Hematopoietic Stem Cell Transplantation in Iran: 1991 through 2010

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Abstract

Introduction: This review reports the current results of hematopoietic stem cell transplantation (HSCT) in patients who had received transplantation in the Hematology-Oncology and SCT Research Center, Tehran, Iran.
Methods: In Iran, from 1991 through 2010, a total of 3170 hematopoietic stem cell transplantation have been carried out. The male/female patient ratio was 1909/1261 with a median age of 23 years (range: 4 months-71 years). The most common transplanted disorders were acute myelogenous leukemia (799 patients; 25.2%), thalassemia major (500 patients; 15.8%) and acute lymphoblastic leukemia (447 patients; 14.1%). The donor types for 2147 allogeneic HSCT patients were 2007 (93.5%) human leukocyte antigen (HLA) matched-identical siblings, 66 (3.1%) HLA matched (other relatives), 52 (2.4%) HLA mismatched sibling/other relatives and 22 (1%) unrelated donors; also 16 (0.5%) of transplanted patients had syngeneic twins as donor.
Results: There were 2147 cases which had received allogeneic HSCT and 1007 cases which had received autologous HSCT. The number of allogeneic and autologous HSCT patients had increased during that time, but the allogeneic to autologous ratio remained constant. Out of 2147 allogeneic HSCT cases, there were 1730 (80.6%) cases of peripheral blood, 370 (17.2%) cases of bone marrow, and 13 (0.6%) combined peripheral blood and bone marrow cases and 34 (1.6%) cord blood cases as product types. Of the 1007 autologous patients with the first HSCT, 937 (93%) received peripheral blood, 65 (6.5%) bone marrow and 5 (0.5%) mixed bone marrow and peripheral blood as stem cell sources.
Conclusion: Hematopoietic stem cell transplantation is a choice treatment for many malignant, nonmalignant and genetic diseases. In Iran, HSCT has been successfully adapted in routine clinical care. Recently, new methods have been used, for example double cord blood and haploidentical transplantation.

Keywords

Allogeneic, Autologous, Stem Cell Transplantation

Introduction

hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for a wide variety of life-threatening congenital and acquired hematopoietic stem cell disorders and other neoplastic diseases;(1) also, Bone marrow transplantation (BMT) was the original term used to describe the collection and transplantation of hematopoietic stem cells, but with the demonstration that the peripheral blood and umbilical cord blood are also useful sources of stem cells, HSCT has become the preferred generic term for this process. The procedure is usually carried out for one of two purposes: 1- to replace an abnormal but nonmalignant lymphohematopoietic system with one from a normal donor, or 2- to treat malignancy by allowing the administration of higher doses of myelosuppressive therapy than would otherwise be possible. The use of hematopoietic cell transplantation has been increasing, both because of its efficacy in selected diseases and because of increasing availability of donors. The International Bone Marrow Transplant Registry estimates that about 50,000 transplants are performed each year.(2)

Our center is one of the International Blood and Marrow Transplantation Registry (IBMTR) and European group of Blood and Marrow

Transplantation (EBMT) members. In association with these organizations, our center has been gathering databases on patients who have undergone transplantation and cooperates with the other centers in specific scientific and research fields. Also this center is a member of the Asian Pacific Cancer Center (APCC) and Asian Pacific Blood and Marrow Transplantation (APBMT). Our center has also collaborated with blood and cancer associations such as the American Society of Hematology (ASH), the International Society of Hematology (ISH), the European School of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and other centers. The plans and aims include the protraction of cytogenetice and molecular biological diagnostic tests, the expansion of the first Iranian Cord Blood Bank (ICBB) and the first Iranian Stem Cell Donor Program (ISCDP), and the development of the research activities in this fields.(3)

Patients and Methods

The first stem cell transplantation was performed on March 3th, 1991 in this center. From 1991 untill 2010, a total of 3170 first hematopoietic stem cell transplantations were carried out.The male/female ratio was 1909/1261 with a median age of 23 years (range: 4 months-71 years). The most common transplanted disorders were acute myelogenous leukemia, thalassemia major and acute lymphoblastic leukemia. The product types were from bone marrow, peripheral blood, cord blood, a combination of bone marrow and peripheral blood, and mesenchymal origins. The donor types for the 2147 allogeneic patients were 2007 (93.5%) human leukocyte antigen (HLA) matched-identical siblings, 66 (3.1%) HLA matched other relatives, 52 (2.4%) HLA mismatched siblings/other relatives and 22 (1%) unrelated; also 16 (0.5%) of transplanted patients had syngeneic twins as donor.

According to a particular patient's situation, we used allogeneic, autologous or syngeneic stem cell grafts.(4) All patients were treated in completely isolated rooms during the peri- transplant period. They were conventional, private and HEPA filtered rooms with minimal entertainment centers to avoid patient depression.(5)

The Hematology- Oncology and Stem Cell Transplantation Research Center has a research office where a department for data management exists, consisting of gathering the stem cell transplantation data from the stem cell transplantation wards, checking reports for completeness of data and identifying missing data, reporting missing fields and, after completing them, entering report forms into the computer database program (software version 3.2.4 which meets the needs of hematopoietic stem cell transplantation centers) for statistical analysis and preparation of statistical reports. Finally, the information is sent to CIBMTR. This office is also responsible for the quality control of data entry processes and advising of patients, providing information regarding stem cell transplantation and staff data management. Iran has a population of about 75 million people. The incidence of transplantable diseases is estimated at about 2 per 100000, or, about 1500 patients per year. The cost of transplant procedures is borne by insurance companies and boards of trustees.

