeneic transplantation developed GVHD Grade III, which all improved with taking methylprednisolone. In two studies by Macmillan *et al.*[15] in 2002 and Cahn *et al.*[16] in 2005, the Grade III prognosis was reported to be approximately 30%, while the rate was reported over 80% for Grades I–II. Interestingly, the engraftment occurred in all patients and none of the patients died due to a primary or secondary failure. The

Table 5: Statistical analysis of quantitative variables of all enrolled patients

	Age at transplant (mont)	MNC ($\times 10^8$/kg)	CD34$^+$ ($\times 10^6$/kg)	CD3 ($\times 10^8$/kg)	PMN engraftment (d)	Platelet engraftment (d)	Duration of follow up (mont)
Valid (*n*)	20	18	18	18	20	19	20
Missing (*n*)	0	0	0	0	0	1	0
Mean	90.450	6.288	6.573	2.466	16.150	22.260	21.550
SEM	15.636	0.587	0.772	0.323	0.604	1.0280	5.086
Median	69.500	5.090	5.885	2.050	15.500	21.000	12.500
SD	69.926	2.489	3.275	1.370	2.700	4.483	22.745
Range							
Minimum	2.500	3.000	1.480	1.160	12.000	15.000	1.500
Maximum	219.000	10.600	12.000	6.040	21.000	34.000	92.000

SEM: Standard error of mean; SD: Standard deviation; MNC: Mononuclear cell; PMN: Polymorphic mononuclear cell

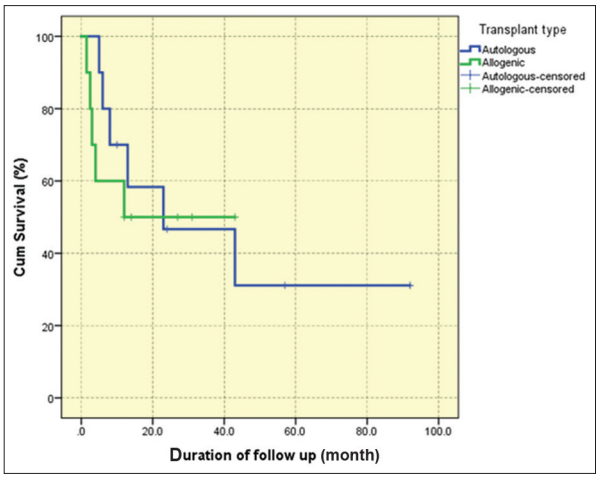

Figure 2: Estimated event-free survival of all enrolled patients for transplant type

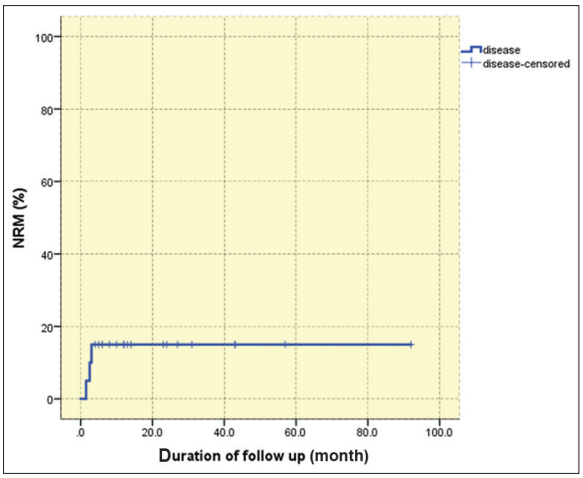

Figure 3: Nonrelapse mortality of all enrolled patients

main reason can be attributed to the injection of adequate cells and choosing the proper full-matched donor. Xiao *et al*.[14] (2014), on examining the risk factors for developing primary graft failure, suggested three independent factors of the patient's high age, cytomegalovirus (CMV) infection, and transplant recipient and donor blood incompatibility as the responsible factors. Fortunately, there was no incompatibility of blood groups among our patients, and the CMV infection that occurred in three patients was quickly diagnosed and treated. In addition, all of our patients were under 18 years.

All the conditioning regimens used were the current versions and were selected based on the latest beneficial and low-risk regimens listed, as well as the availability of the drugs in Iran.[17] For example, in the case of patients with ALL, due to the unavailability of thiotepa in Iran, the fludarabine + busulfan + VP16 diet was used. Using this regimen, Lee *et al*.[18] performed allogeneic transplantation on 44 children with ALL from appropriate donors and achieved the 1-year overall survival and EFS >80%. In another study by Peters *et al*.,[19] the 4-year EFS has been reported at about 71%. The causes for significant differences in the consequence of ALL-transplanted patients at our center can be due to the inability to perform minimal residual disease by real-time polymerase chain reaction in Iran. As a result, the patients are not transplanted during the golden age and the risk of recurrence will increase. In addition, one of the patients who was transplanted with the cord blood stem cells from his brother unfortunately had two recurrences. However, he was not in CR1 at the time of transplantation and the operation was done as the last resort. Obviously, using umbilical cord blood stem cells, as a risk factor for increasing a recurrence due to a failure to develop an appropriate graft-versus-leukemia, increased the risk.

The outcomes of neuroblastoma patients at our center after autologous HSCT were not good compared to other valid centers, but they are comparable to domestic centers. In a study published by Hamidieh *et al*.,[20] seven of the nine transplanted patients relapsed. Overall, the survival rate of these patients has significantly increased after immunotherapy with anti-GD2 monoclonal antibody.[21] Currently, the best conditioning regimen recommended by the European Society for blood and marrow transplantation is the busulfan/melphalan/thiotepa triple-drug regimen along with immunotherapy with the drug mentioned above. We are unfortunately not able to use thiotepa and immunotherapy in Iran. Out of four patients who underwent HSCT due to primary immunodeficiency, two patients with primary HLH achieved a long-term full remission while maintaining full chimerism and without a significant complication despite receiving a nonmyeloablative regimen. According to a study by Hamidieh *et al*.[22] in 2013, the conditioning regimen using fludarabine/melphalan/antithymocyte globulin seems to be the best drug regimen for these patients in transplants from appropriate donors. Three patients with refractory Hodgkin's disease with CEAM (Lomustine, Etoposide, Cytarabine and Melphalan) regimen (the use of Lomustine due to the absence of Carmustine in Iran) underwent autologous transplantation. Among them, only one patient showed a recurrence who is still alive with chemotherapy. One patient is also being treated with brentuximab as a consolidation therapy after HSCT in addition to bone marrow transplantation, which is known as one of the most advanced therapies in the world.[23,24]

Conclusions

Overall, considering the hardware and software limitations mentioned, the HSCT results in our center are comparable to other centers in Iran. Furthermore, our center

exhibits a high capability to treat patients requiring HSCT. Following from this, if the diagnostic and therapeutic limitations are resolved (for example, increasing the facilities from a standard room setup to at least 12 standard rooms), we can expect excellent results from this country's level 3 treatment center.

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Conflicts of interest

There are no conflicts of interest.

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