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REVIEW ARTICLE

Hematopoietic Stem Cell Transplantation in Southern Iran: History, Current Status and Future Direction

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Abstract

Transplantation of hematopoietic stem cells (HSCT) has become the standard treatment for many patients with congenital or acquired disorders of the hematopoietic system or with chemo-radio or immuno-sensitive malignancies. HSCT has undergone rapid expansion over the past two decades. Despite the high cost and the complexity of the procedure, HSCT has developed in developing countries. The transplant program was established in Shiraz University of Medical Sciences in 1993 in Shiraz, southern Iran and is a referral center for about 10 million patients with hematology-oncology diseases. From 1993 to 2009, more than 450 allogeneic and autologous transplantations were undertaken. Since 2003, stem cell sources from the bone marrow have changed to peripheral blood for almost all disease indications. The main indication for HSCT is now the hematologic malignancies instead of hemoglobinopathy (thalassemia major). From 1993 to 2007, HSCT was performed on 155 blood transfusion dependent patients with thalassemia major with disease-free survival and overall survival of 71% and 77%, respectively. During this time, 127 leukemia patients underwent allogeneic HSCT including AML (n=68), ALL (n=30) and CML (n=29). In this group, long term disease-free survival rate (cure rate) was 67%, 60% and 62%, respectively**.** Even HSCT is rising rapidly in during the five past years; however, when the total transplantation to the total number of population is compared in our region, the rate is still low. It seems that the government should support the therapeutic approaches more in our country and help to overcome the difficulties.

Keywords: Stem cell; Transplantation; Hematopoietic; Thalassemia major; Hematologic malignancy; Iran

Introduction

Transplantation of hematopoietic stem cells (HSCT) has become the standard treatment for many patients with congenital or acquired disorders of the hematopoietic system or with chemo-radio or immuno-sensitive malignancies.[1-3] Its introduction to clinical medicine dates back to 1968 with the first reports of successful bone marrow transplantation from human leukocyte antigen (HLA) identical siblings for patients with immune deficiency disorders.[4]

HSCT has rapidly expanded over the past two decades and has evolved from an experimental procedure to the standard of care and is integrated into the treatment algorithm for many disease categories. Better management of patients, improved supportive care, increased donor pools and novel conditioning regimens have extended its use to a new category and new disease indication. Hematopoietic stem cells (HSC) from different donor types (autologous, syngeneic, allogeneic related and allogeneic non-related) and different stem cell sources (bone marrow, peripheral blood and cord blood) are applied depending on the clinical situation and need. On the basis of current data, more than 25000 patients are now treated annually in Europe with HSCT and approximately 100000 patients worldwide.[1,2]

History

HSCT is now an established treatment modality with definitive indication for many diseases. Despite the high cost and the complexity of procedure, HSCT has developed in developing countries. Iran is located in the eastern Mediterranean (EM) region and its total population is about 70 million. In Iran, HSCT has

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started in Tehran as the first center in 1991 and then in Shiraz as the second one.[5-7]

The transplant program was established in our center in Nemazee Hospital affiliated to Shiraz University of Medical Sciences in Shiraz, Fars Province, southern Iran in 1993. The first allogeneic bone marrow transplantation was conducted on a thalassemic patient in May 1993. Immediately the first allogeneic bone marrow transplantation for hematologic malignancy was performed for a case of acute myelogenous leukemia in June 1993. Our center is a referral center for about 10 million patients with hematology-oncology diseases. We have started transplantation with 2 beds and 8 transplants annually but now we can perform approximately 100 transplants per year (2 transplants per week).

From 1993 to 2009, more than 450 HSCT were carried out (Figure 1) showing that HSCT increased significantly during the last 5 years. In 2008, 78 stem cell transplantations (30 allogeneic and 48 autologous) were conducted. Since 2003, stem cell sources from bone marrow changed to peripheral blood, for almost all disease indications. The main indication for HSCT has changed and hematologic malignancy is now the main indication instead of hemoglobinopathies such as thalassemia major. We have participated in European Group for Blood and Marrow Transplantation (EBMT) survey activity as a member and have reported all HCST since 2003. On the basis of 16 years of experiences and more than 450 transplants, this article will focus on special important issues for HSCT practices in developing countries including southern Iran.