Definitions: Hematopoietic stem cell transplantation numbers indicate the numbers of first-time patients treated with hematopoietic stem cell transplantation. Transplant rates were defined as the number of HSCTs per 1 million inhabitants.(6) Population data has been obtained from the Statistical Center of Iran (www.amar.org.ir). Re-transplantation was defined as an unplanned HSCT due to the rejection or relapse after a first HSCT. Donor lymphocyte infusion (DLI) is a method of treatment of patients with recurrent or persistent malignancy after allogeneic HSCT, with an infusion of additional lymphocytes obtained from the original donor, without the cover of immunosuppressive agents.(7) Cell therapy is a technology that relies on replacing diseased or dysfunctional cells with healthy, functioning ones.

Results

HSCT has increased tenfold compared to the last decade. The hematopoietic stem cell transplantation rate during the past 19 years was 49.4 transplants per one million inhabitants. Also, the rate of HSCT has increased from 1991 to 2010 (Figure- 1, 2).

Out of the 3170 first transplantations, 2147 patients (67.7%) were allogeneic and 1007 (31.8%) were autologous HSCT (Figure- 3). The number of allogeneic and autologous HSCT has increased during this time period, but the standard rate of transplantations has stayed the same in both allogeneic and autologous (Figure- 4).

Out of the 2147 allogeneic first HSCT patients, there were 1730 (80.6%) peripheral blood, 370 (17.2%) bone marrow, 13 (0.6%) combined peripheral blood and bone marrow and 34 (1.6%) cord blood; 85 (4%) of all got mesenchymal with bone marrow or peripheral blood as product types.

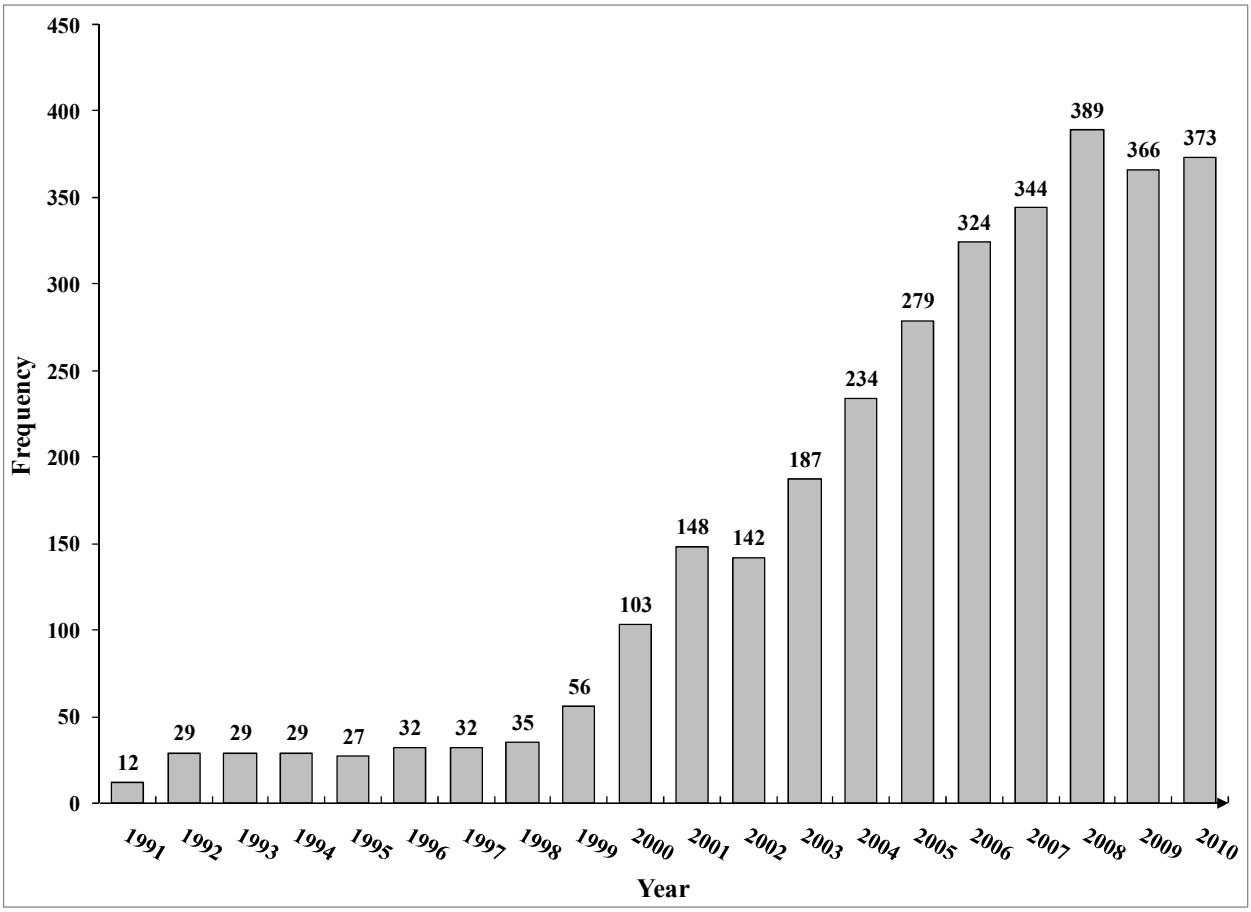

Figure-1. Number of Hematopoietic Stem Cell Transplantation from 1991 to 2010

Figure- 2. The Total Rate of Hematopoietic Stem Cell Transplantations during the Past 20 years

