BONE MARROW TRANSPLANTATION DATA FOR MARMARA UNIVERSITY SCHOOL OF MEDICINE: 1989-1998

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ABSTRACT

Objectives: The aim of this study was to analyse the bone marrow transplantation data at the Haematology Department of Marmara University Hospital between 1989 and 1998.

Methods: The transplant data and survival of 56 patients, who had allogeneic (n=42) or autologous (n=14) bone marrow transplantation, were evaluated retrospectively.

Results: The most common complications encountered in bone marrow transplant patients were infections and graft versus host disease (GVHD). The primary causes of death were acute and chronic GVHD. Chronic GVHD was significantly higher in the allogeneic peripheral stem cell transplantation (Allo-PBSCT) in comparison with allogeneic bone marrow transplantation (Allo-BMT) .

Disease free survival for allo-BMT, allo-PBSCT, and autologous PBSCT was 61.2%, 54,5% and 30.7% respectively, Transplant related mortality in allo-BMT, and allo-PBSCT was 32.2%, and 36.3% respectively. Disease free survival in acute myeloid leukaemia and acute lymphocytic leukaemia patients were 70.5% and 66.6% respectively at median 3.5 years follow up.

Conclusion: Bone marrow transplantation at Marmara University Hospital has survival data in line with the tranplantation units of most Western countries. The number of transplants is expected to rise in the future provided better conditions are established for maintenance and expansion of the transplant centre.

Key Words: Bone marrow transplantation, allogeneic, autologous, peripheral blood stem cell.

INTRODUCTION

The idea of utilising bone marrow for treatmet of leukaemia and anaemia dates back to the end of the last century. Anaemia as a result of leukaemia was treated by ingestion of bone marrow for the first time in 1891. Intramuscular injection of bone marrow was used afterwards in an attempt to treat the haemolytic anaemia due to malaria in 1937 (1). Intravenous route was attempted for the first time in 1939 in order to treat a case of aplastic anaemia, but it failed (2). Syngeneic bone marrow transplantation was then found to protect the lethally irradiated mice from death at the beginning of 1950's (3). This finding led to a renewed interest in bone marrow transplantation and culminated in the landmark finding in 1957 by Dr. E Donall Thomas, who showed that a large volume of bone marrow can be intravenously infused safely in humans (4).

In 1959, Mathé et al (5), from Paris Gustave Roussy Hospital succeeded in performing an allogeneic bone marrow transplantation to 4 patients, who had been lethally irradiated accidentally. In 1963, the same group reported the first case of allogeneic bone marrow transplantation with prolonged survival. Unfortunately, the patient died of varicella zoster encephalitis during the 20th month post-transplantation (6). In the ensuing years, Mathé et al (7), presented a larger study of 21 allogeneic bone marrow transplantations. Nowadays, bone marrow transplantation is utilised in the treatment of several disorders including haematological malignancies and potentially fatal congenital and acquired haematological illnesses. A new type of transplantation, named peripheral blood stem cell transplantation was introduced in 1989 (8). Granulocyte colony stimulating hormones were utilised in order to mobilise the stem cells from the bone

marrow to the peripheral blood, where they were collected with the aid of an apheresis machine (9, 10). Nowadays, this has permitted bone marrow transplantations to be less burdensome to perform.

Bone marrow transplantation in Turkey was performed for the first time in 1977 by Prof. Dr. Korkut Özerkan from Hacettepe School of Medicine in Ankara. This was followed by transplantations at Gülhane Academy of Medicine and Ankara University School of Medicine. The first bone marrow transplantation in Istanbul was carried out in 1989 at the haematology department of Marmara University School of Medicine. This was followed by a rapid rise in the number of transplantation centres in Turkey, whose number reached 9 during 1996 (11).

The bone marrow transplant centre at Marmara University Hospital was accepted to the European Bone Marrow Transplantation Registry (EBMT) in 1993.

The aim of this study was to retrospectively analyse the bone marrow transplantation data at Marmara University School of Medicine between the foundation year of 1989 and 1998.

METHOD

Fifty six patients, who had allogeneic or autologous transplantation at the haematology department of Marmara University Hospital between 1989 and 1998, were included in the study.

Data, including patients' age, sex, transplant type, tranplanted mononuclear cell number, type of stem cell collection, acute and chronic graft versus host disease and other complications of transplantation, durations for neutrophil and platelet engraftment, and the current status of the patients were recorded from the patients' notes retrospectively.

Ecosoft Inc Microstat statistics programme, and where necessary, Wilcoxon Signed Rank and Chi square tests were employed for statistical analysis. Values of $p<0.05$ was accepted as being statistically significant.

