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...
donors have been received abundantly during the past two decades, due to the lack of matched-related donors.\cite{8,9}
As some diseases do not permit sufficient time to find an appropriate donor, an alternative procedure has had to be established. The haploidential 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.\cite{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.\cite{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.\cite{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 $>500 \times 10^9/L$.\cite{12} Platelet engraftment is usually defined as an independence from platelet transfusion for at least 7 days with a platelet count $>20 \times 10^9/L$.\cite{13}

Poor graft function criterion was diagnosed in patients with two or three cytopenic lines (hemoglobin 100 g/L, neutrophil count $<1.0 \times 10^9/L$, and platelet count $<30 \times 10^9/L$) 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.\cite{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 (LADSI) (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 $5 \times 10^9/kg$, 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
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].

**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

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**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 |
| MNC (×10⁸/kg)         | Autologous    | 9  | 4.643      | 1.287 | 0.429 | 0.003 |
| CD34 + (×10⁶/kg)      | Autologous    | 9  | 4.974      | 2.977 | 0.992 | 0.034 |
| CD3 (×10⁴/kg)         | Autologous    | 9  | 1.812      | 0.502 | 0.167 | 0.049 |
| PMN engraftment (d)   | Autologous    | 10 | 17.500     | 2.759 | 0.872 | 0.020 |
| Platelet engraftment (d) | Autologous | 9  | 23.100     | 3.381 | 1.069 | 0.400 |

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

| Age at transplant (mont) | MNC (×10⁸/kg) | CD34⁺ (×10⁶/kg) | CD3 (×10⁴/kg) | PMN engraftment (d) | Platelet engraftment (d) | Duration of follow up (mont) |
|--------------------------|---------------|-----------------|---------------|---------------------|-------------------------|-----------------------------|
| Valid (n)                | 20            | 18              | 18            | 18                  | 19                      | 20                          |
| Missing (n)              | 0             | 0               | 0             | 0                   | 0                       | 0                           |
| Mean                     | 90.450        | 6.288           | 6.573         | 2.466               | 16.150                  | 22.260                      |
| SEM                      | 15.636        | 0.587           | 0.772         | 0.323               | 0.604                   | 1.028                       |
| Median                   | 69.500        | 5.090           | 5.885         | 2.050               | 15.500                  | 21.000                      |
| SD                       | 69.926        | 2.489           | 3.275         | 1.370               | 2.700                   | 4.483                       |
| Range                    | 2.500         | 3.000           | 3.180         | 0                   | 21.000                  | 34.000                      |

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

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Figure 1: Estimated event-free survival of all enrolled patients treated by hematopoietic stem cell transplantation
main reason can be attributed to the injection of adequate cells and choosing the proper full-matched donor. Xiao et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.,\textsuperscript{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.,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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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