Intermediate term results of total lymphoid irradiation for the treatment of non-specific graft dysfunction after heart transplantation

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Abstract

Background: A proportion of heart transplant recipients develop poor graft function in the absence of cellular infiltrate in endomyocardial biopsies or transplant associated coronary artery disease. The condition has a poor prognosis and its aetiology is poorly understood.

We report encouraging intermediate term results with total lymphoid irradiation (TLI) in the management of this condition. Methods: Eleven adult cardiac transplant recipients who developed severe allograft dysfunction (NYHA class-4) at a median period of 4 months after orthotopic heart transplantation were successfully treated with TLI. Endomyocardial biopsies and coronary angiography were normal in each patient and biventricular failure developed in spite of immunosuppression with Cyclosporin-A, Azathioprine, oral Prednisolone, Cyclophosphamide and intravenous Methylprednisolone therapy. Total lymphoid irradiation was given with standard Mantle and inverted Y-fields over ten treatments to achieve a cumulative dose of 8 Gy. Results: Each patient had a significant improvement in clinical response and in ventricular performance within 2 months of commencing TLI. Nine patients are currently well (four NYHA class-1, five NYHA class-2) at 4–48 (median 26) months following TLI. Two patients died; one from bacterial sepsicaemia and one as a consequence of chronic renal failure. Three patients developed opportunistic infection which was successfully treated with appropriate antimicrobial agents. An Epstein–Barr virus associated lymphoproliferative disorder occurred in one patient and was successfully treated by reduction in immunosuppression and high dose Acyclovir. Two patients developed transient bone marrow suppression. Conclusion: The intermediate term results of TLI in the management of poor graft function in cardiac transplant recipients with normal endomyocardial biopsies and coronary angiography are encouraging. Although complications of opportunistic infection, bone marrow suppression and lymphoproliferative disorder occurred, treatment was successful in each case. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

The mechanisms responsible for allograft dysfunction occurring in a proportion of heart transplant recipients without a cellular infiltrate in endomyocardial biopsies or evidence of transplant associated coronary artery disease remain unclear. Evidence that it may reflect a type of humoral rejection includes observations of deposition of immunoglobulin and complement in the coronary vasculature with endothelial swelling or vasculitis [1,2]. Predisposing factors may include a positive lymphocytotoxic cross match [1,2]. Although some success has been reported with immunoadsorption [3], the prognosis is usually poor as the condition usually fails to respond to augmented immunosuppression. Total lymphoid irradiation (TLI) is effective in the management of refractory recurrent cellular rejection in adult and paediatric heart transplant recipients [4,5]. We reported encouraging early experience with TLI in three cardiac transplant recipients with severe allograft dysfunction in the absence of cellular rejection or coronary artery disease which was unresponsive to augmentation in immunosuppressive therapy [6]. We have subsequently encountered a further eight patients with this condition who we
treated with TLI and we report intermediate term follow-up on these 11 patients.

2. Patients and methods

2.1. Irradiation procedure

Each patient was simulated in the supine position and TLI targeted major lymph node bearing areas above and below the diaphragm in two fields. The technique employed has been described elsewhere [6]. Ten patients received a total of 8 Gy over ten treatments. One patient received 4 Gy but TLI could not continue on account of persistent bone marrow suppression. In general treatment was interrupted if the white blood cell count fell below $2 \times 10^9/l$. A full blood count was measured twice weekly throughout the course of TLI and for the first 2 weeks after completion of treatment.

2.2. Patients

Since 1986, 330 patients received cardiac transplantation at our Unit. Eleven patients developed severe allograft dysfunction (NYHA class-4) with normal endomyocardial biopsies and coronary angiography at a median period of 4 months after orthotopic cardiac transplantation. Each patient had clinical evidence of biventricular failure and 2D transthoracic echo cardiology showed globally poor biventricular function. Four patients were on inotropic support. Two of these patients were intubated and mechanically ventilated and one also required haemofiltration and one intra-aortic balloon counterpulsation. There were eight males and three females with an age range of 35 to 62 (median 54) years. The indication for transplantation was ischaemic heart disease in six patients, dilated cardiomyopathy in four and post-partum cardiomyopathy in one. One patient (the patient with post-partum cardiomyopathy) had a positive B cell (Immunoglobulin G) lymphocytotoxic cross match with 100% lysis of all donor lymphocytes [6].

Routine immunosuppression consisted of Cyclosporin-A (maintaining trough levels of 250–350 ng/ml) Azathioprine 2 mg/kg per day and Prednisolone 10 mg/day (for the first 3 post-operative months). The patient with a positive lymphocytotoxic cross match received Cyclophosphamide 50 mg daily instead of Azathioprine. Episodes of acute allograft rejection were treated with intravenous Methylprednisolone 1g daily on 3 consecutive days. These patients did not encounter acute cellular rejection more frequently (averaging 1–2 episodes) than the remainder of our heart transplant population. When patients developed allograft dysfunction with normal endomyocardial biopsies and coronary angiography, Methylprednisolone 1 g (i.v.) was given on 3 consecutive days followed by oral Prednisolone at a dose of 60 mg/day, reducing by 5 mg/day and continuing at 0.2 mg/kg per day maintenance. Cyclophosphamide 2 mg/kg per day was prescribed, Azathioprine stopped and Cyclosporin-A continued. Four patients developed this latter complication during the first post-operative month, and two at 4, and one at 5, 9, 30, 35 and 62 months, respectively, post-transplantation.