RESULTS

Twenty nine out of 56 patients in the study were male, and 27 were female. The mean age of the patients was 26.01 ± 8.75 years (SE: 1.1799). Table I illustrates the haematological illnesses for which transplantation was performed.

Disease status of the patients at the time of the transplantation was as follows: 18 AML patients in first complete remission (CR), 5 AML patients in second CR, 11 ALL patients in first CR, 2 ALL patients in second CR, 8 CML patients in chronic phase, 2 Hodgkin's disease patients in first remission, 2 Hodgkin's disease refractory patients, 3 Non Hodgkin's disease patients in first remission and 1 multiple myeloma patient in plateau phase.

The mean age of the patients who had an allogeneic bone marrow transplantation was 23.19 ± 6.27 years (SE = 1.1278). Patients who had an allogneeic peripheral blood stem cell transplantation were significantly older (28.54 ± 8.90 years, SE = 2.6845, $p < 0.05$). Virtually all patients with autologous transplantation received peripheral blood stem cells, and they were also significantly older in comparison with the allogeneic bone marrow transplantation patients (30.61 ± 11.42 years, SE = 3.1694, $p<0.05$).

The mean duration for neutrophil engraftment was 17.36 ± 6.69 days (SE = 0.9280), and platelet engraftment was 28.97 ± 12.50 days (SE = 1.9292) for the whole group. There was no relationship between the type of transplantion and the engraftment durations. A patient with aplastic anaemia, who had not had a platelet engraftment, a relapsed acute myeloid leukaemia patient, who had not had neutrophil or platelet engraftment, and patients who died prior to neutrophil or platelet engraftment post-transplant, were excluded from the statistical analysis.

The mean mononuclear cell numbers infused for the whole group was 5.00 ± 3.52 x 10^8 /kg (SE=0.4758). The mononuclear cell numbers infused during the peripheral stem cell transplantations were significantly higher in comparison with those infused during the bone marrow transplantations (Table II).

The commonest complications encountered in the bone marrow tranplant patients were bacterial sepsis, pneumonia, acute and chronic graft versus host disease, poor graft function and graft rejection (Table III).

Transplant related mortality in allogeneic bone marrow transplantion, allogeneic peripheral stem cell transplantation, and autologous peripheral stem cell transplantation was 32.2%, 36.3% and 23.0% respectively. The primary causes of death in decreasing order of frequency were acute graft versus host disease, chronic graft versus host disease, poor graft function, graft rejection, disease relapse, and disease progression (Table IV).

Disease free survival for allogeneic bone marrow transplantion, allogeneic peripheral stem cell transplantation, and autologous peripheral stem cell tranplantation was 61.2%, 54.5% and 30.7% respectively. Despite the fact that disease free survival

for autologous peripheral stem cell tranplantation was the lowest, this was not statistically significant.

There was no difference between allogeneic bone marrow transplantion and allogeneic peripheral stem cell transplantation with respect to the incidence of acute graft versus host disease. However, chronic graft versus host disease was significantly more common in the allogeneic peripheral stem cell transplantion group ($p<0.05$) (Table V).

The commonest disease group, which had been transplanted was the acute leukaemias. Disease free survival in acute myeloid leukaemia and acute lymphocytic leukaemia were 70.5% and 66.6% respectively at median 3.5 years follow up (1.7 - 4.1 years). Table VI illustrates the mortality and survival data with respect to the primary disease prior to transplantation.

The median post-transplantation disease free survival for the whole group was 41.7 months. The median disease free survival for each type of transplantation are not statistically comparable as the follow up periods for each group are different, the longest follow up being the allogeneic bone marrow transplantion group.

Table I. Distribution of patients with respect to disease groups.

DISEASE	Number of Patients	Median age	Sex
AML	23	23.13 ± 6.29	11 F, 12 M
ALL	13	23.16 ± 6.87	7 F, 6 M
CML	8	27.62 ± 8.46	6 F, 2 M
HD	4	26.75 ± 4.42	4 M
NHL	3	22,35,50	1 F, 2 M
AA	2	23,42	1 F, 1 M
Bca	1	38	F
PNH	1	29	F
MM	1	54	M
TOTAL	**56**	**26.01 ± 8.75**	**29 F, 27 M**

AA: Aplastic anaemia, BCa: Breast cancer, AML: Acute myeloid leukaemia, ALL: Acute lymphocytic leukaemia, CML: Chronic myeloid leukaemia, HD: Hodgkin's disease, NHL: Non-Hodgkin's Lymphoma, PNH: paroxysmal nocturnal hemoglobinaemia, MM: Multiple Myeloma F: Female, M: Male

Table II. Mean mononuclear cell numbers infused during bone marrow transplantation