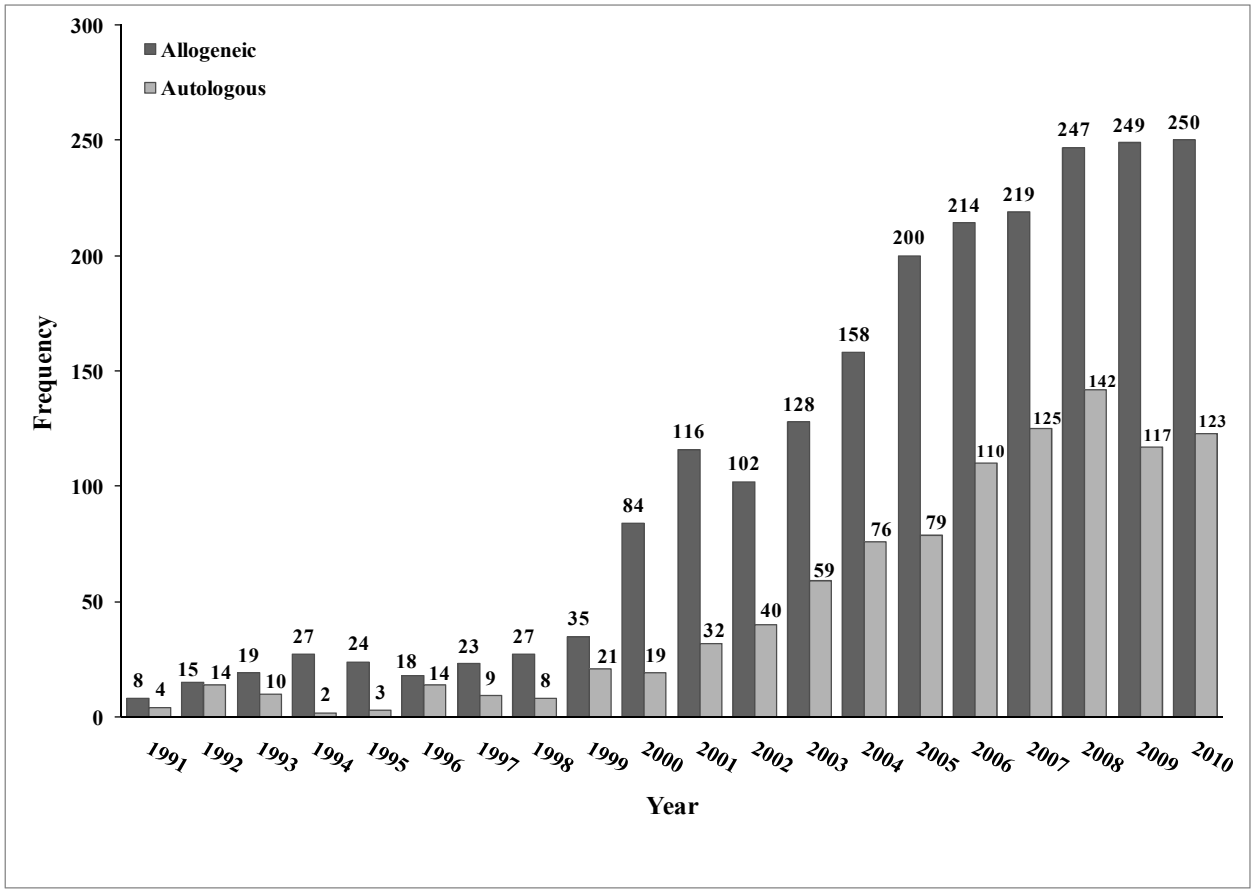

Figure 3. The Number of Allogeneic and Autologous Hematopoietic Stem Cell Transplantations

