Acute graft-versus-host disease in thalassaemic marrow transplantation with low-dose antithymocyte globulin

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حالات الرفض الفوري للطّعم بعد غرس نقي العظم في مرضى الثلاسيمية بعد إعطائهم جرعة منخفضة من الغلوبلين المضاد للخلايا التوتية

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خلاصة: أجريت في وحدتنا عمليات غرس في واحد وعشرين مريضاً بالتلاسيمية من الصنفين الثاني والثالث (حيث كان مرضى الصنف الثاني يعانون من تضخم بالكبد أوتليُّف بابي، بينما كان مرضى الصنف الثالث يعانون من الحالتين معاً). وقد أعطينا المرضى بوسولفان (15 مغ/كغ) وسيكلوفسفاميد (200 مغ/كغ). أما الأدوية الواقية من رفض الثوي للطعم فكانت سيكلوسبورين وبردنيزولون وجرعة منخفضة من الغلوبلين المضاد للخلايا التوتية. وتبيَّن من بيانات مرضانا أن معدل رفض الأثوياء للطعم كان منخفضاً بعد عمليات الغرس. ونحن نزكي هذا المقرَّر الدوائي باعتباره معالجة مقبولة لمرضى التلاسيمية الذين يجرى لهم غرس لنقي عظمي من مصدر مخالف، إذ هي طريقة مأمونة بصرف ا(حيث كان مرضى الصنف الثاني يعانون من تضخم بالكبد أوتليُّف بابي، بينما كان مرضى الصنف الثالث يعانون لنظر عن صنف حالة المريض.

ABSTRACT Our unit performed transplantations on 21 classes II and III thalassaemic patients (class II patients had either hepatomegaly or portal fibrosis and class III patients had both). We used busulfan (15 mg/kg) and cyclophosphamide (200 mg/kg). Graft-versus-host disease (GVHD) prophylaxis was cyclosporin, prednisolone and low-dose antithymocyte globulin. Our patient data showed a low incidence of acute GVHD following transplantation. We offer this regimen as an acceptable therapy for thalassaemic patients undergoing allogeneic marrow transplantation as a safe clinical procedure, irrespective of the class of patient.

Réaction du greffon contre l'hôte dans la greffe de moelle osseuse chez des patients thalassémiques avec administration d'une globuline antithymocytes à faible dose

RESUME Notre service a effectué des transplantations chez 21 patients thalassémiques de classe II et III (les patients de classe II avaient soit une hépatomégalie soit une fibrose porte et les patients de classe III avaient les deux). Nous avons utilisé le busulfan (15 mg/kg) et la cyclophosphamide (200 mg/kg). La prophylaxie pour la réaction du greffon contre l'hôte comportait la ciclosporine, la prednisolone et l'administration d'une globuline antithymocytes à faible dose. Les données relatives à nos patients ont indiqué une faible incidence de la réaction du greffon contre l'hôte (rejet aigu) après une transplantation. Nous proposons ce schéma thérapeutique comme traitement acceptable pour les patients thalassémiques subissant une greffe de moelle osseuse allogénique en tant que procédure clinique sans danger, quelle que soit de la classe des patients.

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Introduction

Allogeneic marrow transplantation is a principal means of treating thalassaemic patients who have human lymphocyte antigen- (HLA-) identical donors. Since Thomas and Lucarrelli began treating patients two decades ago [*1–3*], many of those with the disease have been cured, and have been able to enjoy a normal life expectancy. However, underlying problems of the disease as a result of iron overload and consequent organ damage, conditioning toxicity, graft-versus-host disease (GVHD) and graft failure are major limiting factors in the success of the procedure [*3,4*]. Here we describe modified conditioning and GVHD prophylaxis for transplantation in thalassaemic patients with HLA-identical donors, with acceptable results.

Patients and methods

Between 1994 and 1996, 21 thalassaemic patients underwent allogeneic marrow transplantation from HLA-identical donors in our unit. The patients' ages ranged from 5 years to 16 years. The conditioning regimen used was busulfan (15 mg/kg) and cyclophosphamide (200 mg/kg). Concomitant acute GVHD prophylaxis consisted of the following:

- prednisolone 0.5 mg/kg, from 1 day prior to until 21 days after transplantation;
- ciclosporin (Sandimmune) 5 mg/kg, delivered intravenously 2 days prior to until 6 days after transplantation, followed by 12.5 mg/kg per day delivered orally, for 2 months, tapering gradually (5% weekly) for up to a year after transplantation;
- antithymocyte globulin (Pasteur, Merieux, Connaught), using a modified dosage of 10 mg/kg, 2 days before, 1 day before, 1 day after and 2 days after transplantation.

Methotrexate was not used because of the possibility of liver and gastrointestinal toxicity. All patients received prophylactic antibiotics parenterally and orally, and acyclovir (Zovirax), at dosages of 15 mg/kg per day beginning 1 day before transplantation up to 180 days after transplantation, as well as intravenous immunoglobulin (Sandoglobulin), dosage 500 mg/kg per day, from 1 day before transplantation and every 3 weeks thereafter, up to day-180 after marrow transplantation.