3. Results

Nine patients are currently well (four NYHA class-1, five NYHA class-2) at 4, 16, 17, 21, 26, 31, 35, 44 and 48 months following TLI. Clinical examination is normal and 2D transthoracic echo cardiology shows good cardiac function with improved shortening fractions (Fig. 1). In each case clinical improvement was noted between 1 and 2 months after completing TLI.

Two patients died. One patient had received five treatments (4 Gy) of TLI. On account of persistent bone marrow suppression, further treatments were not possible. The patient subsequently developed systemic Cytomegalovirus (CMV) infection and *Pneumocystis carinii* pneumonia which was successfully treated with intravenous Ganciclovir (5 mg/kg per day) and initially Co-trimoxazole (1.92 g orally b.d.), respectively. As he subsequently developed pancytopenia (white cell count $<1 \times 10^9/l$, platelets $30 \times 10^9/l$ and haemoglobin 8 g/dl), Co-trimoxazole was stopped and Clindamycin 600 mg daily and Primaquine 7.5 mg daily were prescribed in addition to nebulized Pentamidine Isethionate 600 mg daily. His pancytopenia normalized but the patient developed chronic renal failure necessitating haemodialysis. He died from bacterial septicemia. One patient died 20 months after completing TLI as a consequence of chronic renal failure.

One patient developed *Haemophilus influenzae* pneumonia during TLI and this was successfully treated with i.v. Fig. 1. Shortening fractions before and after TLI. One patient did not have a calculated shortening fraction before TLI although 2D echocardiography demonstrated poor biventricular function. Her post-TLI shortening fraction was 38%.
Ceftazidime and subsequently oral Amoxicillin. Eighteen months following TLI the patient developed myelodysplasia and requires regular blood transfusion. One patient developed systemic CMV infection with retinitis 6 months after TLI which responded fully to i.v. Ganciclovir therapy (10 mg/kg per day) for 2 weeks. One patient developed a mediastinal B-cell lymphoproliferative disorder associated with Epstein–Barr virus 11 months after TLI. She was treated successfully with reduction in immunosuppression (Cyclosporin-A trough level of 70-90 ng/ml) and Ganciclovir (500 mg i.v. tds for 2 weeks and thereafter, 800 mg orally five times daily for 6 weeks). Two patients developed transient bone marrow suppression which normalized without intervention. Neither patient developed infection. Four patients had no complications following TLI.

4. Discussion

Cardiac transplant recipients who develop severe allograft dysfunction in the absence of evidence of cellular rejection or coronary artery disease, present a difficult management problem and have a poor prognosis. The origin of their haemodynamic compromise is unclear, but may reflect a type of humorally mediated vascular rejection. Our patients show that TLI can play an important role as adjunct therapy with conventional immunosuppression in the management of this condition. In each case the treatment led to significant improvement in clinical well-being and in ventricular performance. Although one of the patients who died had only received five treatments with TLI to achieve a cumulative dose of 4 Gy, his NYHA status improved from 4 to 3 following this treatment.

The origin of the allograft dysfunction for the ten patients with a negative lymphocytotoxic cross match is unclear. It is possible that other antigens were eliciting antibody responses in these patients and, although little is known about such non-HLA antigens, possibilities include vascular endothelial cell and heart specific antigens [7]. We did not attempt to document immunoglobulin and complement deposition in endomyocardial biopsies as these findings are difficult to interpret and reproduce. However endomyocardial biopsies were histologically normal and of adequate size in each case. We did not repeat biopsies immediately prior to TLI and left ventricular biopsies were not performed.

Patients treated with TLI develop long lasting impairment of cell-mediated immunity [8]. Small lymphocytes are particularly susceptible to ionizing radiation which leads to DNA damage. As a consequence, strand breakage and cross-linking occurs which often results in cell death during mitosis [9]. How TLI led to improved graft function in our patients is not clear. However, the improvement has been sustained. This would appear to be in agreement with published data on graft tolerance in renal transplant recipients treated with TLI [10]. Further studies are required to improve our understanding of the immunosuppressive action of this treatment.

Although three patients developed opportunistic infection, treatment was successful in each case with appropriate antimicrobial therapy. Similarly the patient who developed a lymphoproliferative disorder, responded completely to reduction in immunosuppression and Ganciclovir. Two patients developed transient and uncomplicated bone marrow suppression. It remains unclear following detailed haematological assessment as to whether the myelodysplasia which occurred in one patient 18 months following TLI was related to this treatment, although, clearly the combination of TLI and Cyclophosphamide may have been causative.

We appreciate that, as this is a non-randomized retrospective trial, specific conclusions about the value of the therapy cannot be firmly made. Nevertheless each patient experienced a significant improvement in cardiac function following TLI. Furthermore, this improvement has been sustained at up to 48 months following treatment. Although complications, such as opportunistic infection, bone marrow suppression and a lymphoproliferative disorder were observed, medical treatment was successful in each case.

Our experience suggests that TLI leads to a sustained improvement in graft function in cardiac transplant recipients with severe allograft dysfunction in the presence of normal coronary arteries and endomyocardial biopsies. We suggest, therefore, that TLI should be considered as a therapeutic adjunct to conventional immunosuppression in the management of this condition following cardiac transplantation.

References

