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Allogeneic Stem Cell Transplantation for Hematological Malignancies and Severe Aplastic Anemia: A Single Center Experience from Turkey

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Abstract: Allogeneic stem cell transplantation is used with an increasing frequency in malignant and non-malignant hematological diseases. Although its results are superior to other therapy modalities in certain diseases, transplant related morbidity and mortality remain as a considerable issue. In this report, we describe the results of 97 allogeneic transplantations performed in our center. Transplantations were mostly for hematological malignancies (80 patients) and the remaining were for severe aplastic anemia. GvHD incidence, engraftment rates and times, complications rates we observed were similar with the reported literature. Further efforts should be made for obtaining better results from allogeneic transplantations with improvements in transplant methodology and supportive care.

Key words: Allogeneic stem cell transplantation · hematological malignancy and aplastic anemia

INTRODUCTION

Hematological malignancies still have poor prognosis despite advances in treatment modalities and introduction of new antineoplastic drugs. Allogeneic stem cell transplantation (Allo-SCT) is a treatment option which serves a relatively high disease free survival for most of hematological malignancy patients especially for those having acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML). Allo-SCTs are being performed more frequently and more successfully with improvements in supportive care of the patient [1].

Severe aplastic anemia (SAA) has also a lethal outcome without treatment. In the past 30 years, rates of morbidity and mortality have significantly decreased as a better understanding of the pathophysiology of the disease has led to innovative treatments: Allo-SCT and immunosuppressive treatment [2]. Hematopoietic recovery after transplantation is rapid, complete and usually durable while these results can not be achieved with non-transplant modalities. Additionally, development of clonal diseases such as paroxysmal nocturnal hemoglobinuria (PNH) or myelodysplastic syndrome (MDS) is observed mostly with non-transplant strategies. For these reasons, despite higher procedure related morbidity and mortality, Allo-SCT from a matched sibling is the treatment of choice for suitable patients.

The purpose of the present study is to review the results of allo-SCT's performed for hematological malignancies and aplastic anemia in our center.

MATERIALS AND METHODS

Patients: Between 1996 and 2005, 97 consecutive patients received Allo-SCT at Gulhane Military Medical Academy Hematology Department for the treatment of AML, ALL, CML and SAA. The primary diagnosis was AML in 41, ALL in 18, CML in 12, MDS in 7, multiple myeloma (MM) in 2 and SAA in 17 patients. The median age at transplantation was 24.5 years (range 16-52) for hematological malignancies and 22 years (range 16-48) for aplastic anemia patients. Patient characteristics at transplantation are summarized in Table 1.

Preparative regimen and supportive care: All of the performed transplantations were myeloablative. Preparative regimen protocols were generally cyclophosphamide and total body irradiation (CY+TBI) (60 mg kg^{-1} cyclophosphamide for 2 days and total 12 Gy irradiation for 3 days) in AML and ALL patients, cyclophosphamide and busulphan (CY+BU) (60 mg kg^{-1} cyclophosphamide for 2 days and 16 mg kg^{-1} busulphan per oral for 4 days) in CML patients and CY (50 mg kg^{-1} cyclophosphamide for 4 days) in SAA patients. Prophylaxis for graft versus host disease (GvHD) consisted of methotrexate (MTX) (9 mg m^{-2} on day +1 and 6 mg m^{-2} on days +3 and +6) and cyclosporin A (2.5 mg kg^{-1} iv bid) in all patients except one patient who received MTX and mycophenolate mofetil (MMF) because of drug incompliance. Stem cell source was unmanipulated bone marrow in 61 patients and G-CSF mobilized peripheral stem cells harvested from HLA-matched siblings in 36 patients. Intestinal

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Table 1: Patient characteristics

Characteristic	No. of patients
Sex (M/F)	78/19
Median age (range)	22 (16-52)
Diagnosis	
AML	41
ALL	18
SAA	17
CML	12
MDS	7
MM	2
Status of disease at time of transplantation	
First remission	26
Second or higher remission	29
Stable disease	35
Relapsed or refractory disease	7

Table 2: Transplant characteristics

Characteristic	No. of patients
Stem cell source	
Bone marrow	61
Peripheral blood	36
Conditioning regimen	
CY+TBI	60
CY+BU	18
CY	17
High dose melphalan	2
GvHD prophylaxis	
CsA+MTX	96
MMF+MTX	1

Table 3: Engraftment results

	Malignancy (n = 80)	Aplastic anemia (n = 17)
Infused $CD34^+$ cells ($x10^6$ kg^{-1})	3.28 (0.46-12.1)	2.88 (1.44-7.94)
Neutrophil engraftment (median days)	11.00 (7-40)	11.00 (8-13)
Platelet engraftment (median days)	16.00 (10-54)	16.00 (13-26)
GvHD		
None	16.00	7.00
Grade I	29.00	5.00
Grade II-III	22.00	3.00
Grade IV	4.00	0.00
Febrile episodes (median days)	3.00 (1-30)	3.00 (1-6)
Erythrocyte transfusions	4.00 (2-48)	4.00 (2-10)
Platelet transfusions	6.00 (2-55)	6.00 (1-11)
Peritransplant mortality (n)	13.00 (16.3%)	2.00 (11.8%)

decontamination was with the use of oral gentamicin and ciprofloxacin. Nutritional support was supplied with total parenteral nutrition (TPN) until patients were able to intake adequate amount of food orally. Extended spectrum antibiotics were given in cases of febrile episodes. Cytomegalovirus (CMV) prophylaxis was performed with acyclovir and pneumocystis carinii pneumonia (PCP) prophylaxis with trimetoprim-sulphamethoxazole (TMP-SMX) bid 2 days a week after engraftment. Transplantation characteristics are summarized in Table 2.