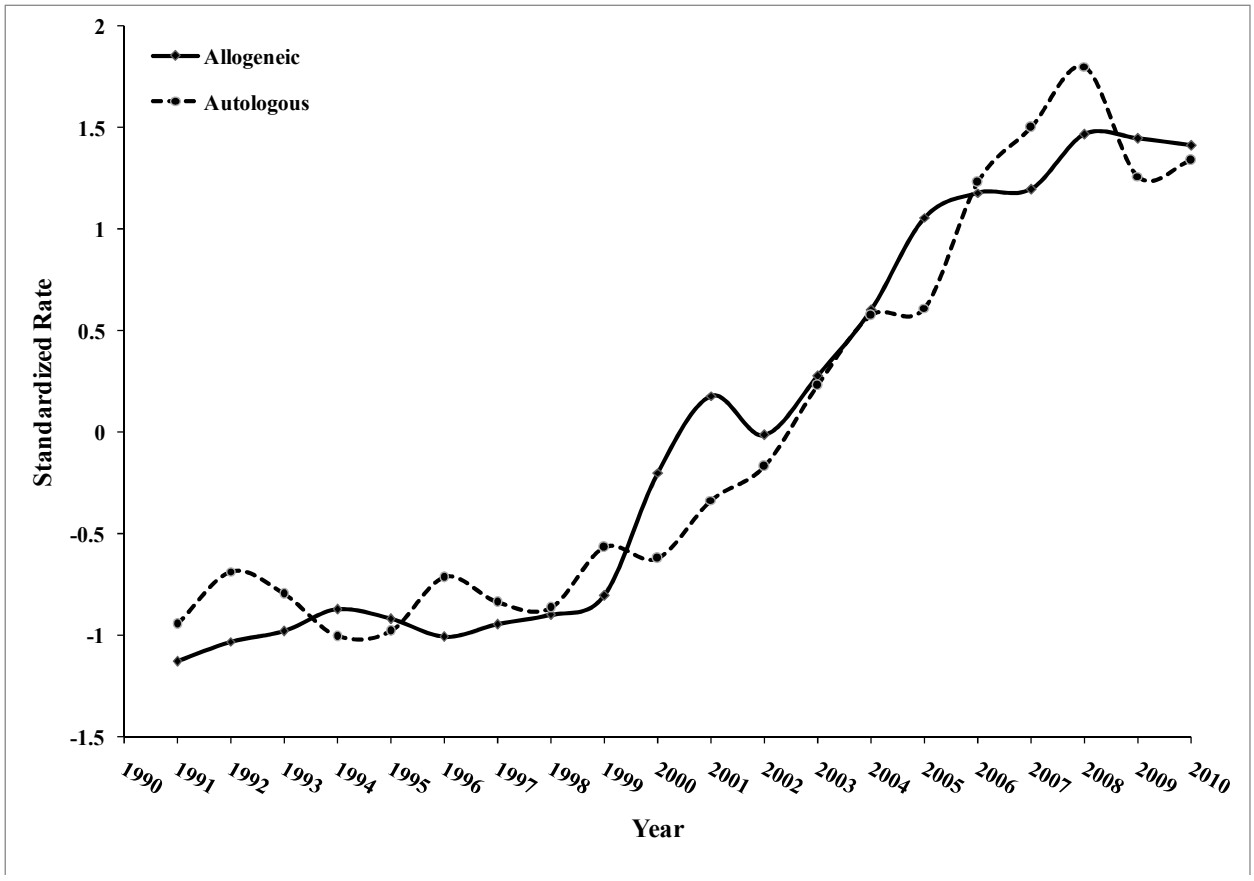

Figure 4. The Standardized Rate of Allogeneic & Autologous Hematopoietic Stem Cell Transplantations During the Past 20 years

