Chronic Graft versus Host Disease after Allogeneic Bone Marrow Transplantation; An Analysis of Incidence and Risk Factors.

Ghavamzadeh A, Alimoghaddam K, Bahar B, Foroughi F.

Hematology- Oncology and BMT Research Center, Shariati Hospital, Tehran, Iran.

Background: Chronic graft versus host disease (cGVHD) is one of the most serious potential complications of allogeneic bone marrow transplantation.
Study design and method: We analyzed the incidence of cGVHD and its associated risk factors in a group of 161 Iranian recipients of HLA-identical sibling transplants, with at least 90 days post-transplantation survival. In the majority of cases (n=73), cGVHD occurred in the first year after the transplant (median 273 days). The actual probability of cGVHD within 1 year was 45.3±7% (CI 95%).
Results: In a univariate analysis, the most important risk factor was the type of transplant. Peripheral blood stem cell transplants (PBSCT) showed a significant increase in cGVHD compared with bone marrow transplants (BMT) (RR=2.34, p<0.001). In addition, male recipients were at a greater risk than female recipients (RR=2.08, p=0.004). Other risk factors were the presence of prior acute GVHD (RR=2.37, p=0.04) and the previous acute GVHD grade (p=0.03); The probabilities of cGVHD in patients with grade 0, I, II, III, IV acute GVHD were 24%, 44.7%, 42.6%, 56.8%, 64.3%, respectively.
Conclusion: In a multivariate analysis, the only independent predictive factors for the development of cGVHD were the type of transplant (PBSC>BM, p<0.001) and male recipient (p=0.005). The survival rate was 88.8% and there was no significant difference in the probability of survival between BPSCT vs BMT (93.8% vs 86.6%, p=0.5).

Keywords: Bone Marrow Transplantation, Chronic GVHD, and Complications

Allogeneic bone marrow transplantation from HLA-identical related donors has been established as the treatment of choice for various hematologic, neoplastic, and congenital disorders.[1] However, cGVHD remains the most devastating complication of this procedure and is mediated by donor T cells.[2,3] Previous reports have described certain and probable risk factors associated with the development of cGVHD.[4,8]
In this study we evaluated the factors that may affect the risk of chronic GVHD development in patients after marrow transplantation.

Patients and Method:
The study was performed on a group of patients who underwent bone marrow transplantation between June, 1990 and December, 2000 in the Hematology-Oncology & BMT Research Center of Tehran University of Medical Sciences.
We reviewed the clinical records of 195 consecutive patients receiving HLA-identical sibling allogeneic transplants. Among this population, 33 patients expired within the first 3 months after the transplant, and, therefore, were excluded from the study.
The main clinical characteristics of the patients are summarized in Table1. Disease status was categorized into seven groups: Thalassemia(89), CML(25), AML(18), ALL(5), Aplastic anemia(16), Fanconi anemia(3), and others(5). There were 90 males and 71 females with an average age of 9 years (ranging from 2.5 to 40 years). Donors were fully HLA-matched siblings with an average age of 13 years (ranging from 2.5 to 42). There were 79 males and 82 females with a donor-recipient sex mismatch in 72 cases. GVHD prophylaxis regimens consisted of CysA alone, and CysA in combination with MTX. All patients were followed up for at least 1 year until the second BMT, occurrence of cGVHD, relapse or death.

