Transplant Int (1992) 5 [Suppl 1]: S259–S261

TRANSPLANT
International

Occurrence of lymphoproliferative disorder after heart transplantation is related to the total immunosuppressive load

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Abstract. Heart transplant recipients are at a high risk for the development of post-transplant lymphoproliferative disorders (PTLD). We explored the relationship between the incidence of PTLD and the immunosuppressive therapy in 150 consecutive patients who received a cardiac transplant at our centre. None of our patients treated with cyclosporin A and prednisone only ($n = 41$) developed PTLD. In contrast, 6 of 101 patients who were previously treated with anti-T-cell preparations suffered from PTLD. No relationship was found between the type of anti-T-cell therapy and the incidence of PTLD. We conclude that the high incidence of PTLD in heart transplant recipients is related to the total immunosuppressive load and not related to a single agent like OKT3.

Key words: Heart transplantation – Lymphoproliferative disorders – Immunosuppressive load

The long-term use of immunosuppressive drugs after organ transplantation is associated with an increased incidence of neoplasia. Of great concern is the striking number of lymphoproliferative disorders in heart and heart-lung recipients [4]. These tumours, commonly of B-cell origin, frequently occur at extranodal sites, are associated with Epstein-Barr virus infections, are often fatal, but may undergo regression if immumnosuppressive therapy is reduced [1, 2, 3, 6]. A major factor influencing the development of post-transplant lymphoma appears to be the intensity and type of immunosuppression. Several authors reported an additional increased risk after the administration of OKT3 [5, 7]. The objective of our study was to explore the relationship between the use of anti-T-cell therapy and the incidence of PTLD in heart transplant recipients.

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Methods

Patients

Between 1 January 1985, the beginning of the cardiac transplantation programme, and 20 December 1990, 150 orthotopic heart transplantations were performed at the University Hospital, Rotterdam. One patient received a second transplant, for whom the data are combined. Six patients who died within 15 days of transplantation and two patients with a follow-up less than 1 month were excluded from the present analysis. We therefore were able to include data on 142 patients in our variables associated with the risk of having post-transplantation lymphoproliferative disorder after cadiac transplantation (PTLD). The mean age of our patients was 44 ± 1 years, and were male. The indications for transplantation were dilated cardiomyopathy (69 patients), ischaemic cardiomyopathy (70) and other severe cardiac diseases (3).

Immunosuppressive regimens

Immunoprophylaxis. Maintenance immunosuppression consisted of the prednisone-cyclosporin A combination in all patients. For immunoprophylaxis in the first week after transplantation several protocols were used. All patients received high-dose steroids in the perioperative phase which was gradually decreased to a maintenance dose of 10 mg prednisone after 3 months. In 62 patients cyclosporin A was given intravenously during the first 5 days after transplantation and oral administration of CsA was started at day 4, in the remaining patients equine antithymocyte globulin (hATG) (Institute Merieux, Lyon, France), 425 lymphocytotoxic units (0.5 ml) per kilogram for 3–7 days ($n = 28$) or anti-T-cell monoclonal antibody OKT3 (Orthoclone OKT3, Ortho Pharmaceutical, Raritan, N.J., USA), 5 mg/day for 7 days ($n = 51$) was given. These 79 patients also received short-term (5 days) azathioprine (100 mg/day) and CsA was started at day 5 (8 mg/kg orally per day).

In all patients, CsA dosage was adjusted to the plasma levels of the drug. Until November 1988, a non-specific assay for CsA (RIA, Sandoz, Basle, Switzerland) was used (target range 100–200 ng/ml). After November 1988, a specific monoclonal antibody (Cyclo-Trac SP, Incstar, Stillwater, Minnesota, USA) was used to measure the plasma concentration of the parent drug (target range 50–125 ng/ml).