Donor Type and Availability

Approximately 25-30% of the patients who have siblings can be expected to have an HLA identical donor. This percentage is somewhat higher, reaching up to 40% in our country due to the lager family size. The EM region where country is located consists of communities of large families with high population growth rate which certainly increases the likelihood of finding a fully HLA matched sibling donor.[8] The chance for HLA identical sibling is higher than the likelihood of finding a sibling donor for European and North American patients. In some cases, we have to choose the best donor among several HLA-matched sibling candidates. In our center, 100% of the donors for allogeneic HSCT were HLA compatible relatives of patients, including 93.5% siblings (291 of 311) and 6.5% other family members (20 of 311).

In spite of this high family member donor availability, an alternative donor source for HSCT is necessary and demand on alternative donor is rising inevitably. Initiation of cord blood banking which should offer a great potential for suitable alternative donor, in an area where child bearing potential is high, will decrease the incidence of not finding a HLA-matched donor. Also, unrelated donor program is another good choice.

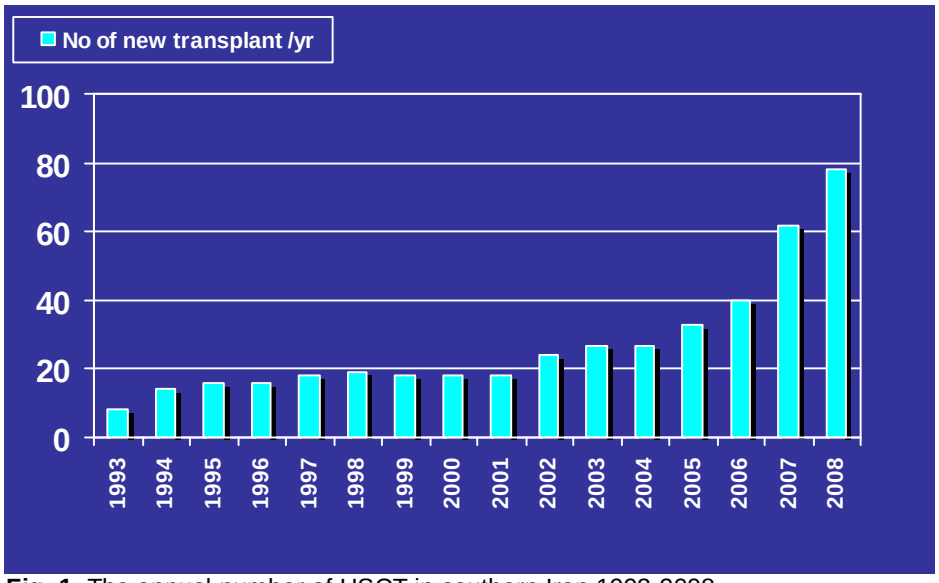

Fig. 1: The annual number of HSCT in southern Iran 1993-2008

Indication

Hematological malignancy currently represents the main indication for HSCT.[3,9-13] Clearly, autologous and allogeneic HSCT are established therapies in many of hematologic malignancies.[14] In EBMT survey about indication of HSCT in 2006, the main indication was lymphoproliferative disorder with 56% (11% allogeneic and 89% autologous), leukemia 32% (85% allogeneic and 15% autologous), solid tumors 6%, and non-malignant disorders 5%.[15]

Indications for HSCT from 1993 to Octobers 2008 in Shiraz are shown in Table 1. The main indications were thalassemia major (36%), leukemia (34%), lymphoma (16%0, and multiple myeloma (7%) (Figure 2). Table 1 showed that the most common indication for HSCT was different from reported data by EBMT. In our center, the main indication for allogeneic HSCT was thalassemia major, 155 of 311 (49.8%), which reflects the high prevalence of thalassemia major in our region (in south of Iran). This is compatible with Grathwohl et al.'s report indicating that there were clear differences in transplant rate for certain disease indications in different areas in EBMT survey (2006), which might be related to a different prevalence of disease, for example hemoglobinopathies.[16]