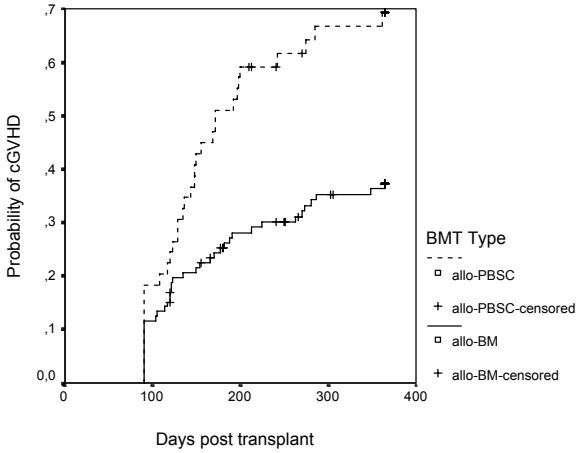

Figure 1: Probability of chronic GVHD related to the type of transplant

Acute GVHD was identified clinically and four grades were assigned using modified Seattle criteria.[9]
Diagnosis of clinical cGVHD and its classification into clinically limited or clinically extensive diseases was performed using Seattle criteria.[12,13] Chronic GVHD was considered as de novo if patients had no prior

aGVHD; quiescent if it reapeared after resolution from previous aGVHD; and progressive when it appeared as a continuation of the previous aGVHD.[6]

Statistical analysis:
The incidence of cGVHD was determined using the Kaplan-Meier product limit method, with a 95% confidence interval.

Tatable 1: Patients characteristics

	N	%
Disease Category		
Thalassemia	89	55.3
AML	18	1.2
ALL	5	3.1
CML	25	15.1
Aplastic Anemia	16	9.9
Fanconi Anemia	3	1.9
Others	5	3.1
Age: Median (range), yr		
Recipients	9 (2.5-40)	
Donors	13 (2.5-42)	
Sex		
Recipients male	90	55.9
female	71	44.1
Donors male	79	49.1
female	71	50.9
Donor: Recipient		
Match	89	55.3
mismatch	72	44.7
female: male	42	26.1
Transplant type		
BM	112	69.6
PBSC	49	30.4
GVHD Prophylaxis		
CsA	89	55.2
CsA+ MTX	72	44.8
GVHD Prophylaxis		
CsA	89	89
CsA+ MTX	72	44.8
Infused cell number:		
Median (range) $n\times10^8$/kg	4.86(1.76-27)	

A univariate model was fit in addition to a multivariate model. Analysis of variables which were accounted as potential predictive factors for chronic GVHD was performed with the Cox's proportional hazard method. Statistical analysis were done using SPSS 10.0 statistical software.

Results:
Out of 195 patients who underwent HLA-matched sibling allogeneic marrow transplantation, 161 survived beyond day 100 and were considered eligible to develop chronic GVHD.
Seventy-three patients developed clinical chronic GVHD, representing 45.3%±10 (CI 95%) by Kaplan-Meier projection. The average time for the diagnosis cGVHD was 273 days (ranging from 100 to 365 days). Only three patients developed cGVHD later than 1 year after transplantation (day 395, 456, and 500). Chronic GVHD manifestations are summarized in table 2.

Clinical extensive cGVHD occurred in 46 patients (63.1%) compared with 27 patients (36.9%) who experienced limited form. The majority of cases (76.7%) developed cGVHD after a clinical resolution of prior aGVHD, while 16.4% sustained active aGVHD and only 6.8% experienced de novo onset. Grade I to VI aGVHD occurred in 84.5% (n=136) patients. The most involved organs were the liver (67.6%), skin (66.2%) and mouth (45.1%) respectively. The involvement of various organs with cGVHD is displayed in table 2.

Risk factors for cGVHD:
The following variables were incorporated into the univariate analysis in order to determine their influence on the occurrence of cGVHD: recipient and donor age, recipient and donor sex, recipient-donor sex match, female donor- male recipient, disease category, type of transplant, type of GVHD prophylaxis, marrow cell number, and prior aGVHD. The most important predictive factor for developing cGVHD was the type of transplant; 67.3% (33/49) of patients who underwent allogeneic peripheral blood stem cell transplant (allo-PBT) developed cGVHD compared with 35.7% (40/112) of those who underwent allogeneic bone marrow transplant (allo-BMT) [RR=2.34 (CI 95%: 1.47-3.72), p<0.001]. In addition, the risk of developing clinical extensive cGVHD within one year was 5.2 times higher among PBT recipients compared to BMT recipients (p<0.001). However, in the limited form, no significant difference was found between the types of transplants. In addition, male patients showed a higher risk of developing cGVHD compared female recipients [RR=2.08 (CI 95%:1.27-7.42) p=0.004]. Another risk factor was the number of infused cells [RR=1.08 per 10^8/kg (CI 95%: 1.03-1.15) p=0.001].