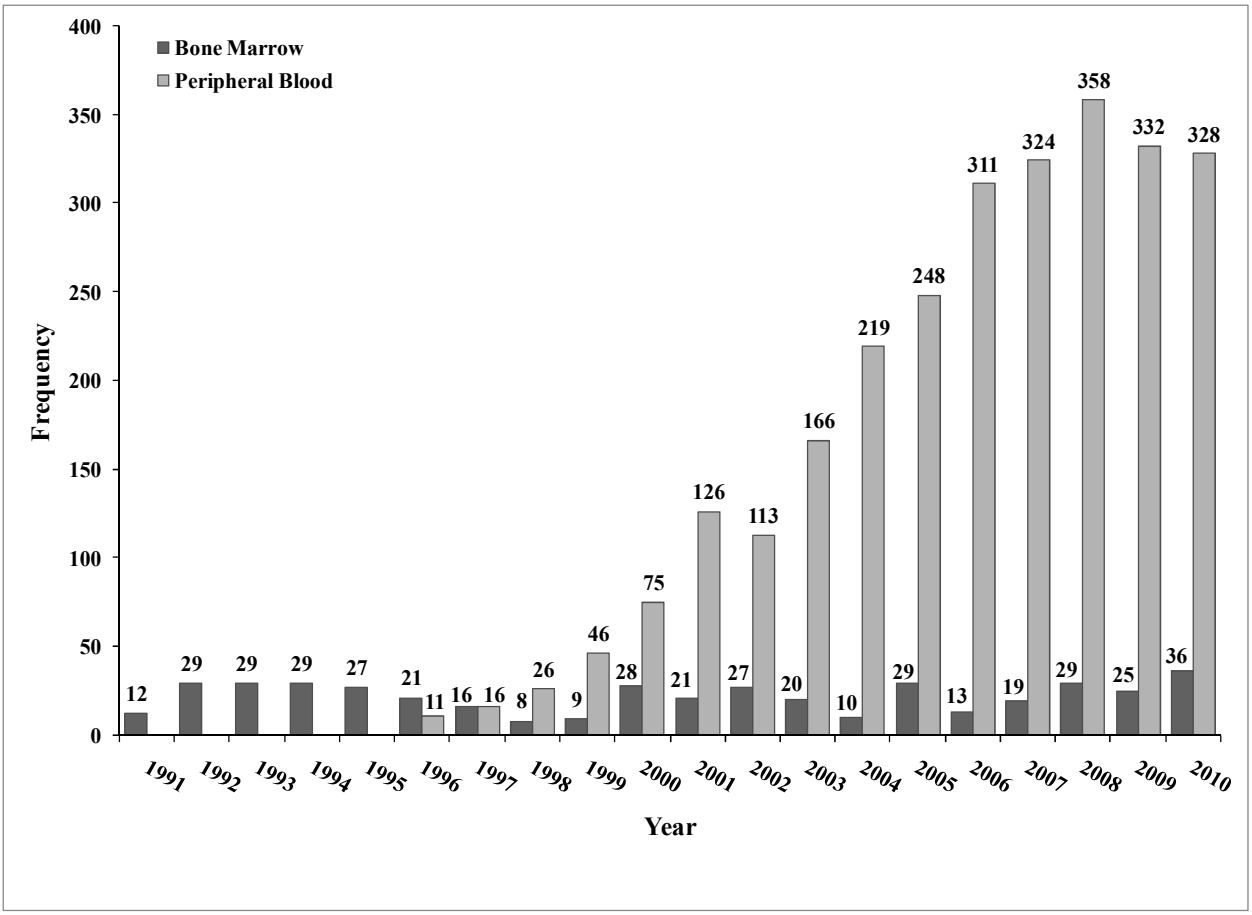

Figure 5. The Number of Peripheral Blood and Bone Marrow Hematopoietic Stem Cell Transplantations

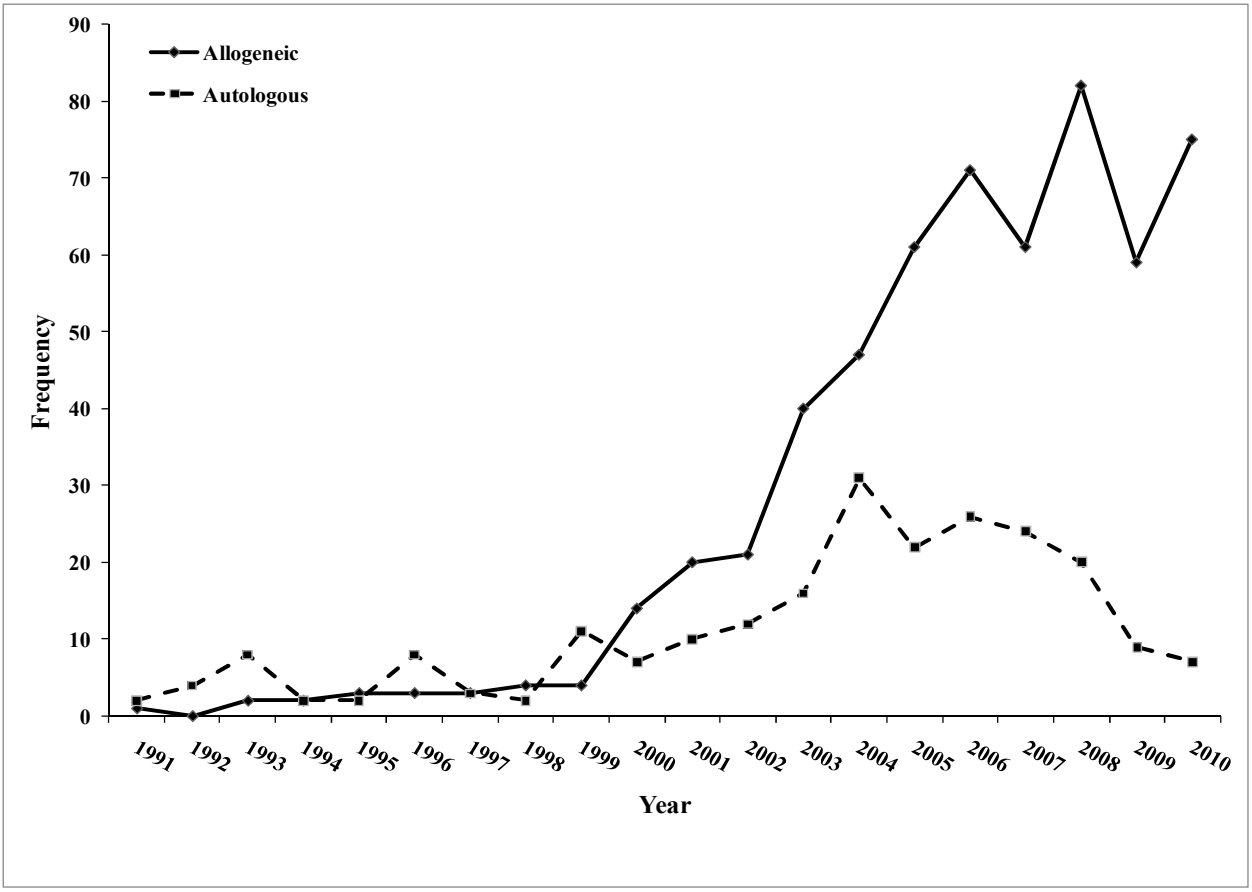

Figure 6. An Evaluation of Hematopoietic Stem Cell Transplantation Numbers by Graft Type for AML Patients

