Autologous and Allogeneic Hematopoetic Stem Cell Transplantation for Solid Tumors in Iran

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Abstract

Introductio: Hematopoietic stem cell transplants (HSCT) are considered as treatment options for patients with solid tumors. Transplant numbers have changed significantly over the last decade. We have done Autologous and Allogeneic HSCT for treatment of solid tumor patients in our center.

Methods: In order to show the transplant effect on solid tumor treatment, we collected data from 71 patients (7 allogeneic, and 64 autologous) who had undergone HSCT from 1991 to 2011 in our center. The median age of patients was 19.5 years (range: 2-58). The Male/Female ratio was 41/30. The most common transplant diseases were Neuroblastoma (18, 25.7%), Germ Cell Tumors (13, 18.6%) and Breast Cancer (11, 15.7%). 67 patients (95.7%) received peripheral blood and the 3 other ones (4.3%) received bone marrow as a source of SCT.

Results: The median time of hospitalization after high-dose therapy was 24 days (range: 11-50 days; 23 days for autologous and 29 days for allogeneic patients). At present, 57 patients (80%) are still alive with median follow-up of 9 months. Transplant-related mortality (TRM) was 4.3%. The causes of death were progressive disease, metastasis and multi-organ failure. 2-year overall and disease-free survivals were 81.7% and 72%, respectively (for the autologous patients overall and disease-free survivals were 80.7% and 71.1%, respectively). Among 7 patients with allogeneic transplantation, 2 developed acute-graft-versus host disease (GVHD) and 4 developed chronic GVHD. One patient had chronic GVHD following acute GVHD.

Conclusion: Our study reveals promising results of HSCT in the treatment of some solid tumors. In other hand, more additional trial study is needed.

Keywords: Hematopoietic Stem Cell Transplantation, solid tumors, Allogeneic transplantation, Autologous transplantation.

Introduction

Hematopoietic Stem cell Transplant (HSCT) refers to any procedure where hematopoietic stem cell of any source are given to a recipient with intention of replacing the hematopoietic system in total or in part.(1) HSCT after Intensive chemotherapy has been considered as an effective therapy for patients with chemo-radiosensitive malignancies as well as for many hematopoietic congenital or acquired severe disorders of over the last 30 years.(2-6) Hematopoietic stem cells can restore bone marrow function in patients who have received marrow-toxic doses of cytotoxic regimens for cancers. Hematopoietic stem cells can be obtained from two sources; from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT).(7-8) HSCT is an established therapy for certain hematologic malignancies; however, its use in solid tumor cancers still continues to be largely experimental.(7-9) HSCT has been used for the treatment of many solid tumors, such as neroblastoma, breast cancer, melanoma, and ewings'sarcoma. This approach to therapy has lead to higher tumor response rates than have been achieved with conventional treatment and may improve long-term survival rates.(10-17) Major

improvements have occurred in HSCT over the past years. Stem cells have been achieved from peripheral blood instead of bone marrow for almost all disease indications in autologous HSCT. Unrelated donor pools have been expanded to more than 7.5 million registered donors worldwide. Additionally, Cord blood banks have been set up in North America and Europe and haploidentical HSCT have been introduced. All of these progressions helped patients without an HLA-identical sibling donor with allogeneic HSCT.(4, 18-20) Based on retrospective and prospective data in the early 1990s, HSCT has been used massively as a treatment approach for breast cancer and other similar tumors with enthusiasm over several years,(10) but frustration about the results has halted the use of HSCT in these tumors.(21) There are doubts and uncertainties about the use of HSCT in the treatment of breast cancer.(2) Transplants are being continued for other indications such as neuroblastoma, based in part on results of some controlled studies. Definitive answers are still lacking and optimal information is not available.(20, 22)

Correct assessment of current status, trends, and predictions for the near future are essential for planning health care strategies worldwide. Moreover, patients and physicians need optimal information for treatment decisions today. There are surveys in Europe in which current practice of HSCT for solid tumors, including changes over time in transplant numbers and differences in transplant rates between European countries have been analyzed.(20) Now, this study attempts to investigate the current state of HSCT for solid tumors to assess the transplant rate, indication, and prognosis of solid tumors in Iran.

