



Immune Modulation in Organ Allograft Recipients by Single or Multiple Donor Bone Marrow Infusions

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THE discovery of persistent alloantigen (i.e., chimerism) in the lymphoid and nonlymphoid tissues of successful long-term organ transplant recipients has prompted many to conclude that this phenomenon plays an important role in allograft acceptance.^{1,2} These findings have been corroborated in experimental models of transplantation (Tx) tolerance.³ Although the precise phenotype of cells involved in the induction of observed donor-specific tolerance (DST) is unclear, there exists overwhelming evidence suggesting that perhaps immature dendritic cells, which are resident within the graft and known to migrate after Tx, modulate host anti-donor effector responses.⁴ As these cells are of bone marrow (BM) origin, it was rational to propose that perioperative donor BM infusion may augment this phenomenon with resultant salutary effect on patient and graft survivals. In 1992 we initiated a clinical trial involving perioperative infusion of unmodified BM cells obtained from the vertebral bodies of cadaveric donors into abdominal and thoracic organ allograft recipients. An interim analysis of the outcome in these patients is reported at their most recent follow-up.

MATERIALS AND METHODS

Bone Marrow Augmentation

To augment donor cell chimerism, a single dose of $3-5 \times 10^8$ unmodified donor BM cells/kg body weight was infused into 226 nonconditioned primary allograft recipients. The mean recipient and donor age was 40 and 29 years, respectively, with follow-up ranging from 3 to 2023 days (933 ± 507 days). Additionally, since April 30, 1996, we have also accrued 39 organ recipients (liver $n = 6$, kidney $n = 19$) into a concurrent protocol involving multiple sequential infusions of unmodified BM ($1-2 \times 10^8$ cells/kg per day) from days 0 to 4 posttransplantation; the mean recipient age being 45 ± 11 years, with a follow-up from 4 to 790 days. Organ recipients ($n = 131$) for whom BM was not available were monitored as controls. Immunosuppression was with tacrolimus and steroids, CellCept being administered to 53 study and 17 control patients.

In Vitro Analysis

Using procedures described previously,⁵ the presence of donor cell chimerism (by polymerase chain reaction [PCR]) and cellular immune response (by mixed leukocyte response [MLR]) was serially determined using the peripheral blood of the recipients.

RESULTS AND DISCUSSION

The infusion of BM (both single and multiple) was safe and, except for 55 patients (21%), all study patients have optimal graft function, none being lost to causes uniquely ascribed to ancillary BM infusion. Of the control patients, allografts in 31 (24%) have been lost during the course of follow-up. Mild to moderate acute cellular rejection was evidenced in 158/251 (63%) study and 101/131 (77%) control patients. Mild, easily reversible graft-vs-host disease (GvHD) was witnessed in only 2/226 (1%) patients receiving single BM infusion. In contrast, fulminant GvHD was discerned in 1/37 (3%) recipients of multiple BM infusions, exhorting an immediate discontinuation of this protocol. Owing to concomitant existence of refractory donor-type EBV⁺ post-transplant lymphoproliferative disease (PTLD) this patient initially benefited from autologous lymphokine activated killer [LAK] cell therapy, eventually succumbing at day 147 post-Tx. Among those at least 1 year post-Tx, a steroid-free existence has been achieved in 94 (53%) study and 39 (40%) control patients.

As reported previously, the presence of a higher incidence of multilineage chimerism was confirmed in the peripheral blood of evaluable study (~95%) patients as compared to that of the control (~53%) patients. Furthermore, serial in vitro immunological monitoring revealed the presence of a relatively higher incidence of donor-specific hyporeactivity (DSH) in 57% of study (liver, lung, kidney) recipients as compared to that of controls (44%). Conversely, a relatively lower incidence of DSH was evidenced in both study and control heart and kidney + pancreas recipients. Although BM infusion is safe with incontrovert-

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ible evidence for augmentation of chimerism, its effect on allograft survival and on our ability to reduce or withdraw nonspecific immunosuppression is still indeterminate. It must be emphasized that, unlike that in rodents, a longer follow-up will be required in outbred species such as humans for the discernment of the beneficial effects of BM infusion.

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