TYPE OF TRANPLANTATION	MEAN MONONUCLEAR CELL NUMBER INFUSED
ALLOGENEIC BMT	$3.1048 \pm 1.3585 \times 10^8$ / kg
ALLOGENEIC PBSCT	$9.0364 \pm 2.7692 \times 10^8$ / kg
AUTOLOGOUS PBSCT	$6.1177 \pm 4.4119 \times 10^8$ / kg
ALLO BMT vs ALLO PBSCT	$p < 0.05$
ALLO BMT vs AUTOLOG	$p < 0.05$
ALLO PBSCT vs AUTOLOG PBSCT	NS (p=0.0355)

NS: Non-significant
BMT: Bone Marrow Transplantation
PBSCT: Peripheral blood stem cell transplantation

Table III. Complications of bone marrow transplantation

COMPLICATIONS	BM %	PBSC %	AUTO %
BACTERIAL SEPSIS or PNEUMONIA	% 41.9	% 81.8	% 69.2
HAEMORRHAGIC CYSTITIS	—	% 18.1	% 7.6
RELAPSE / PROGRESSION	% 6.4	—	% 38.4
ACUTE HEPATITIS B	% 6.4	—	% 7.6
ARDS	—	—	% 7.6
SECONDARY MALIGNANCY	% 3.2	—	—
TTP	% 3.2	—	—
HAEMOLYSIS	% 3.2	—	—
PULMONARY HAEMORRHAGE	% 3.2	—	—
SYSTEMIC FUNGAL INFECTION	% 9.6	% 9.0	—
POOR GRAFT FUNCTION or REJECTION	% 16.1	% 9.0	% 23.0
CEREBRAL MICROEMBOLI	% 3.2	—	—
VENO-OCCLUSIVE DISEASE	—	% 9.0	—
SEPTIC ARTHRITIS	% 3.2	—	—
NEUROPATHY	—	—	% 7.6
DERMATOLYSIS	—	—	% 7.6
CMV INFECTION	% 3.2	% 8.1	—
ACUTE HEPATITIS C	% 3.2	—	—
HERPES SIMPLEX (SYSTEMIC)	% 3.2	—	—
TOXOPLASMOSIS	—	—	% 7.6
ACUTE RENAL FAILURE	—	—	% 7.6
ACUTE GVHD	% 67.7	% 81.8	—
CHRONIC GVHD	% 12.9	% 45.4	—
NO SERIOUS COMPLICATIONS	% 29	% 9.0	% 15.3

ARDS: Adult respiratory distress syndrome
TTP: Thrombotic thrombocytopenic purpura
CMV: Cytomegalovirus
GVHD: Graft versus host disease

Table IV. Causes of mortality post bone marrow transplantation

CAUSES OF MORTALITY	NUMBER AND PERCENTAGE OF THE PATIENTS		
	ALLO-BM	ALLO-PBSC	AUTO
ACUTE GRAFT VERSUS HOST DISEASE	6 (50)	1 (25)	—
CHRONIC GRAFT VERSUS HOST DISEASE	1 (8.3)	1 (25)	—
POOR GRAFT FUNCTION or REJECTION	2 (16.6)	1 (25)	1 (16.6)
RELAPSE or PROGRESSION	2 (16.6)	—	3 (50)
SEPSIS	1 (8.3)	—	—
ACUTE RENAL FAILURE	—	—	1 (16.6)
ACUTE FULMINANT HEPATITIS	—	—	1 (16.6)
VENO-OCLUSIVE DISEASE	—	1 (25)	—
TOTAL	12 (100)	4 (100)	6
TRANSPLANT RELATED MORTALITY	10/31 (32.2)	4/11 (36.3)	3/13

BMT: Bone Marrow Transplantation
PBSCT: Peripheral blood stem cell transplantation

Table V. Comparison of graft versus host disease with respect to the type of allogeneic bone marrow transplantation.

	NUMBER AND PERCENTAGE OF THE PATIENTS	
	ALLO-BM	**ALLO-PBSC**
ACUTE GVHD STAGE 1	11 (35.4)	4 (36.3)
ACUTE GVHD STAGE 2	1 (3.2)	2 (18.1)
ACUTE GVHD STAGE 3	6 (19.3)	1 (9.0)
ACUTE GVHD STAGE 4	3 (9.6)	2 (18.1)
CHRONIC GVHD (LIMITED)	1 (3.2)	4 (36.3)
CHRONIC GVHD (EXTENSIVE)	3 (9.6)	5 (45.4)
TOTAL (ACUTE GVHD)	21 (67.7)	9 (81.8)
TOTAL (CHRONIC GVHD)	4 (12.9)	9 (81.8)
NO EPISODE OF ACUTE GVHD	10 (32.2)	2 (18.1)
NO EPISODE OF CHRONIC GVHD	21 (67.7)	2 (18.1)

GVHD: Graft versus host disease
BMT: Bone Marrow Transplantation
PBSCT: Peripheral blood stem cell transplantation

Table VI. Survival and mortality post bone marrow transplantation with respect to disease groups at median 41.7 months (1.7 - 4.1 years) follow-up.