Materials and Methods

We collected data from 71 patients with various types of solid tumors who had undergone hematopoietic stem cell transplantation (HSCT) from March 1991 to June 2011 at the Hematology-Oncology and Stem Cell Transplantation Research Center affiliated to Tehran University of Medical Sciences. Of these transplants, 64 were autologous stem cell transplantation, and 7 allogeneic stem cell transplantation. Their diseases in order of frequency included Neuroblastoma (18, 25.4%), Germ Cell Tumors (13, 18.3%), Breast Cancer (11, 15.5%), Ewing Sarcoma (9, 12.7%), Medulloblastoma (4, 5.7%), Ovarian Cancer (3, 4.2%), Bone sarcoma (2, 2.8%), Renal cell carcinoma (2, 2.8%), Rhabdomyosarcoma (2, 2.8%), Soft tissue sarcoma (2, 2.8%), Clear cell sarcoma of kidney (2, 2.8%), Nasopharyngeal carcinoma (1, 1.4%), Pancreatoblastoma (1, 1.4%) and Wilm's tumor (1, 1.4%), (Table- 1).

Table- 1. Number of patients with hematopietic stem cell transplantation listed by diseases.

Specific Disease	Graft Type	
	Allogeneic	Autologous
Neuroblastoma	1	17
Germ Cell Tumors		13
Breast Cancer	3	8
Ewing Sarcoma		9
Medulloblastoma		4
Ovarian Tumors		3
Bone sarcoma		2
Clear Cell Sarcoma of Kidney		2
Renal Cell Carcinoma	2	
Rhabdomyosarcoma	1	1
Soft tissue sarcoma		2
Head & Neck Tumors		1
Pancreatoblastoma		1
Wilm's Tumor		1

Autologous SCT: 64 patients underwent this type of transplant. Patients who were treated by intensive chemotherapy followed by reinfusion of non-cryopreserved autologous stem cells received a median of 6.09×10^8/kg nucleated cells (range: 0.58 – 43×10^8/kg). 61 patients (95.3%) received peripheral blood while the other three patients (4.7%) received bone marrow as a source of SCT.

Allogeneic SCT: 7 patients underwent allogeneic SCT included 3 breast cancer, 2 renal cell carcinoma, 1 neuroblastoma and 1 rhabdomiosarcoma. The donor types of allogeneic SCTs were histocompatible siblings (n=7). The patients who were treated by allogeneic SCT received a median of 5.82×10^8/kg nucleated cells (range: 4.24 – 8.49×10^8/kg). All patients (100%) received peripheral blood as a source of SCT. Methotrexate (Mtx) and cyclosporine (CSA) were given for the prevention of GVHD in allogeneic SCT. Acute and chronic GVHD were graded according to the Seattle criteria (23).

Neurobelastoma: Among 18 neuroblastoma patients who received transplantation, 17 received autologous transplantation and 1 received full-matched sibling allogenic transplantat. The median age of transplantation was 5.5 years (range: 2-32 years). 12 patients were in stage IV of NBL, 3 in stage 4S and 3 in stage of III. Primary involved

sites at diagnosis were adrenal gland in 11 patients (61%), retroperitoneal in 2 (11%) and thoracic cavity in 4 recipients (22%). The common site of metastasis consists of bone marrow in four patients, bone in two, liver in two and lymph node in four recipients. Some patients had multiple sites for metastasis. Before transplantation, patients had prior chemotherapy in different centers. Before transplantation, parents were informed about transplant's side effects and advantages. Parental consent was obtained for transplant and clinical intervention. The patients were in different status before transplantation; 10 were in first complete remission (CR1), 5 in CR2 and 3 in PR1. The main conditioning regimen used in seven patients was CEM; consisted of Carboplatin (400 mg/m^2 for 3 days), Etoposide (200 mg /m2 for 3 days), and Melphalan (75 mg /m^2 for 2 days). Patients received all agents in the in-patient clinic. After discharge, patients were followed-up in out-patient clinic.