Table 2: Chronic GVHD manifestations

	N	%
Onset		
- Progressive	12	16.4
- Quiescent	56	76.7
- De novo	5	6.8
Grade		
- Limited	27	36.9
- Extensive	46	63.1
Organ involvement		
- Liver	48	67.6
- Skin	47	66.2
- Mouth	32	45.1
- Eye	26	36.6
- GI	13	18.3
- Lung	6	6.5
- Joint	2	2.7

Subsequently the relationship of prior aGVHD, as the strongest predictor of cGVHD in previous studies, was examined.[5,7] Most notably, at our center there was a fair relationship between the development of cGVHD and prior aGVHD [RR=2.37 (CI 95%: 1.02-5.47),

p=0.04]. We also evaluated the incidence of cGVHD in relation to the severity of the preceding aGVHD; while there was an incremental risk of developing cGVHD in patients with grade III and IV compared with grade 0 aGVHD (p=0.02, p=0.005 respectively), no significant increase was seen in grade I and II.
The probabilities of cGVHD were 24%, 45%, 43%, 57% and 64% for patients with grade 0, I, II, III, and IV aGVHD, respectively.
None of the other variables were associated with the development of cGVHD in the univariate analysis.
In the multivariate analysis, using Cox's proportional hazard method, the only factors independently associated with the development of cGVHD, were the type of transplant (PBT>BMT, RR=3.42, p<0.001) and male patients [RR=2.03, p=0.005]. None of the other factors identified in the univariate analysis, were shown to be independent predictive values.

Outcome:
By the end of the study, 18 patients had already died, five from relapse, three from infection, and five from cGVHD. The probabilities of survival and relapse-free survival were 88.8% and 83.2%, respectively. There was no significant difference in the probability of survival and relapse free survival between allo-PBT and allo-BMT (94% vs 87% and 92% vs 80%, p=0.57 and p=0.37, respectively).

Discussion:
The incidence of cGVHD was 30-60% in previous studies.[2,3] Our patients showed an acceptable incidence of cGVHD, (45%), after allogeneic marrow transplantation. Unfortunately, since we did not perform biopsy for a pathological study, cGVHD diagnosis was merrely based on clinical manifestations and the time of onset after transplantation; consequently our results might be overestimated.
Prior acute GVHD was considered as the most important predictor of cGVHD in previous reports; but in this study, there was only a fair relationship between aGVHD and development of chronic GVHD.
This data suggests that allo-PBT is the stronger predictor of cGVHD when compared to allo-BMT. Other researchers have also reported the same results.[12,16]
Although the incidence and severity of chronic GVHD was greater among patients who underwent allo-PBT than allo-BMT, . overall survival did not differ significantly between two groups (94% vs 87%). Therefore, since using allo-PBT is safer and needs no hospitalization, no general anesthesia for the donor and neutrophil and platelet engraftment is faster,[16,18] this method might be of more advantage than conventional marrow transplantation. Currently, it is unclear whether the advantages of using allo-PBT outweigh the disadvantages of frequent cGVHD, so, more controlled randomized trials will be required to provide further evidence.
Another risk factor related to an incremental risk of cGVHD was male recipients. However, we did not find any evidence showing its predictivity in other reports. Maybe it can be explained by immunologic antigens on the Y chromosome.
In addition, increasing patient's age was considered one of the predictors of developing cGVHD in previous reports. In our study, however, it just increased the incidence of extensive cGVHD. In other words, it might suggest that the severity of cGVHD is rising with increasing patient's age.
We did not find any relationship between some factors such as the donor's age, donor and recipient's sex mismatch, female donor for male recipient and type of GVHD prophylaxis and chronic GVHD. Finally, the identification of patients vulnerable to the development of cGVHD might provide several benefits in planning and assessing clinical trials of cGVHD prophylaxis and treatment.