	NUMBER AND PERCENTAGE OF THE PATIENTS			
	DISEASE FREE SURVIVAL	**RELAPSE**	**ENGRAFTMENT FAILURE**	**MORTALITY**
AML	12 (70.5)	—	1 (5.8)	4 (23.5)
AML - M3	4 (66.6)	—	—	2 (33.3)
ALL	8 (61.5)	1* (7.6)	—	4 (30.7)
CML	3 (37.5)	—	—	5 (62.5)
HD	2 (50.0)	—	—	2 (50.0)
NHL	1 (33.3)	1 (33.3)	—	1 (33.3)
AA	—	—	1	1
Bca	1	—	—	—
PNH	—	1	—	—
MM	—	1	—	—

* The patient was initially transplanted for ALL, but relapsed as AML M1 40 months post-transplant. She died due to sepsis following the second allogeneic transplantation.

AA: Aplastic anaemia, BCa: Breast cancer, AML: Acute myeloid leukaemia,
ALL: Acute lymphocytic leukaemia, CML: Chronic myeloid leukaemia, HD Hodgkin's disease,
NHL: Non-Hodgkin's Lymphoma, PNH: paroxysmal nocturnal hemoglobinaemia, MM: Multiple Myeloma.

DISCUSSION

Five year survival post allogeneic transplant for acute myeloid leukaemia has been reported to be between 50-60% for adults in most transplant centres (12). Five year survival post allogeneic transplant for acute lymphocytic leukaemia varies depending on the prognostic factors, but it is usually between 40-60% for adults in most transplant centres (13).

Overall disease free survival at 3.5 year follow up in our unit is 70.5 % for acute myeloid leukaemia and 66.6% for acute lymphocytic leukaemia. After this stage, only a minority of these patients would be expected to relapse, and therefore 5 year survival will either be similar to or perhaps slightly lower than the above rate. However, it should be borne in mind that the apparent success in our transplantation data could be partly due to selection bias of patients who had better prognostic features.

In line with the transplantation literature, the number of mononuclear cells collected and infused has also increased in our unit after the introduction of peripheral blood stem cell trnasplantation. Currently, the recommended mononuclear cell numbers for allogeneic bone marrow transplantion, allogeneic peripheral stem cell transplantation, and autologous peripheral stem cell transplantation are 2-4 x 10^8, 7-12x10^8 , 5-10 x 10^8 respectively (14). The average number of mononuclear cells infused in our unit for allogeneic bone marrow transplantion, allogeneic peripheral stem cell transplantation, and autologous

peripheral stem cell tranplantation were 3.1 ± 1.3 x10^8, 9.0 ± 2.7 x 10^8 , and 6.11 ± 4.4 x 10^8 respectively. The larger the number of stem cells infused, the shorter the duration of neutropenia and thrombocytopenia, but the more severe the acute and chronic graft versus host disease in allogeneic transplantation (15). This probably explains the high incidence of chronic graft versus host disease following allogeneic peripheral blood stem cell transplantation in our unit. In addition, better recognition of chronic graft versus host disease over the years could have contributed to the reported incidence of this complication. Despite transplant related mortality is higher in allogeneic in comparison with autologous transplantation, overall mortality is similar. This is due to a higher rate of post-transplant relapse rate and death among the autologous transplant group.

The commonest transplant related complications encountered in our unit were infection and graft versus host disease. These are also major factors responsible for transplant related mortality in most bone marrow transplant centres worldwide. Poor graft function and graft rejection in the allogeneic transplants, and relapse of disease post-transplantation in the autologous transplants were other major factors of mortality in our unit.

Currently, bone marrow transplantation is utilized in the treatment of several nonhaematological malignancies, as well as several congenital and acquired haematological diseases. Recently, it was also shown to have a place in the treatment of autoimmune disorders. The number of patients, who are transplanted for non-haematological conditions is expected to rise in the near future.

In conclusion, bone marrow transplantation, in particular allogeneic transplantation, requires a significant amount of expertise, and therefore it is performed by only a limited number of units in Turkey. The tranplantation unit at Marmara University Hospital is one such centre. Fiftysix bone marrow transplantions have been performed ever since its establishment in 1989, with an average annual transplant rate of 7 patients. This is a significant achievement considering the major economic problems encountered in the development and maintenance of such a centre. The number of transplants is expected to rise in the future provided better conditions are established for the maintenance and expansion of the transplant unit.

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