During the past ten years, screening and preventing marriage of thalassemia minor patients with each other and prenatal diagnosis and abortion of thalassemia major in our area resulted in a decreased rate of the disease. Now in our center, leukemia and lymphoproliferative disorders are the most common indications for allogeneic and autologous transplantation, being similar to other reports by EBMT.[12,15]

Table 1: Indication for HSCT in Shiraz 1993-2008

Disease entity	Number of cases (%)
Thalassemia major	155 (36)
Leukemia	144 (34)
AML	85 (20)
ALL	30 (7)
CML	29 (7)
Lymphoma (HD,NHL)	79 (17)
Multiple myeloma	24 (6)
Aplastic anemia & fanconi's	20 (5)
Germ cell tumor	4 (1)
Ewing sarcoma	1 (0.2)
Mylodysplastic syndrome	1 (0.2)
Inborn error of metabolism	1 (0.2)
Total	429 (100)

In autologus setting, the major indications for HSCT in our center were lymphoma (Hodgkin lymphoma; HD and non-Hodgkin's lymphoma; NHL), acute myelogeneic leukemia (AML), and multiple myeloma. As clearly demonstrated in our data, the transplant rate for lymphoproliferative disorder is rising continuously that is in concordance with the reports of EBMT activity survey.[12,15]

Stem Cell Source

Traditionally, HSC was harvested from the iliac crests under general anesthesia. Thereafter, mobilized peripheral blood source of the stem cell (PBSC) has been increasingly used in both auto and all-HSCT. The use of different cell sources for HSCT has varied over time. EBMT in 2004, in an autologous setting,

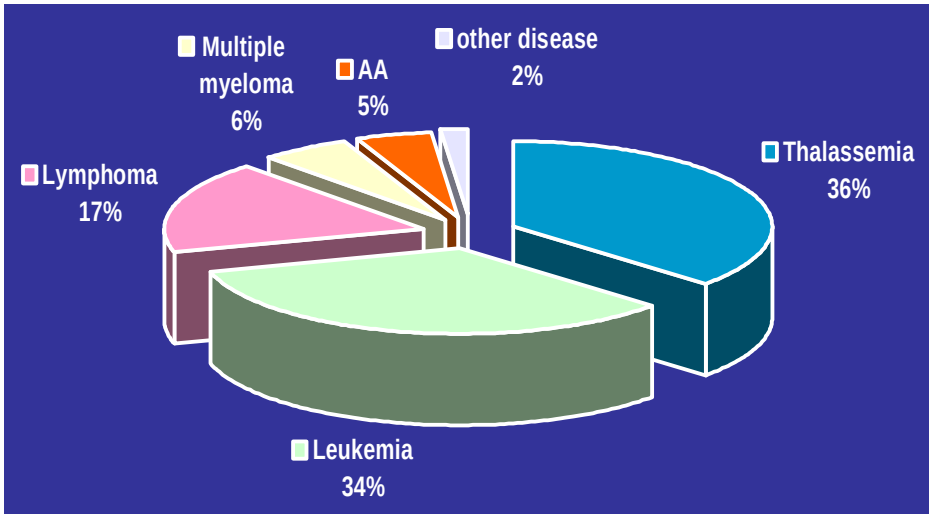

Fig. 2: Indications for hematopoietic stem cell transplantation in southern Iran

reported that there were 2% bone marrow derived and 98% peripheral blood stem cell transplantations. In allogeneic setting, 31% were marrow and 69% peripheral blood stem cell transplantations.[17]An EBMT survey on HSCT in 2005 reported that the stem cell source for auto-HSCT was 98% peripheral blood and 2% BM, but in the allogeneic setting, bone marrow was used in 21% and PBSC in 74%, confirming the increasing use of this new source of stem cells.[18]

In our center, all 112 autologous stem cell transplantations during 2003-2008 were performed, using PBSC. We have done 311 allogeneic HSCT until October 2008, including 198 (64%) bone marrow and 113 (36%) PBSC transplantations. This higher ratio of BM to PBSC transplantation has resulted from previous methods of our stem cell harvesting until 2003. We have changed our method to PBSC during the last five years and now almost 100% of stem cell harvesting in adult patients is performed by using GCSF to mobilize the peripheral blood in our center.