References:
1- Tabbara IA. Allogeneic bone marrow transplantation. SMJ 1996; 9: 1-27.
2- Atkinson K. Chronic graft-versus-host disease. Bone Marrow Transplant 1990; 5: 69-82.
3- Sullivan KM, Agura E, Anasetti C et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol 1991; 28: 250-259.
4- Gale RP, Bortin MM, Bekkum DW, et al. Risk factors for acute graft-versus-host disease.Br J Haematol 1987; 67:397-406
-5 Atkinson K, Horowitz MM, Gale RP et al. Risk factors for chronic graft-versus-host disease after HLA-identical sibling bone marrow transplantation. Blood 1990; 75: 2459-2464.
6- Ochs LA, Miller WJ, Filipovich AH et al. Predictive factors for chronic graft-versus-host disease after histocompatible sibling donor bone marrow transplantation. Bone Marrow Transplant 1994; 13: 455-460.
7- Gaziev D, Polchi P, Galimberti M et al. Graft-versus-host disease after bone marrow transplantation for thalassemia: an analysis of incidence and risk factors. Transplantation 1997; 27: 854-60.
8- Niederwieser D, Pepe M, Storb R et al. Factors predicting chronic graft-versus-host disease and survival after marrow transplantation for aplastic anemia. Bone Marrow Transplant 1989;2: 151-156.
9- Glucksberg H, Storb R, Fefer A et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. Transplantation 1974; 18: 295-304.
10- Atkinson K, Horowitz MM, Gale RP et al. Consensus among bone marrow transplanters for diagnosis,grading and treatment of chronic graft-versus-host disease. Bone Marrow Transplant 1989; 4: 247-254.
11- Shulman HM, Sullivan KM, Weiden PL et al. Chronic graft-versus-host syndrome in men. A long-

term clinicopathologic study of 20 Seattle patients. Am J Med 1980; 69: 204-217.
12- Bensinger WI, Clift R, Martin P et al. Allorgeneic peripheral blood stem cell transplantation in patients with advanced hematologic malignancies: A retrospective comparison with marrow transplantation. Blood 1996; 88: 2794-2800.
13- Majolino I, Saglio G, Scime R et al. High incidence of chronic graft-versus-host disease after primary allogeneic peripheral blood stem cell transplantation in patients with hematologic malignancies. Bone Marrow Transplant 1996; 17: 555- 560.
14- Miflin G, Russell NH, Hutchinson RM et al. Allogeneic peripheral blood stem cell transplantation for haematological malignancies-an analysis of kinetics of engraftment and GVHD risk. Bone Marrow Transplant 1997; 19: 9-13.
15- Schmitz N, Bacigalupo A, Labopin M et al. Transplantation of peripheral blood progenitor cells from HLA-identical sibling donors. Br J Haematol 1996; 95: 715- 23.
16- Anderlini P, Korbling M. The use of mobilized peripheral blood stem cell from normal donors for allografting. Stem Cells 1997; 15: 9-17.
17- Bjerke J, Bensinger W, Anasettic C et al. Circulating hematopoietic progenitor cell transplantation from unrelated donors: Is this the future? Progressi in Ematologia Clinica 1996; 15: 135-141.
18- Solano C, Martinez C, Brunet S et al. Chronic graft-versus-host disease after allogeneic peripheral blood progenitor cell or bone marrow transplantation from matched related donors. A case-control study. Bone Marrow Transplant 1996; 95: 715-23.