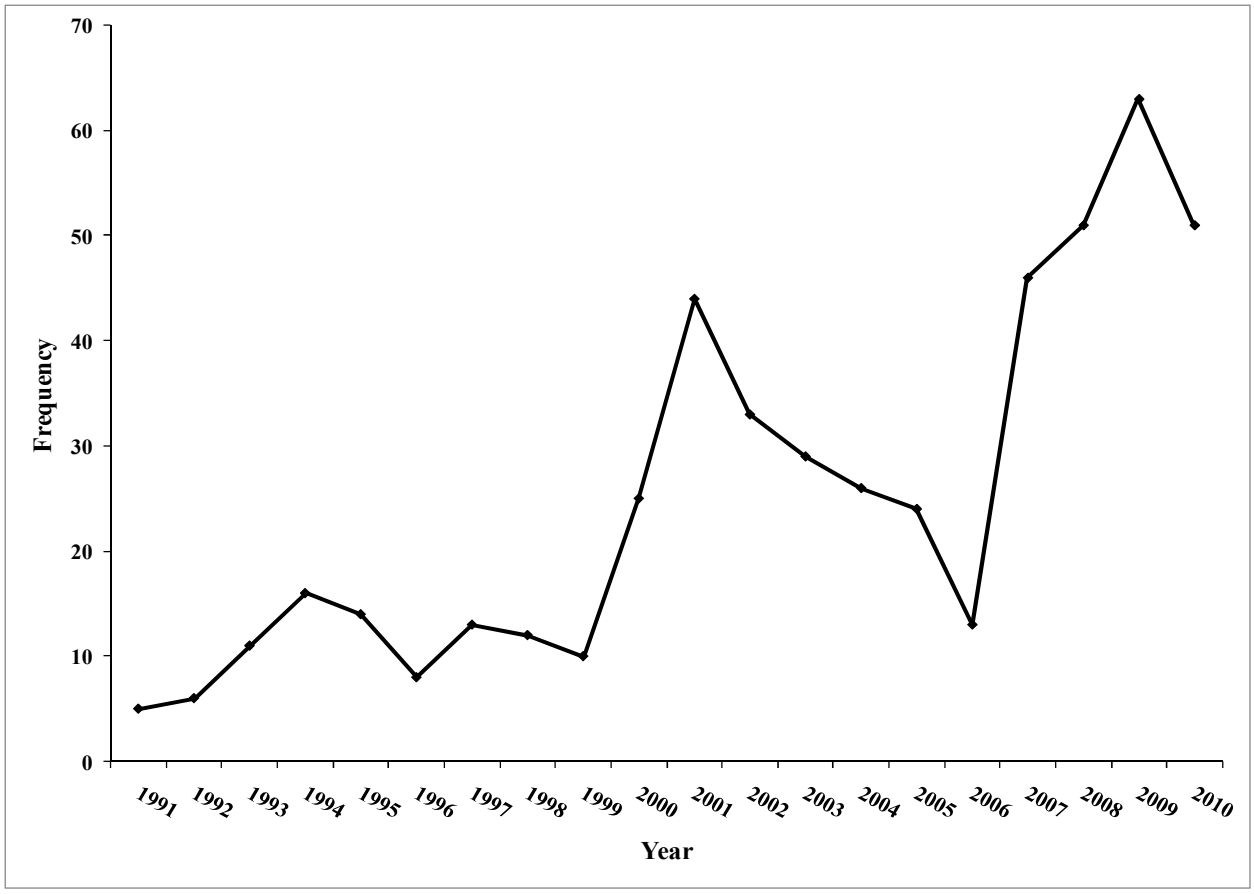

Figure 7. An Evaluation of Hematopoietic Stem Cell Transplantation Numbers for Thalassemia Patients