Germ cell

All of 13 patients with germ cell tumor received autologous transplantation. The median age was 25 years (16-58). Among these patients, 5 were in CR1, 3 in CR2, 1 in CR3+, 3 in relapse and 1 in VGPR. The conditioning regimens containing Etoposide (500mg/m^2 for 3 days), carboplatin (600 mg/m^{2}for 2 days) Cyclophosphamide (1.6 gr/m^2 for 3 days) were used.

Breast cancer 3 out of 11 patients enrolled in this study, received alloSCT. The median age at transplant was 45 years (range, 30-53) and the median follow-up duration for the survivors was 18 months. At the time of transplantation, 9 patients (37%) had responsive disease (partial responses), 1(29%) had stable disease, and 1 (24%) had progressive disease. Two of our patients had metastatic breast cancer .A total of 3 patients received stem cells from matched sibling donors. All of the 11 patients received peripheral blood stem cells transplants. Conditioning regimens are listed in the following table.

Table- 2. Breast Canser Conditioning Regimens

Carboplatine/Endoxan/Etoposide	3
Carboplatine/Melphalan	1
Cisplatine/Endoxan/Etoposide	3
Endoxan/Fludarabine	3
Etoposide/Melphalan	1

Table- 3. Patient's information.

	Autologous	Allogeneic
Patients number	64	7
Median age, y	18.5	32
Sex (male/female)	37/27	4/3
Median time to ANC	12	11
Median time to Plt	20	11

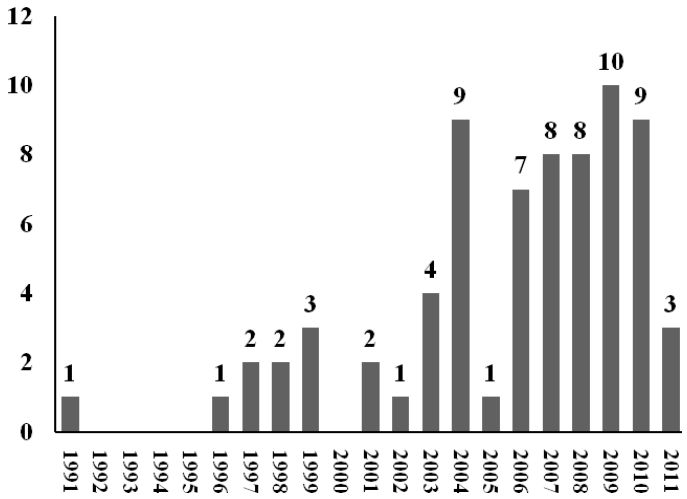

Figure1. Number of solid tumor HSCT per year.

Statistical analysis: Mean, median and standard deviations of numerical variables were calculated on an Excel spreadsheet. Overall and Disease-free survival was estimated by Kaplan-Meier method.

Result

The total numbers of HSCT per year is presented in figure 1.The increased number of patients who underwent transplants between 2006 to 2011, may be resulted from the operation of pediatric unit. The small number of transplant patients in 2011, is due to reporting the results of the study within the first semester of the year.

There were 64 patients who underwent autologous transplant consisting of 37 males and 27 females, with median age of 18.5 years (range: 2-58) for autologous SCT. The male/female ratio was 4/3, with a median age of 32 years (range: 10- 53) for allogeneic SCT. The median duration of hospitalization after high-dose therapy was 24 days (range: 11-50) days; 23 days for autologous and 29 days for allogeneic patients). The median duration needed to achieve an Absolute Neutrophil Count (ANC) $\geq 500\times10^9$/µl were 12 (range: 8-51 days) and 11(range: 10-12 days) days for autologous and allogenic transplants, respectively (Table-3).