We are ready to start cord transplantation for patients especially children who do not have a match-related donor. But one of the main limiting factors is the cost and logistic facilities required for such transplantation .We are in the process of establishing an umbilical cord blood bank in our center.

HSCT for β Thalassemia Major

B thalassemia is the most common worldwide genetic disease. Although improvement of conservative treatment has considerably improved the prognosis but still HSCT remains the only currently available cure for these patients.[19] The HSCT therapeutic approach pioneered by Pesaro group is now applied widely in the world.[20] The EBMT has established the hemoglobinopathy registry which now contains detailed epidemiological data on over 3000 patients. Since the early 90s, between 133 and 197 transplantations per year were registered. The EBMT registry highlights the pioneering role of Pesaro group in this field and showed the wide diffusion of the procedure after 1993.[20]

In Iran, the carrier rate for B thalasemia is 4.1% of population, which varies from 0.4% to 9.4% in different provinces. The carrier state is especially prevalent (7.1-9.4) in the south of Iran near the Persian Gulf. From 1993 to 2007, HSCT was performed on 155 blood transfusion dependent patients with thalassemia major in our center with disease-free survival and overall survival of 71% and 77%, respectively. According to the published data, allogeneic stem cell transplantation has changed the outcome of this disease dramatically in our region.[7,21,22]

In one report in 2004, 112 patients with diagnosis of B thalassemia major underwent allogeneic marrow transplantation in our center. The mean age of the patients was 9.5 years with the range of 2 to 20 years. According to the Lucarelli's risk classification, the distributions of cases were 27 cases class I, 38 cases class II, and 47 cases class III. Out of 112, eighty seven patients (77.6%) were living with full engraftment at a median follow up of 6 years (range=3-119 months). According to our results, stem cell transplantation is the treatment of choice for class I and class II (Lucarelli's risk group classification), and also we recommend transplantation as a curative method for treatment of class III thalassemia major patients.[7] In this report, using a low dose of Anti Thymocyte Globuline (ATG) as a part of conditioning regimen in the majority of cases of class II and III thalassemia resulted in a lower risk of rejection and severe graft versus host disease, high chance of full engraftment, and better survival in class II and III.[7]

Stem Cell Transplantation in Hematologic Malignancies

HSCT are considered as the best treatment option for many hematological malignancies. According to EBMT report, the number of transplant has increased five-fold during 1990-2001 and transplant rates increased in all European countrie and for all indications from 1990-2001. Transplant rates have declined for chronic myelogenous leukemia (CML) since 1999.[14]

In this report, acute leukemia, CML, myelodysplastic syndrome (MDS) and NHL were considered as accepted indications for allogeneic and autologous transplantation as the preferred choice for multiple myeloma (MM), NHL, and HD.[14]

We have increased our stem cell transplantation activity by focusing on hematologic malignancies from 2003 to 2008. Since then, with establishing peripheral blood autologous and allogeneic stem cell transplantation, the main indication for HSCT is hematologic malignancy in our center.

A total of 127 leukemia patients underwent allogeneic HSCT including acute myelogenous leukemia (n=68), acute lymphoblastic leukemia (n=30),

and chronic muelogenous leukemia (n=29) with a mean age of 29 years and range of 5-57 years. In this group, long term disease-free survival (cure rate) was 67%, 60% and 62%, respectively. Mortality rate after stem cell transplantation in this group was 35 % (45 of 127), mainly due to the relapse of malignancy.

According to the results of acute leukemia (AML, ALL) transplantation, which are better than other methods of treatment in our center, we highly recommend HSCT for these indications (AML, ALL).

Cytomegalovirus Infection

Cytomegalovirus (CMV) disease has historically been the main cause of death in allogeneic transplant patients except for when both donor and recipient are seronegative. Seroepidemilogical studies have shown that approximately 60% of adults in developed countries and up to 100% of adults in developing countries are seropositive for antibodies against human CMV (HCMV). BMT recipients who are negative for anti-HCMV antibody are at risk of primary infection.[23] In our region, HCMV antibody is positive in 88% of donors and 92% of recipients of BMT.[24]

