THALASSEMIA: INCIDENCE AND PREDITICIVE FACTORS FOR CHRONIC GVHD AFTER HLA-IDENTICAL SIBLING MARROW TRANSPLANTATION

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Abstract: ***Allogeneic bone marrow transplantation is the only definite cure in thalassemia and its most important complication is chronic graft-versus-host disease (cGVHD). We analysed the incidence of cGVHD and its associated risk factors in a group of 89 Iranian thalassemic patients of HLA-identical sibling transplants surviving at least 90 days after transplantation.***

In the majority of cases (39) cGVHD occurred in the first year following transplant (median 271 days). Actuarial probability of cGVHD in 1 year was 43.8±10% (95% CI). In univariate analysis, the most important risk factor was the type of transplant: 78.9% (15/19) of patients who underwent peripheral blood stem cell transplant developed cGVHD compared with only 34.3% (24/70) of those who underwent bone marrow transplant (RR= 3.65 p<0.001). Other risk factors were infused cell number (RR= 1.09 p= 0.001) and prior acute cGVHD grade (p= 0.02); the probabilities of cGVHD in patients with grade 0, I, II, III-IV acute cGVHD were 17.6%, 36.4%, 46.4% and 68.2%, respectively. In multivariate analysis, the only independent predictive factor for development of cGVHD was the type of transplant (BPT> BM p<0.001). The probability of survival was 93.3% and there was no significant difference in the probability of survival between PBT vs BMT (94% vs 92% p= 0.6).

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INTRODUCTION

Allogeneic marrow transplantation from HLA-identical related donors is currently the only rational therapeutic modality for patients with homozygous beta-thalassemia (1-4).

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However, chronic cGVHD remains as the most devastating complication of this procedure which is mediated by donor T cells (5,6). Previous reports have described certain and probable risk factors associated with the development of chronic GVHD (7-10).

In this study we evaluated the factors that might affect the risk of chronic GVHD in thalassemia after marrow transplantation.

PATAIENTS AND METHODS

The study centered on a group of thalassemic patients who underwent bone marrow transplantation between June 1990 and December 2000 in Hematology-Oncology-BMT Research Center in Shariaty Hospital, Iran.

We reviewed the clinical records of 103 consecutive thalassemic patients receiving HLA-identical sibling allogeneic transplant. Among this population, 14 patients died before 3 months after transplant and so were excluded from the study.

The main clinical characteristics of the patients are summarized in table 1. Disease status was categorized into three classes using established criteria (4), 22 patients were in class I, 43 were in class II and 24 were in class III. There were 47 males and 42 females with a median age of 5.5 years (range 2.5-17 years). Donors were fully HLA-matched siblings with a median age of 10 years (range 2.5-28). There were 39 males and 50 females with a donor-recipient sex mismatch in 43 cases. GVHD prophylaxis regimens were Cys A alone, Cyclosporine A (Cys A) in combination with methotrexate (MTX) or Cys A plus mycophenlate (MP). All patients were observed until death, relapse, second BMT or occurance of chronic GVHD for a minimum 1 year.

Acute GVHD was identified clinically and four grades were assigned using published criteria (11).

Diagnosis of clinical chronic GVHD and its classification into clinical limited or clinical exten-

sive disease was performed using Seattle criteria (12-13). Chronic GVHD was considered as de novo if they had no prior acute GVHD; quiescent if it had reappeared after resolution from previous acute GVHD; and progressive when it had appeared as a continuation of previous acute GVHD (8).

Statistical analysis: The incidence of chronic GVHD was determined using Kaplan-Meier product limit method with 95% confidence limits. A univariable model was fit in addition to a multivariate model. Analysis of variables that were potential predictive factors for chronic GVHD was performed with the Cox's proportional hazard method. Statistical analyses were done using SPSS statistical software.

RESULTS

Among 103 patients who underwent HLA-matched sibling allogeneic marrow transplantation, 89 were alive beyond day 90 and were considered eligible to develop chronic GVHD.

Thirty-nine patients developed clinical chronic GVHD, representing 43.8%±10 (CI 95%) by Kaplan-Meier projection. The median time of diagnosis chronic GVHD was 281 days (range 90-365 days). Only two patients developed chronic GVHD after 1 year post-transplant (13 and 17 months). Chronic GVHD manifestations are summarized in table 2. Clinical extensive chronic GVHD occurred in 17 patients (43.5%) compared with 22 patients (56.5%) who experienced limited form. The majority of cases (74.3%) developed chronic GVHD after a clinical resolution of prior acute GVHD, while 17.9% progressed from active acute GVHD and only 7% experienced de novo onset. Acute GVHD of grade I-IV occurred in 80.9% (n= 72) patients, 24.7% had grade I, 31.5% grade II, 15.7% grade III, and 9% grade IV. The most involved organs were liver (69%), skin (56.4%) and mouth (30%), respectively. The involvement of various organs with chronic GVHD is displayed in table 2.