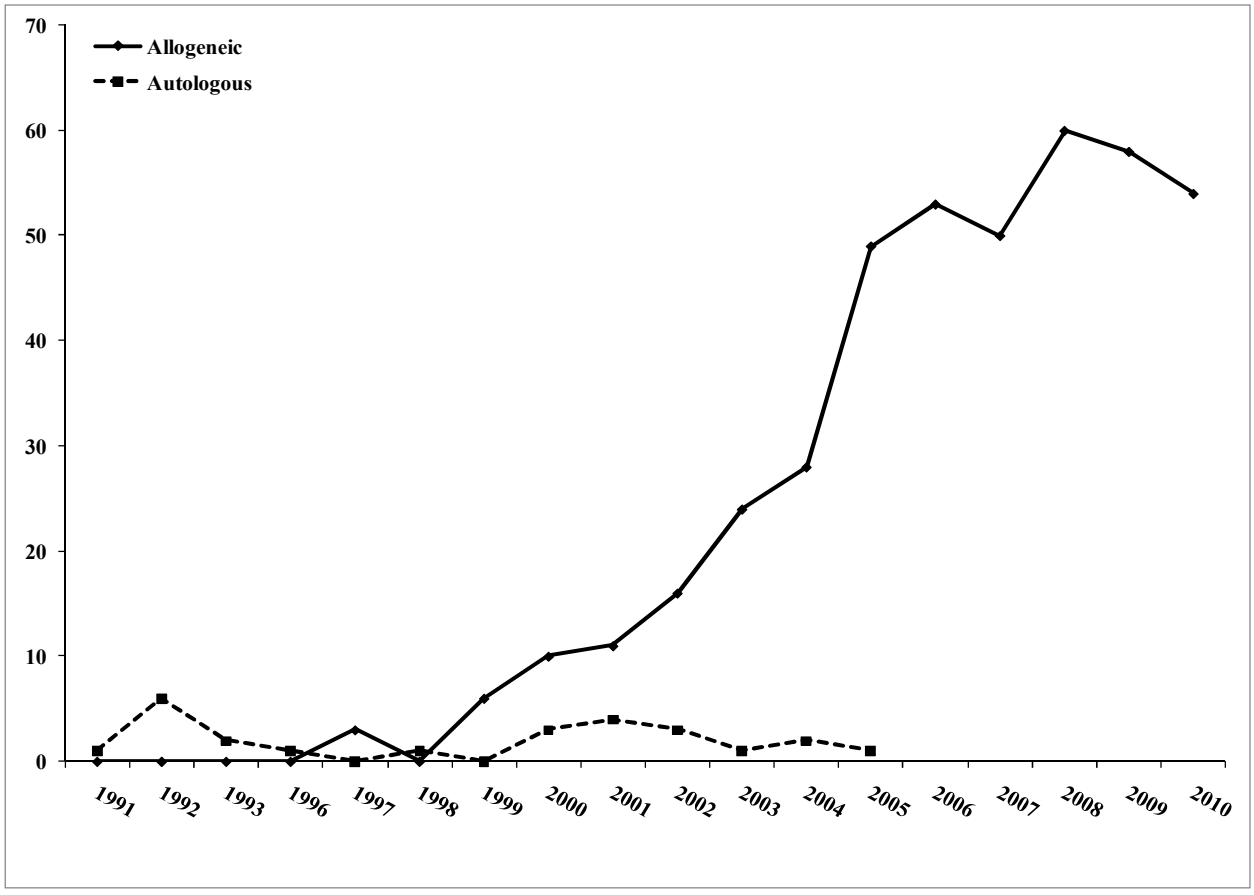

Figure 8. An Evaluation of Hematopoietic Stem Cell Transplantation Numbers by Graft Type for ALL Patients

Table 1. Number of patients with a first Hematopoietic stem cell transplantation listed by diseases

Specific Disease	Graft Type		Total
	Allogeneic	Autologous	
AML	573	226	799
ALL	422	25	447
Other Leukemia	10		10
CML	240		240
Thalassemia Major	500		500
Inherited Abnormalities of RBC	70		70
Lymphomas	37	393	430
Multiple Myeloma	11	277	288
Plasma Cell Disorders	2	19	21
Severe Aplastic Anemia	187		187
Solid Tumors	6	62	68
MDS/MPS	50		50
Disorders of Immune System	31		31
Inherited Disorder of Metabolism	20		20
Autoٔ Immune Diseases		5	5
Histiocytic Disorders	4		4
Total	**2163**	**1007**	**3170**

Of the 1007 autologous patients with their first HSCT, 937 (93%) received peripheral blood, 65 (6.5%) bone marrow and 5 (0.5%) mixed bone marrow and peripheral blood as stem cell sources (Figure- 5).

The first cord blood hematopoietic stem cell transplantation was performed in 1998 and since then, there have been 34 patients that have obtained cord blood transplantations. The greatest numbers of cord blood transplantations were in 2009 and 2010 (each year 9 patients). All of the cord blood HSCT was allogeneic and there was no autologous cord blood HSCT.

The primary diseases for which transplants were performed are shown in Table 1. The main diseases were acute myelogenous leukemia with 799 patients (25.2%), 573 (71.7%) with allogeneic HSCT, 226 (28.3%) with autologous HSCT; thalassemia major 500 allogeneic patients (15.8%); acute lymphoblastic leukemia, with 447 patients (14.1%), 422 patients (94.4%) with allogeneic HSCT, 25 patients (5.6%) with autologous HSCT; Furthermore, autologous HSCT in ALL patients has been stopped since 2005; lymphomas characterized 430 patients (13.6%), 37 patients (8.6%) had allogeneic HSCT, 393 patients (91.4%) had autologous HSCT; chronic myelogenous lymphomas were found in 240 allogeneic patients (7.6%); multiple myeloma, with 288 patients (9.1%); sever aplastic anemia, with 181 patients (5.7%) and 8.9% of the patients had other diseases.(8)

In the acute myelogenous leukemia and acute lymphoblastic leukemia patients, the allogeneic HSCT was more than the autologous HSCT patients, but in patients with lymphomas, multiple myeloma, plasma cell disorders and solid tumors, autologous HSCT was greater than allogeneic HSCT. On the other hand, patients with chronic myelogenous leukemia, sever aplastic anemia, hemoglobinopathies, disorders of immune system, myelodysplasia and inherited disorders of Metabolism, were treated with allogeneic HSCT. Autoٔ immune disease patients were treated only with autologous HSCT. The most common disorders requiring transplantation were acute myelogenous leukemia, thalassemia major and acute lymphoblastic leukemia, respectively.(9) Acute myelogenous leukemia showed a fixed increase in both allogeneic and autologous HSCT (Figure- 6) and the allogeneic to autologous ratio was stable.

Thalassemia major rates indicate a peak in 2001, then, a rapid decline until 2006 and after that there was further growth (Figure- 7). Acute lymphoblastic leukemia initially started with autologous HSCT in 1991. Then, they were treated with an allogeneic HSCT augment in 1995 and, thereafter, there was an increase in allogeneic HSCT with stable low numbers for autologous HSCT (Figure- 8).

There were 114 patients that had received donor lymphocyte infusion (DLI). Some patients were treated with DLI more than once. The total number of DLI procedures was 155. The most frequency of that was in 2005. During the past 19 years, 43 patients have been retransplanted. The common disorders in retransplanted patients were thalassemia major, acute myelogenous leukemia, lymphomas and sever aplastic anemia, respectively. Cellular therapy was done on 219 patients, 52 patients were post-myocardial infarction, 30 had cirrhosis, 85 patients had thalassemia major, 11 patients had multiple sclerosis, 13 patients had head

of femour necrosis, 21 patients suffered from diabetes mellitus and 7 patients for GvHD treatment.