Engraftment, relapse and GvHD: Engraftment was defined as the first of three consecutive days with an absolute neutrophil count (ANC of $>0.5x10^9$/L). Platelet recovery was defined as a platelet count of $>20x10^9$/L for 7 days without any transfusions. Relapse was identified by recurrence of a prior cytogenetic abnormality or by return of morphologic evidence of disease. Acute GvHD was diagnosed according to conventional criteria [3]. Graft failure was defined as lack of donor cell engraftment by 28 days post-SCT, or marrow hypoplasia following engraftment and loss of donor cells with or without return of host hematopoiesis.

Statistical analysis: Results were given as median (range). An α level of 0.05 was considered to be statistically significant. Statistical analysis was done with MS Excel 2000 software.

RESULTS

Engraftment: The median number of infused CD34 cells in hematological malignancy patients were $3.28x10^6$ kg^{-1} (0.46-12.1). Neutrophil engraftment was achieved in 71 patients and median time for neutrophil engraftment was 11 days (range 7-40). Platelet engraftment was achieved in 69 patients and median time for platelet engraftment was 16 days (range 10-54). Aplastic anemia patients received bone marrow containing $2.88x10^6$ CD34 cells per kg of body weight. Neutrophil and platelet engraftments were achieved at median 11(8-13) and 16 (13-26) days, respectively. There was a negative correlation between the number of infused CD34+ cells and the median time to neutrophil engraftment ($r = -0.28$, $p<0.05$). There was also a weak negative correlation between the number of infused CD34+ cells and the median time to platelet engraftment ($r = -0.25$) but it was not statistically significant ($p>0.05$).

GvHD: The 11 patients who died without achieving engraftment were not evaluable for development of GVHD. Among the 86 patients evaluable for acute GVHD, 57 developed grades 0-1.25 had grades II-III and 4 had grade IV.

Infectious complications: Febrile episodes were noted in 63 patients and the median duration of febrile episodes were 3 (1-30) days. Antifungal treatment used in 14 patients empirically or for documented fungal infections.

Supportive care: TPN was started if oral intake of the patient falls below 50% of daily requirements and continued until patient was able to receive more than 50% of the daily requirements orally. The median duration of TPN use was median 16 (range 4-32) days. G-CSF was routinely given to the patients and started the day after the infusion of stem cells and discontinued after achieving neutrophil engraftment.

Mortality: Peritransplant mortality (up to 30 days) was 15.5% (n = 15). The causes of death were infection in 8, extensive GvHD in 3, VOD in 2 and intracranial bleeding in 2 patients. Results are summarized in Table 3.

DISCUSSION

Hematological malignancies still have poor outcomes despite all improvements in treatment protocols. Among these therapy modalities, Allo-SCT is the only one promising a high disease free survival chance. Besides its promising results, Allo-SCT procedure has a high rate of transplant-related morbidity and mortality [4]. Improvements in conditioning regimens, GvHD prophylaxis and supportive care of the patients has led to considerable decrease in tranplant complications.

Severe aplastic anemia, like malignancies, is a disease hard to treat and has a poor outcome without treatment. The two major treatment approaches, immunosuppressive treatment and Allo-SCT have comparable results [5]. Because of hematopoietic recovery is more rapid, complete and durable after transplantation and the probability of development of a clonal disease like PNH or MDS is lesser with transplantation, Allo-SCT is the treatment of choice in severe aplastic anemia. Unlike patients with hematological malignancy, the aplastic anemia patients are not heavily treated with intensive chemotherapy protocols, the duration of disease is short and these patients have more controlled transfusions. These factors positively affect the transplant procedure and its undesirable events [6].

It is well known that clinical GVHD is associated with a beneficial graft-versus-tumor effect. Rationale for the use of prophylaxis is the high incidence of 'hyperacute' acute GVHD which approaches 100% and is associated with overwhelming morbidity in the absence of prophylaxis. Many strategies of GVHD prophylaxis have been explored, but the most common is the combination of CSP with MTX given on days 1, 3, 6 and 11 after allogeneic transplant [7]. Nowadays, its dose and moreover its existence in protocols are debated. The addition of MTX to cyclosporin A (CsA) leads to more extensive mucositis and in conclusion more complications. Replacing MTX with other agents such as MMF does not deteriote GvHD control and when taking into account the graft versus leukemia effect of grade I and II GvHD, it might be more appropriate to remove MTX from protocols [8]. We use mini dose MTX, that is 9 mg m^{-2} on day +1 and 6 mg m^{-2} on days +3 and +6, along with CsA. Although we use MTX in reduced doses and omit the dose on day +11, mucositis and its complications are frequent in our patients, so we generally need to use TPN in Allo-SCT patients.

The optimum number of infused $CD34^+$ cells to achieve a complete hematopoietic recovery is accepted to be more than $2.0x10^6$ kg^{-1} of body weight. The number of infused CD34+ cells in our transplantations are in accordance with general practice and the median times to neutrophil and platelet engraftments we achieved are in accordance with literature [9].

Finally, the results of allo-SCT's performed by our center are quite successful when compared with the results of other treatment modalities suggested for hematological malignancies and aplastic anemia. It is important to reevaluate and improve the methodology and factors that lead to complications for obtaining better results from allo-SCT.

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