The probabilities of chronic GVHD were 54.5%, 37.2% and 45.8% for persons with class I, II, and III thalassemia, respectively.

The following variables were included into the univariate analysis in order to determine their influence in the occurance of chronic GVHD: recipient and donor age, recipient and donor sex, recipient: donor sex match, female donor: male recipient, type of transplant, type of GVHD prophylaxis, marrow cell number and prior acute GVHD. The most important predictive factor for developing chronic GVHD was the type of transplant: 78.9% (15/19) of patients who underwent allogenic peripheral blood stem cell transplant (allo-PBT) developed chronic GVHD compared with only 34.3% (24/70) of those who underwent allogeneic bone marrow transplant (allo-BMT) [RR= 3.65 (1.88-7.08) p<0.001]. In addition, for clinical extensive chronic GVHD, the hazard of being developing within one year was 17.9 times higher among PB recipients than BM recipients (p<0.001), however, there was no significant difference in limited form between the type of transplants. Another risk factor for developing chronic GVHD was infused cell number [RR= 1.09 (1.03-1.15) p= 0.001].

We next examined the relationship of prior acute GVHD as the strongest predictor of chronic GVHD in previous works (7,9). Importantly, at our center there was a fair relationship between development of chronic GVHD and prior acute GVHD [RR= 3.2 (0.98-10.4) p= 0.05]. We also evaluated incidence of chronic GVHD in relation to the severity of preceding acute GVHD; while there was an incremental risk of developing chronic GVHD in patients with grade III and IV compared with grade 0 of acute GVHD (RR= 5.43 p= 0.01, RR= 5.57 p= 0.01, respectively), no significant increase was seen in grade I and II.

The probabilities of chronic GVHD were 17.6%, 36.4%, 46.4% and 68.2% for patients with grade 0, I, II, and III-IV acute GVHD, respectively.

Finally, there was no statistical difference between different classes of thalassemia (p= 0.27). None of the other variables were associated with development of chronic GVHD in univariate analysis.

In multivariate analysis, using cox's proportional hazard method, the only factor which was independently associated with development of chronic GVHD, was the type of transplant (PBT>BMT, RR= 3.42 p<0.001). None of the other factors identified in univariate analysis, were shown to be independent predictive value.

At the end of the study, 6 patients had died (3: rejection, 2: infection 1: chronic GVHD) one from chronic GVHD. The probabilities of survival and rejection free survival were 93.3±5% and 83.5±7%, respectively. There was no significant difference in the probability of survival and rejection free survival between allo-PBT and allo-BMT (94% vs 92% and 89% vs 81% respectively). Finally, the probabilities of survival and rejection free survival were 96% and 86% in class I, 98% and 86% in class II, and 83% and 75% in class III patients.

DISCUSSION

Known risk factors for developing chronic GVHD after marrow transplantation in thalassemic patients are: prior acute GVHD and its grade, female donor sex, use of alloimmune female donors for male recipients and GVHD prophylaxis with Cys A/MP or MTX/MP (9).

Table 1. Patient characteristics

	n (%)
Thalassemia class	
1	22(24.7)
2	43 (48.3)
3	24 (27)
Age: Median (range), yr	
Recipient	5.5 (2.5-17)
Donor	10 (2.5-28)
Sex:	
Recipient	
Male	47 (52.8)
Female	42 (47.2)
Donor	
Male	39 (43.8)
Female	56.2)
Donor: Recipient	
Match	46 (51.7)
Mismatch	43 (48.3)
Female: male	26 (29.2)
Type of transplant	
BM[a]	70 (78.7)
PBSC[b]	19 (21.3)
GVHD prophylaxis	
Cys A	37 (41.6)
Cys A+MTX	51 (57.3)
Cys A+MP	1 (1.1)
Infused cell number: median (range)	
n 10^8/kg	5.1 (1.76-27)

a Bone marrow
b Peripheral blood stem cell

The incidence of chronic GVHD in our patients was higher than previous reports (9). What is the reason for this difference? It may be due to differences in GVHD prophylaxis, age, definition of chronic GVHD or unknown reasons. In the present study, the high incidence of chronic GVHD does not seem to be influenced by a high occurance of previous acute GVHD as the strongest predictor of chronic GVHD in previous works (7,9). We assume that the reason is the use of allogeneic peripheral blood stem cell transplantation (allo-PBT) in some of our patients. This data suggests that using allo-PBT is the strongest predictor of chronic GVHD compared to allogeneic bone marrow transplantation (allo-BMT). If we subtract PBSC transplanted patients from our patients, the risk of chronic GVHD drops to 34%. Other groups have also reported a high incidence of chronic GVHD after allo-PBT (14-17).