Rejection treatment. Rejection episodes were treated in a uniform manner throughout the study period. Endomyocardial biopsies

Table 1. Indication for anti-T-cell therapy

	Number of patients
Prophylaxis only	
hATG	10
OKT3	28
For treatment of rejection	
rATG	17
OKT3 and rATG	5
Both for prophylaxis and treatment of rejection	
hATG and rATG	16
OKT3 and rATG	23
hATG, rATG and OKT3	2
Total	101

rATG, rabbit antithymocyte globulin; hATG, equine antithymocyte globulin
Cumulative dose: OKT3 43 mg (25–100 mg); rATG 1090 mg (299–4200 mg)

were graded using the criteria as proposed by Billingham. In the case of moderate or severe rejection in the first 4 weeks after transplantation, patients were treated with rabbit ATG (rATG, National Institute for Public Health, Bilthoven, The Netherlands) in a dosage to keep the T-cell count < 150 mm^3 for 3 weeks). First-line treatment for moderate rejection occurring more than 4 weeks after transplantation was 1 g methylprednisolone per day intravenously for 3 days. Refractory rejection episodes were treated with either rATG (see above) or OKT3 (5 mg/day) for 10 days.

Pathological studies

The diagnosis of post-transplantation lymphoproliferative disorder was based on histological examination of excision biopsy or autopsy material.

Results

One and three year survival in our patients was 91% and 89%, respectively. Detailed information on the indication for anti-T-cell therapy is given in Table 1. In six patients treated with anti-T-cell therapy a diagnosis of post-transplantation lymphoproliferative disorder was made. Three of these patients were treated with OKT3 (two patients with OKT3 alone), three patients with polyclonal anti-T-cell therapy and one patient both with OKT3 and RATG. Detailed information on the characteristics of these patients is given in Table 2.

In contrast, none of the 41 patients treated with CsA and prednisone alone developed PTLD (incidence 0%, 95% CI 0–9%). The difference in incidence between two the groups: 6%, 95% CI of the difference 1–13% ($P < 0.05$).

A number of factors that might be associated with the development of PTLD were examined. No statistically significant differences were found in age, time after transplantation, cumulative CsA dose, plasma levels or cumulative steroid dose.

Four patients died, despite reduction or withdrawal of immunosuppression and treatment with acyclovir i.v.

Discussion

The most striking observation in our study was that none of the patients who was treated with CsA and prednisone alone developed a post-transplantation lymphoproliferative disorder. Of the six patients who developed PTLD, all were treated with anti-T-cell therapy, either as immunoprophylaxis or for treatment of rejection. Of these six patients, only three were treated with OKT3 whereas the remaining three received a polyclonal anti-T-cell preparation. Our findings are in contrast with the observations made by Swinnen et al. [7]. They concluded that a substantial increase in the incidence of post-transplantation lymphoproliferative disorder occurred after the addition of OKT3 to their immunosuppressive regimen. They also found a relationship between the incidence of PTLD and the cumulative dosage of OKT3. How can this discrepancy be explained? One possibility is the type of maintenance immunosuppression. Swinnen et al. used triple drug treatment (CsA, prednisone and azathioprine) whereas at our centre patients are treated with CsA-prednisone only. Furthermore, the cumulative dose of OKT3 given to their patients who subsequently developed PTLD was high (between 70 and 135 mg per patient) and our patients received a median total dose of 35 mg. In view of this difference and our observation that none of our patients treated with CsA and prednisone alone suffered from PTLD, it is more likely that the high incidence of PTLD in their patients was due to a greater total immunosup-

Table 2. Characteristics of the patients with post-transplantation lymphoproliferative disorder

Patient No.	Cumulative OKT3 dose (mg)	Cumulative rATG dose (mg)	Cumulative hATG dose (days)	Time to PTLD (months)	Pathological findings		Clinical status (time from diagnosis)
					Hist	IP	
4	none	4200	5	6	IBL	M	Dead (5 months)
28	none	none	3	30	IBL	P	Dead (1 month)
52	none	920	none	25	PC	M	Dead (1 month)
59	50	960	none	7	IBL	M	Alive in CR (29 months)
79	35	none	none	11			Alive with recurrence (16 months)
84	35	none	none	4	DM	P	Dead (1 month)

rATG, rabbit antithymocyte globulin; hATG, equine antithymocyte globulin; IP, immunophenotype; Hist, histology; IBL, immunoblastic lymphoma; PC, plasma cell tumor; DM, diffuse mixed lymphoma; M, monoclonal; P, polyclonal; CR, complete remission

pressive load, than that a single agent, like OKT3, was responsible.

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