The median duration required to achieve a platelet count of $\geq 20\times10^9$/µl was 20 (range 7-76 days) and 11 days (range 11- 14 days) for autologous and allogeneic transplant, respectively. The median follow- up time was 9 months (range 1-156 months). At present, 57 patients are still alive. Transplant-related mortality (TRM) was 4.3%. Among 7 patients with allogeneic transplantation, 2 developed acute-graft-versus host disease (aGVHD) and 4 developed chronic GVHD. One patient had chronic GVHD following acute GVHD. The most common cause of death for the allogeneic patients

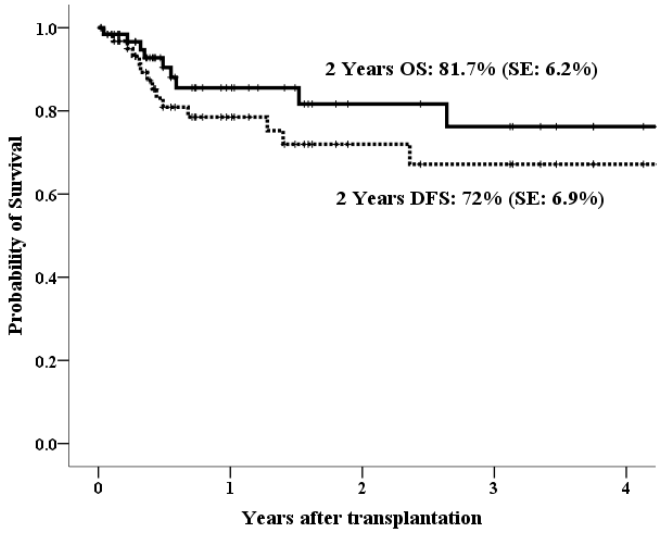

Figure-1. Overall Survival And Disease-Free Survival Of Solid Tumor

(n=4) was progressive disease with chronic GVHD (n=3) and for the autologous patients, was progressive disease (n=8). For the autologous patients 2-year overall and disease-free survivals were 81.7% (SE: 6.2%) and 72% (SE: 6.9%), respectively, (figure-1).

Discussion

The present report provides information on transplant number, donor source, donor type, disease type and outcome for HSCT in Iran. One of the aims of this report is to describe the quantitative and qualitative evolution of HSCT in our country. It has shown that trend of HSCT for solid tumor has been changed during the time and type of disease. In some periods the rate of HSCT for solid tumors was going up and in some periods the clinician didn't have trend for this. Stadtmauer, et al study show HSCT did not improve survival in woman with metastatic breast cancer&. It seems there is no similar result in several analyses. Recent studies have documented the effectiveness of high-dose therapy followed by autologous stem cell transplantation.(24-26) European review shows the continuing increase hematopoietic transplantation for some disease categories, stable situations for others, as well as increase and decrease for indications, such as breast cancer, lung cancer and germ cell tumors.(27) 90% of all HSCTs were autologous transplants. In our study, the quality of results shows a positive trend in terms of reduction of TRM. This procedure is being increasingly utilized for solid tumors. HSCT might be an effective tool in the treatment of solid tumors in some subsets of patients.(17, 24, 28) Ninety percent of all HSCTs were autologous transplants. This analysis also provides information on patient, outcome for each different diagnosis and stage of disease separately for each type of transplant. Allografting in breast cancer is a feasible procedure. One-year OS, DFS of our patients were 71.4%, 65.6%, respectively. Our study shows that HSCT potentially would be a suitable approach for treatment of some solid tumors such as breast cancer and neuroblastoma. But multicenter investigation is needed to confirm this method for treatment of solid tumors cancer.

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