One study in our center showed the simultaneous presence of HCMV DNA in more than 75% of plasma samples and leukocyte of bone marrow transplant (BMT) patients. These data also indicated that molecular detection of active HCMV infection was more sensitive when a double primer PCR (polymerase chain reaction) assay was applied to PMN rather than to plasma samples. Compared with antigenemia assay, the relative sensitivities of the PCR assay with PMN leukocytes and plasma were 100% and 87.5%, respectively. The specificities of PCR assay with PMN and with plasma sample were 100% and 85.7%, respectively. Our results reveal that detection of HCMV DNA in PMN leukocytes of BMT recipients by a double primer PCR assay might be an alternative method to an antigenemia assay.[24]

In another study, we used quantitative competitive PCR to determine the viral load in BMT recipients in our center, for diagnosis and monitoring of CMV infection. It was demonstrated that the chance of viral reactivation and HCMV infection/disease upon transplantation must be seriously considered due to high prevalence of cytomegalovirus in our country. Therefore, the use of quantitative PCR in PCR positive patients is highly recommended to demonstrate active infection that may lead to HCMV disease during the post-transplant period.[25]

The results of another CMV study in our patients showed that the quantitative capture hybrid PCR-ELISA was able to diagnose and monitor CMV infection in patients receiving stem cell transplantation. Detection of CMV DNA in the plasma was more predictive of the onset of CMV related clinical symptoms than its detection in peripheral blood mononuclear cells.[26]

The prognosis in patients with established CMV disease is still poor.[27] The standard therapy for CMV pneumonia has been IV gancyclovir combined with high dose intravenous immunoglobulin (IV Ig), but this standard has never been evaluated in a controlled study. More recent studies have questioned whether addition of immunoglobulin improves the outcome or not.[28] In one reported study in our center for CMV infection, the results showed that pre- and post-transplantation use of IV Ig could not prevent HCMV disease and/or reactivation,[29] but the use of acyclovir as a prophylactic anti-herpetic agent was significantly associated with negative results of HCMV-PCR.[29]

According to previous studies, our strategy for CMV infection is (i) If possible, CMV-seronegative patients should be transplanted from CMV-seronegative donor but it is usually impossible; (ii) To reduce the risk of transmission from blood products which are usually CMV positive, so leukocyte depleted blood product should be used; (iii) The strategy for prevention of seropositive or seronegative patients receiving transplants from seropositive donor include prevention of a recurrence/reactivation of CMV (prophylaxis) or prevention of development of disease when a reactivation has occurred (preemptive therapy). Treatment with low potency antiviral drug (acyclovir) would be our prophylactic strategy. Today, the preemptive therapy with gancyclovir is also our used strategy for prevention of CMV disease after an allogeneic SCT.

Future Direction

It is clear that the need for HSCT will continuously increase in the future. HSCT is a high-cost procedure and can present a financial challenge for patients and health care system in any country.[30-32] A correlation between the economic strength of an individual country and the transplant rate (the number of transplants per number of inhabitants) were reported earlier by EBMT.[14,33]

It is easy to understand that health care providers

would like to have information on future needs. HSCT is a complex procedure which depends on the availability of a specific infrastructure, trained medical personnel and supported staff. Not surprisingly, transplant rate clearly correlates with national economy of a country such as Gross Nation Product (GNP).[34] The transplant rate is also correlated with the team density. A low team density is correlated with a low transplant rate; i.e. there is a need to have several transplant teams in a given county in order to disseminate the technology.[34]

Since 1993, HSCT activity rised rapidly in Shiraz especially during the last five years; however, if we compare the total number of transplantation to the total number of population in our area, the rate of transplantation (Transplant rates were defined as number of HSCT per 10 million inhabitants) is low. In Shiraz, as the referral center of at least 10 million people in the south of Iran, transplantation rate in 2008 was 78 yearly, being still below the rate of developed countries. The transplantion rate should be targeted to the level of 200 per 10 million populations per year within the next 2-3 years.

The government should support to overcome the difficulties and complications and encourage the powerful curative therapeutic approaches in the country including our center.

As mentioned, development of stem cell therapy in our center in the south of Iran was not only effective as a curative method in a variety of malignant and non-malignant diseases, but also it is an expanding field with additional rapid changes in other medical technology too. It was also effective in developing a new field for research in other sciences such as microbiology, virology, genetic, immunology, transfusion medicine and cell therapy.

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