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Perioperative Donor Bone Marrow Infusion in Recipients of Organ Allografts

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DESPITE its attended complications, immunosuppression for graft acceptance and the impending threat of chronic rejection are two of the many overwhelming factors that have necessitated the implementation of strategies aimed at inducing donor-specific tolerance (DST). With the postulation that persistence of donor cell chimerism after organ transplantation (Tx) may play a notable role in allograft acceptance and the establishment of DST,¹⁻³ we initiated a prospective clinical trial to deliberately augment this phenomenon by perioperative donor bone marrow (BM) infusion. We report here the outcome in 198 study patients with a follow-up of 5 to 1387 days. Also summarized are the results in 115 allograft recipients who, owing to unavailability of consent to retrieve vertebral bodies (VB) from the cadaveric donors, were monitored as coetaneous controls.

MATERIALS AND METHODS

Patients

Since the initiation (June 1992) of this study, 188 organ allograft recipients have received a single perioperative infusion of $3-6 \times 10^8$ BM cells/kg body weight. Additionally, 10 recipients have been treated using a modified protocol that required multiple infusions of 1×10^8 cells/kg body weight/day for 5 consecutive days (days 0-4) post-Tx. Immunosuppression (IS) in the majority of the patients was with tacrolimus and steroids, whereas since its approval for clinical Tx, CellCept has been added to the above regimen in 32 study and 15 control patients. As has been reported previously,⁴ BM was isolated from the VB of cadaveric donors and infused without cryopreservation. Dose adjustment of routine IS was initially adopted to treat episodes of acute cellular rejection, whereas the use of OKT3 was reserved for the treatment of steroid-resistant rejection.

Detection of Chimerism and Determination of In Vitro Immune Responses

Using primers specific for either HLA allele or the sex-determining region of the Y (SRY) chromosome (in male → female recipients), the presence of donor DNA was ascertained periodically in the PBMC of study and control patients by PCR. Furthermore, serial immunological monitoring was also performed using MLR assays.

RESULTS AND DISCUSSION

The infusion of BM was uneventful and all patients are alive except 18 (9%) who have succumbed to causes unrelated to

infusion: 13 (11%) control patients have also died during the course of this follow-up. Additionally, grafts in nine study and five control patients have also been lost during their progressive follow-up. The remaining patients have excellent graft function. Although the incidence and severity of acute cellular rejection were comparable in the BM-augmented and control groups, graft-versus-host disease was witnessed in only two (1%) study recipients (both of liver), which for its resolution required minor dose adjustments of routine IS. It is noteworthy that a steroid-free existence has been achieved in 61% study and 46% control patients who are at least 12 months post-Tx. Of greater significance, however, is the observation that a statistically higher number of kidney recipients in the study group (71%) was weaned off steroids as compared to controls (48%). None of the patients are nevertheless IS-independent.

The incidence of chimerism was much higher (94%) in the BM-augmented patients as compared to controls (56%). Additionally, using LDA-PCR, the levels of chimerism were found to be at least 10- to 100-fold higher in BM-augmented recipients compared to that of controls.⁵ As has been reported elsewhere in these proceedings (Aitouche et al), donor cell chimerism was indeed multilineage, and there was explicit evidence for the presence of progenitors of donor dendritic cells in the PBMC of evaluated BM-augmented patients. Furthermore, it is our contention that the absence of obliterative bronchiolitis in BM-augmented lung recipients and its evolvment in 2/7 (29%) surviving control patients who have had a comparable duration of follow-up may herald the beginning of our recognition of the salutary effects of augmented chimerism in allograft recipients.

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