The question is, can allo-PBT be accepted as the method of choice for transplantation in thalassemia or not? Our findings suggest that although the incidence and severity of chronic GVHD were greater among patients who underwent allo-PBT than patients who underwent allo-BMT, overall survival did not differ significantly between two groups (94% in allo-PBT vs 92% in allo-BMT). So since using allo-PBT is safer and needs no admission in hospital and no general anesthesia for donor and neutrophil and platelet engrafment is faster (18-20), this method may be have more advantageous than conventional marrow transplantation. However, although chronic GVHD was the primary cause of death in only one case in the allo-PBT group, and while it had no negative impact on overall survival, it was a major cause of morbidity. Currently, it is unclear whether the advantages of using allo-PBT outweight the disadvantage of frequent chronic GVHD.

Therefore at present, allo-PBT should be performed with caution in thalassemia and ongoing controlled randomized trials will be required to provide further evidence.

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Table 2. Clinical manifestations of chronic GVHD (n= 89)

	n (%)
Time of onset	
Median 271 days (range 90-365)	
Chronic GVHD	
Limited	22 (56.5)
Extensive	17 (43.5)
Onset	
Progressive	7 (17.9)
Quiescent	29 (74.3)
De novo	3 (7)
Affected organs	
Liver	27 (69)
Skin	22 (56.4)
Mouth	12 (30)
Eye	8 (20)
GI	2 (5)
Lung	1 (2)
joints	0 (0)

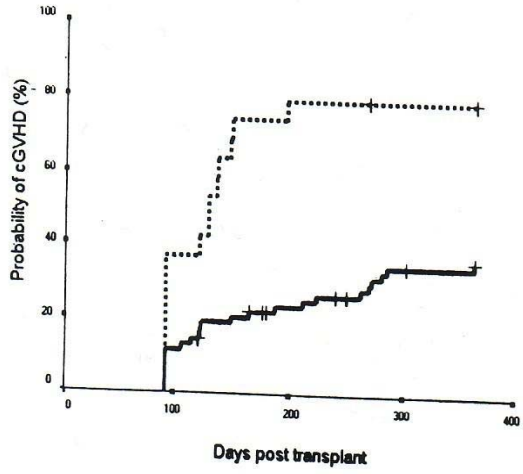

Fig. 1. Probability of chronic GVHD related to the type of transplant

REFERENCES

1. Thomas ED, Buckner CD, Sanders JE et al. Marrow transplantation for thalassemia. Lancet 1982, 2: 227.

2. Lucarelli G, Galimberti M, Polchi P et al. Bone marrow transplantation in patients with thalassemia. N Engl J Med 1990, 322: 417-421.

3. Weatherall D, Bone marrow transplantation for thalassemia and other inherited disorders of hemoglobin. Blood 1992, 80: 1379-1381.

4. Lucarelli G, Clift RA, Galimberti M et al. Bone marrow transplantation in adult thalassemic patients. Blood 1999, 93: 1164-1167.

5. Atkinson K, Chronic graft-versus-host disease. Bone Marrow transplant 1990, 5: 69-82.

6. 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.

7. Atkinson K, Horowitz MM, Gale RP et al. Risk factors for chronic graft-versus-host disease after HLA-identical sibling bone marrow transplantation. Blood 1991, 75: 2459-2464.

8. 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.

9. 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.

10. Niederwieser D, Pepe M, Storb R et al. Factors predicting chronic graft-versus-host disease and survival after marrow transplantation for aplastic anemia. Disease and survival after marrow transplantation for aplastic anemia. Bone Marrow Transplant 1989, 2: 151-156.

11. 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.

12. 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.

13. 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.

14. Bensinger WI, Clift R, Martin P et al. Allogenic peripheral blood stem cell transplantation in patients with advanced hematologic malignancies: A retrospective comparison with marrow transplant-tation. Blood 1996, 88: 2794-2800.

15. 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.

16. Miflin G, Russell NH, Hutchinson RM et al. Allogenic peripheral blood stem cell transplantation for hematological malignancies an analysis of kinetics of engrafment and GVHD risk. Bone marrow transplant 1997, 19: 9-13.

17. Schmitz N, Bacigalupo A, Labopin M et al. Transplantation of peripheral blood progenitor cells from HLA-identical sibling donors. Br Hematol 1996, 95: 715-23.

18. Anderlini P, Korbling M. The use of mobilized peripheral blood stem cell from normal donors for allografting. Stem Cells 1997, 15: 9-17.

19. Bjerke J, Bensinger W, Anasettic C et al. Circulating hematopoietic progenitor cell transplantation from unrelated donors: Is this the future? Progress in hematologia clinica 1996, 15: 135-141.

20. 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. Bonemarrow transplant 1996, 95: 715-23.