Conclusion

Hematopoietic stem cell transplantation is the choice treatment for many malignant, nonmalignant, and genetic diseases. According to statistical reviews during the past 19 years in Hematology- Oncology and Stem Cell Transplantation Research Center, hematopoietic stem cell transplantation numbers and rates have increased, especially after the year 2000. It is remarkable that transplant rates for allogeneic HSCT are more than autologous HSCT, but both of them have increased with a stable ratio. It can be surmised that the number of HSCT for acute myelogenous leukemia and acute lymphoblastic leukemia was more frequent amongst all disorders; also, the predominant type of HSCT in these diseases was allogeneic, which is similar to the survey of the European Group for Blood and Marrow Transplantation (EBMT).(10)Peripheral blood was the main source of hematopoietic stem cell transplantation which was the same as in the EBMT survey.(11) The most frequent donor type was Allogeneic, full HLA-matched siblings. The plans and aims of our center include the protraction of cytogenetic and molecular biological diagnostic tests, creation of a cord blood bank and HLA registry, and the development of research activities in these fields. This center's future planned studies are in the areas of: transplantation in Breast cancer, neuroblastoma, Ewing sarcoma, soft tissue sarcoma, allogeneic hematopoietic stem cell transplantation for renal cell cancer, allogeneic hematopoietic stem cell transplantation for colorectal carcinoma. Also planned is research on cell therapies for post myocardial infarction, cirrhosis, thalassemia major, multiple sclerosis, head of femur necrosis, sever aplastic anemia and renal cell carcinoma, lupus and GVHD treatment.

Acknowledgments

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References

1. Spitzar TR. Bone Marrow Transplantation. In: Bruce A. Chabner, Thomas J. Lynch, Dan L. Longo. Harrison's manual of oncology: McGraw-Hill; 2008. p. 337.

2. Applebaum FR. Hematopoietic Cell Transplantation. In: Anthony S. Fauci, Eugene Braunwald, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson, Joseph Loscalzo. Harrison's principles of internal medicine. 17th ed: McGraw-Hill; 2008. p. 713.

3. Ghavamzadeh A, Alimoghaddam K, Jahani M, Mousavi SA, Iravani M, Bahar B, Khodabandeh A, Khatami F, Jalali A. Stem Cell Transplantation in Iran: 1991 until 2009. International Journal of Hematology-Oncology and Stem Cell Research. 2009;3(1):27-33.

4. Ghavamzadeh A, Nasseri P, Eshraghian MR, Jahani M, Baybordi I, Nateghi J, Khodabandeh A, Sadjadi AR, Mohyeddin M, Khademi Y. Prognostic Factors in Bone Marrow Transplantation for beta Thalassemia Major: Experiences from Iran. Bone Marrow Transplantation. 1998;22:1167-9.

5. Iravani M, Evazi MR, Mousavi SA, Shamshiri AR, Tavakoli M, Ashouri A, Samiee S, Chahardovali B, Alimoghaddam K, Ghaffari SH, Ghavamzadeh A. Fludarabine and Busulfan as a Myeloablative Conditioning Regimen for Allogeneic Stem Cell Transplantation in High- and Standard-risk Leukemic Patients. Bone Marrow Transplantation. 2007;40:105-10.

6. Gratwohl A, Passweg J, Baldomero H, Horisberger H, Urbano-Ispizua A. for the Accrediation Committee of the European Group for Blood and Marrow Transplantation (EBMT). Economic, health care systems and utilization of haematopoietic stem cell transplants in Europe. Br J Haematol. 2002;117:451-68.

7. Ginna G. Laport RSN. Management of Relapse after Hematopoietic Cell Transplantation. In: Fredrick R. Applebaum, Stephan J. Forman, Robert S. Nergin, Karl G. Blume. Thomas' Hematopoietic Cell Transplantation: WILEY-BLACKWELL; 2004. p. 1059-75.

8. Gratwohl A, Baldomero H, Frauendorfer K, Urbano-Ispizua A. Joint Accrediation Committee of the International Society for Cellular Therapy ISCT and the European Group for Blood and Marrow Transplantation EBMT (JACIE). EBMT Actiity Survey 2004 and Changes in Disease Indication over the Past 15 years. Bone Marrow Transplantation. 2006;37:1069-85.

9. Iravani M, Mousavi SA, Gholibeikian S, Bahar B, Samiee S, Ashouri A, Eghbal L, Ghavamzadeh A. Cyclosporin Disease Prophylaxis in Patients with beta Thalassemia Major Undergoing Allogeneic Blood and Marrow Transplantation. Bone Marrow Transplantation. 2005;35:1095-9.

10. Gratwohl A, Baldomero H, Frauendorfer K, Rocha V, Apperley J, Niederwieser D. Joint Accrediation Committee of the International Society for Cellular Therapy ISCT and the

European Group for Blood and Marrow Transplantation EBMT (JACIE). The EBMT Activity Survey 2006 on Hematologic Stem Cell Transplantation: Focus on the Use of Cord Blood Products. Bone Marrow Transplantation. 2007:1-19.

11. Gratwohl A, Baldomero H, Horisberger B, Schmid C, Passweg J, Urbano-Ispizua A. Accrediation Committee of the European Group for Blood and Marrow Transplantation (EBMT). Current Trends in Hematopoietic Stem Cell Transplantation in Europe. Blood. 2002;100:2374-86.