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Enhancement of Donor Cell Chimerism in Whole Organ Allograft Recipients by Adjuvant Bone Marrow Transplantation

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THE ADVENT of novel immunosuppressive agents has made successful transplantation of organ allografts a clinical reality. However, chronic use of these nonspecific drugs is associated with unwanted side effects; necessitating the evolution of strategies that would allow for the induction of donor-specific tolerance, enhancing allograft survival and ultimately leading to reduction or withdrawal of immunosuppression (IS). Having speculated that persistence of donor cell chimerism may play an important role in the acceptance of whole organ allografts,[1-3] we initiated a prospective trial in December 1992 to enhance this phenomenon by adjuvant infusion of unmodified bone marrow (BM) into 85 recipients of primary whole organ allografts. Failure to obtain permission to harvest vertebral bodies from the cadaveric donors resulted in accrual of 54 recipients of organ alone, which were followed as contemporaneous controls. Reported herein is the outcome of these patients at their latest follow-up.

MATERIALS AND METHODS

Patients

Between December 1992 and December 1994, 85 patients were simultaneously transplanted with ABO-compatible unmodified donor BM and liver (n = 34), kidney (n = 36), heart (n = 10), or lung (n = 5). The mean follow-up was 360 ± 179 (range, 90 to 852 days). The mean recipient age was 46 ± 11.3 years, and the mean donor age was 32.7 ± 16.2 years. Additionally, there were 54 recipients of liver (n = 29), kidney (n = 20), heart (n = 4), or lung (n = 1) allografts alone (in whom consent to harvest vertebral bodies from the cadaveric donors was not available were monitored as controls). Their follow-up ranges from 130 to 535 days (405 ± 107 days). Isolated pancreatic islets were infused into one liver and six kidney recipients who also received adjuvant BM. Seven BM-augmented and three nonaugmented kidney recipients also received a concomitant pancreas transplant.

Bone Marrow and Pancreatic Islets Cell Isolation

BM cells were isolated from the vertebral bodies of the cadaveric donors by a method described previously.[4] Following organ revascularization, 3 to 5 × 10^8 unmodified cells/kg body weight were infused via a central IV line into the recipients. Islets from the pancreata of the BM-organ donor were isolated by a modification of the automated method,[5] and subsequently infused into the portal vein of the allograft recipients shortly after revascularization.

Immunosuppression

All patients received tacrolimus along with steroids and did not undergo any cytoablative or cytoreductive conditioning prior to organ transplantation. All episodes of rejection or graft-versus-host disease (GVHD) were treated with minor modifications in doses of routine IS. In the event a steroid-resistant rejection was encountered, it was treated with a short course of OKT3 or ATG.

In Vitro Studies

Pretransplant and serially posttransplant (every other month) in vitro studies were performed using the PBMCs of the recipients to detect chimerism (by flow cytometry and PCR) and to determine their immune status (by MLR, LDA, recall antigens, ConA, and PHA). These methods have been detailed elsewhere.[4]

RESULTS AND DISCUSSION

No complications of BM infusion were witnessed in any of the 85 primary organ allograft recipients, and their convalescence was rapid. All but four (5%) BM-augmented recipients are alive whereas, 7 of 54 (13%) control patients died during this follow-up (Table 1). None of the deaths in the augmented group were related to BM infusion. The two BM-augmented liver patients succumbed to fulminant septicemia 3 and 5 weeks posttransplantation. Two additional heart and BM recipients died with functioning grafts on postoperative days 24 and 267 due to septicemia and pulmonary thrombo-embolism, respectively. Two kidney allografts in the BM-augmented group were lost 16 months posttransplantation (noncompliance in one and rejection in the other). Polyoma virus infection and rejection was the cause for loss of another kidney approximately 375 days posttransplantation. The tempo, severity, and incidence of rejection were comparable in the patients in the study and control group. Only two (2.3%), both BM-augmented liver recipients, developed asymptomatic GVHD. Limited to the skin, it resolved spontaneously in one, whereas a slight increase in routine steroid dose was required for its involution in the other.[4] The most recent blood sample obtained from evaluable patients showed a significantly higher incidence (69 of 79, 87%) of multilineage donor cell chimerism in the BM-augmented as compared to that in the control (23 to 43, 53%) group (Table 1). Additionally, 52% of the

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Table 1. Current Graft Function, Survival, and Donor Cell Chimerism in BM-Augmented and Nonaugmented Whole Organ Allograft Recipients

		Graft survival		Graft function (× ± SD)		Positive for donor cells*	
Transplant groups	*n*	*n*	(%)	T. Bili (mg/dL)	Creatinine (mg/dL)	*n*	(%)
Livers:							
BM-Augmented	34	32/34	(94%)	0.6 ± 2	—	30/31	(97%)
Nonaugmented	29	25/29	(86%)	0.7 ± 3	—	13/25	(52%)
Kidney:							
BM-Augmented	36	33/36	(92%)	—	1.9 ± 1.2	30/31	(97%)
Nonaugmented	20	17/20	(85%)	—	2.1 ± 1.3	09/14	(64%)
Hearts:							
BM-Augmented	10	8/10	(80%)	Good graft function		5/8	(63%)
Nonaugmented	04	4/04	(100%)	Good graft function		3/4	(25%)
Lungs:							
BM-Augmented	05	5/05	(100%)	Good graft function		4/5	(80%)
Nonaugmented	01	0	(0%)	—		—	—

*In evaluable patients at the last sample tested.

BM-augmented liver recipients had evidence of donor-specific hyporeactivity as compared to 26% of the controls. It is noteworthy that in the recipients of other organs, immune modulation was analogous in both the control and the study group at the last sample tested.

In summary, adjuvant BM infusion into whole organ allograft recipients was safe and associated with augmentation of chimerism. Although its eventual effect remains speculative, it could be argued that its presence may have salutary effects on graft and patient survival and may also reduce the risk of chronic rejection.[6]

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