



2034

Adjuvant Bone Marrow Infusion in Clinical Organ Transplant Recipients

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THE two most common causes of late organ allograft failure are complications associated with the long-term use of nonspecific immunosuppression and chronic rejection. Incidentally, this undesirable outcome could be prevented by timely adoption of clinically applicable strategies that would result in the induction of donor-specific tolerance (DST). We have previously advanced the hypothesis that stable existence of donor cell chimerism in organ allograft recipients may induce DST with ultimate enhancement of patient and graft survival.^{1,2} To test this hypothesis, we proceeded to augment chimerism in clinical organ transplant recipients by adjuvant perioperative unmodified donor bone marrow (BM) infusion.^{2,3} Reported herein is the outcome of this prospective trial in which 251 study (BM-augmented) and 129 contemporaneous controls have been accrued since its initiation in June 1992.

MATERIALS AND METHODS

A total of 219 organ allograft recipients (liver, $n = 68$; kidney, $n = 39$; kidney + islets, $n = 7$; kidney + pancreas, $n = 38$; heart, $n = 27$; lung, $n = 19$; small bowel, $n = 18$; and multivisceral, $n = 4$) have received intravenously a single perioperative dose of 3 to 6×10^8 donor BM cells/kg body weight. The median follow up is 753 ± 444 days. Additionally, 16 recipients (liver, $n = 6$; kidney, $n = 4$; kidney + islet, $n = 1$; and kidney + pancreas, $n = 5$) have received five consecutive (from days 0 to 4 posttransplantation) doses of 1×10^8 BM cells/kg body weight/d, whereas 16 recipients (kidney, $n = 5$; kidney + pancreas, $n = 4$; heart, $n = 2$; and lung, $n = 5$) have received three sequential infusions of 2×10^8 BM cells/kg body weight/d from days 0 to 2 posttransplantation. Follow up of patients in the multiple infusion group is 232 ± 184 days. Unavailability of consent to retrieve vertebral bodies (VB) from cadaveric donors has resulted in accrual of 129 control patients whose follow up is 783 ± 446 days. Donor and recipient ages, sex, and HLA mismatches (or matches) are comparable in the study and control populations. Immunosuppression was with tacrolimus and steroids; 66 patients (49 study and 17 control) also received CellCept. BM was isolated from the VB of cadaveric donors by a procedure outlined previously.² During the course of posttransplant follow up, serial peripheral blood samples were obtained to ascertain the

presence of donor cells by flow cytometry and by molecular techniques.² Additionally, *in vitro* immune monitoring was also performed to assess donor-specific modulation.

RESULTS AND DISCUSSION

The safety of BM infusion in organ allograft recipients has already been established.² During the course of follow up, 28/251 (11%) of study patients have died; none due to causes uniquely related to infused BM. Similarly, 21/129 (16%) control patients have succumbed during this follow up (Fig 1B). Furthermore, as is evident in enclosed Fig 1, patient and graft survival were relatively comparable in recipients receiving single versus multiple infusion. The cumulative risk of acute cellular rejection (ACR) was also analogous in the BM-augmented and control patients (Fig 1C). As compared to those receiving single, there was a trend (albeit not statistically significant) for lowered risk of ACR during the initial postoperative period in the recipients of multiple BM infusions.

Of those who are at least 1 year posttransplantation, 89/164 (54%) of study and 43/99 (43%) control patients have been taken off steroids. Interestingly, as compared with the controls (0%), 22% of lung + BM recipients have been taken off steroids. Incidentally, the latter group of patients also had lower incidence (4%) of obliterative bronchiolitis as compared to the controls (33%) and a higher incidence of donor-specific immune modulation as evidenced by *in vitro* proliferative responses.

At their most recent follow up, a relatively higher incidence (89%) of donor cell chimerism was observed in BM-augmented patients as compared to controls (53%).