Engraftment was noted with rising haemoglobin and low fetal haemoglobin levels. Acceptable neutrophil, haemoglobin and platelet levels were achieved 4–5 weeks after transplantation, during which patients were completely isolated (with filtered air). Antibiotics used during this period included: amikacin sulfate (Amikin), dosage 15 mg/kg per day; carbenicillin sodium (Pyopen), 400 mg/kg per day; ceftazidime (Fortum), 100 mg/kg per day; and vancomycin hydrochloride (Vancocin), 15 mg/kg per day. All of the antibiotics were given during periods when the patients were suffering severe neutropenia and fever. All blood products were unfiltered for leukocytes and irradiated with cobalt 60 (3000 rads) for up to 6 months after marrow transplantation.

Results

All the patients underwent transplantation with the fixed conditioning regimen and acute GVHD prophylaxis. The first two deaths were attributable to non-transplant-related factors. The third death was due to an HLA mismatch transplantation, which resulted in stage IV acute GVHD and sepsis. Only one patient, a 16-year-old girl, de-

veloped severe GVHD (post-stage III acute GVHD). Transient acute GVHD stage I developed in two other patients. In 25% of the patients, mild, reversible haemorrhagic cystitis was present.

All patients experienced transient fever and chills of 1 week duration following antithymocyte globulin. Unexplained fever, simulating sepsis, was controlled with supportive care. Rejection, in three patients,

Table 1 **Outcomes and complications in thalassaemic marrow transplantation patients**

Case	Age (years)	Sex	Class	Acute GVHD	Chronic GVHD	Engraftment	Survival: no. of years since transplantation[a]	Compli cations
1	8	M	II	–	–	+	3	–
2	16	F	II	+++	+++	+	3	Severe chronic GVHD
3	10	M	II	–	–	+	2	–
4	9	F	II	–	–	+	2	–
5	6	F	II	–	–	–	N/A: alive, rejected	–
6	6	M	II	–	–	+	2	–
7	12	F	III	+	–	+	2	Pneumonia
8	7	M	II	–	–	±	2	Poor graft function
9	12	F	III	–	–	+	N/A: death	Non-transplant related
10	16	F	III	–	–	–	N/A: early death, sepsis	–
11	12	F	III	–	–	+	3	–
12	11	F	III	–	–	+	2	CVA
13	13	M	III	+	–	+	2	–
14	12	F	III	++	+	+	2	Chronic lung disease
15	11	M	III	–	–	+	1	–
16	12	F	III	–	–	+	1	–
17	16	M	III	–	–	–	N/A: alive, rejected	–
18	16	F	III	–	–	+	0.66	–
19	7	F	II	+++	–	+	N/A: death (severe acute GVHD, sepsis)	–
20	8	F	II	–	–	+	0.50	
21	11	M	III	–	–	+	0.25	

[a] *Recorded in 1997 but no deaths have occured to date.*

GVHD = graft-versus-host disease CVA = cerebrovascular accident N/A = not applicalble
M = male F = female

was treated as follows: for one patient, busulphan (14 mg/kg) was used; the other two patients received marrow, one from the father (phenotypically identical) and the other from the paternal uncle. The average marrow cell dose was 3×10^8/kg. Overall, a disease-free survival rate of 85% was achieved. There was a 10% incidence of severe acute GVHD; in all classes, the rate of engraftment was high (90%) (see Table 1).

Discussion

Thalassaemia major is a fatal disease. Allogeneic bone marrow transplantations can change the outcome of the disease dramatically [*4–7*]. It is estimated that acute GVHD will be a major complication in one-third of all patients undergoing thalassaemic marrow transplantations [*2,3*], with 25% of those patients fatally affected. There is a need therefore to modify the acute GVHD prophylaxis with respect to iron-induced organ damage, and the toxicity of agents used for prophylaxis.

Methotrexate cannot be considered a safe drug in such patients — especially in class III cases — because of the risk of gastrointestinal toxicity and hepatotoxicity, and ongoing organ failure and sepsis. A combined regimen of ciyclosporin and prednisolone is also not ideally suited to such cases. In this study, adding a modified dosage of antithymocyte globulin with a combination of ciclosporin and prednisolone suggested good results, together with steroid control of acute GVHD, and supportive care. This allowed us to perform the transplantations with an unchanged conditioning regimen, irrespective of the class of the disease of the patient. Using non-toxic agents such as ciclosporin, steroids and low-dose antithymocyte globulin, we were able to perform bone marrow transplantations for thalassaemic patients with few complications and low mortality.

Conclusion

As bone marrow transplantation for thalassaemic patients is increasingly common, successfully controlling the resultant complications, especially that of acute GVHD, has a major effect on patient survival. The therapy employed in the transplantations by this unit, with the regimen outlined above, proved to be beneficial. Its use in developing countries is recommended.

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The EMRO Technical Publication entitled *Community control of genetic and congenital disorders* continued to be distributed to countries and relevant organizations. Funds were also provided for publication of various educational materials in the Islamic Republic of Iran to train primary health care workers and to educate the population in relevant aspects of medical genetics.

Source: The Work of WHO in the Eastern Mediterranean Region. Annual Report of the Regional Director, 1 January–31 December 1998, *page 159.World Health Organization, Regional Office for the Eastern Mediterranean, Alexandria, 1999.*