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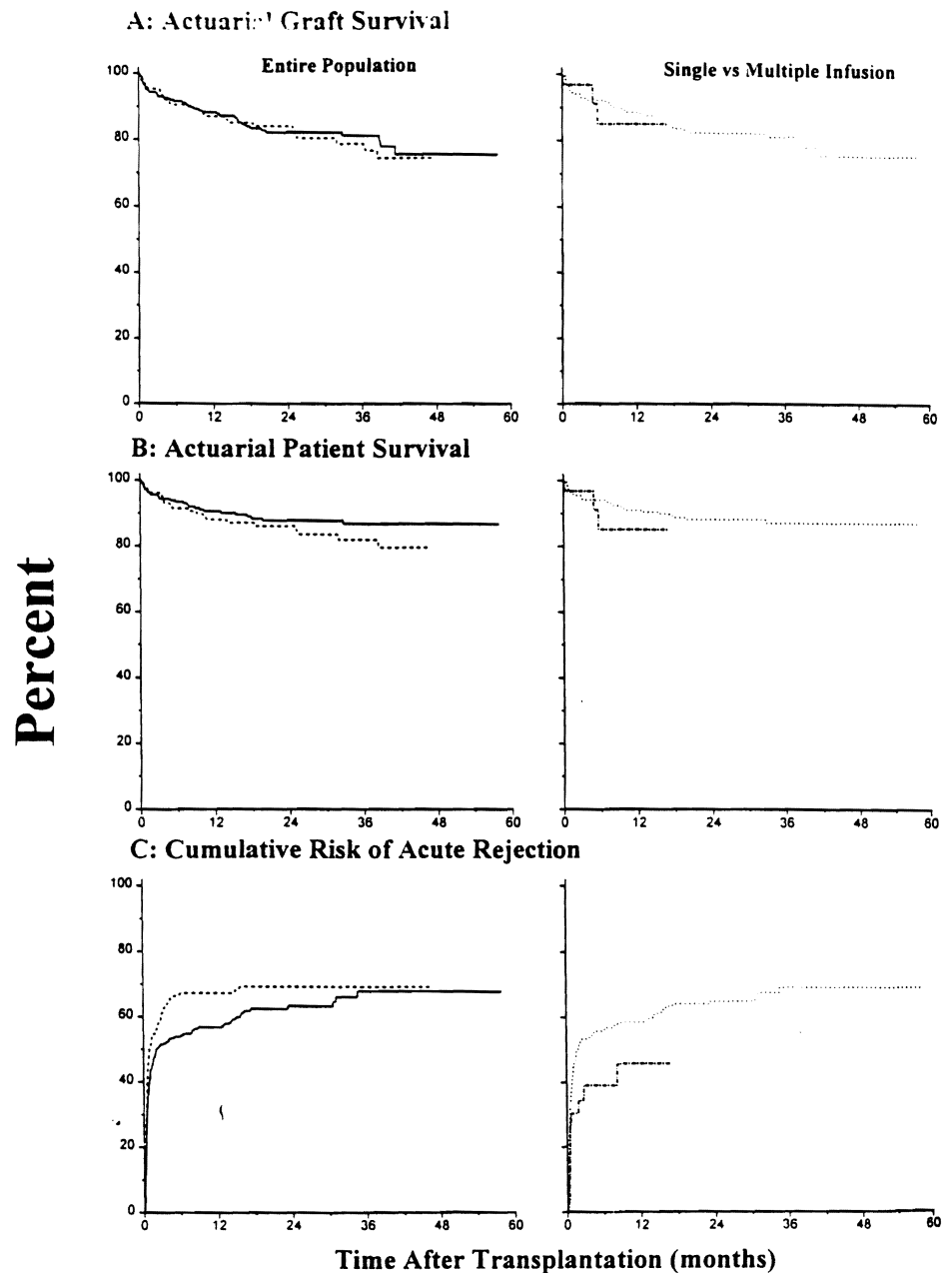


Fig 1. Kaplan-Meier analysis of the actuarial patient and graft survival and cumulative risk of acute cellular rejection in BM-augmented (—) and control (---) organ allograft recipients. A similar analysis in patients receiving single (···) or multiple (— · — · —) infusions of donor BM is also presented for comparative analysis.

Additionally, preliminary results obtained using semi-quantitative dot blot analysis suggested that as compared with controls, the level of donor cell chimerism was at least 2 to 3 times higher in patients receiving a single BM infusion; this was further augmented (4 to 5 times) by the use of the multiple infusion protocol.

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