1937

Concomitant Infusion of Unmodified Donor Bone Marrow Into Unconditioned Recipients of Intestinal Allografts

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TECHNICAL improvements and the advent of Tacrolimus, a potent immunosuppressive agent, have made small bowel transplantation (SBTx) a clinical reality. Despite the initial encouraging results, the necessity for protracted use of high doses of immunosuppression (IS) to prevent intestinal allograft rejection was associated with a surge of infectious complications and posttransplant lymphoproliferative disease (PTLD) in these recipients. This prompted us to terminate this clinical trial at the end of 1994 after an accrual of 63 patients[1] and to intensify our efforts to ascertain an alternative strategy that would allow more successful SBTx. We have previously established that perioperative infusion of donor bone marrow (BM) to whole organ allograft recipients leads to augmentation of chimerism and an increased incidence of donor-specific hyporeactivity.[2] These observations have encouraged us to reactivate the SBTx trial with simultaneous infusion of unmodified donor BM. Reported herein is the clinical outcome of the first seven study and three control patients.

MATERIALS AND METHODS

Patients

Since January 1995, seven nonconditioned recipients have been simultaneously transplanted with 6×10^8 unmodified donor BM cells/kg body weight and isolated small intestine (SI, n = 3), combined liver and SI (n = 3) and liver and small bowel and pancreas (n = 1). The mean recipient age was 17 ± 12 years (pediatric n = 5; adult n = 2) with a follow-up ranging from 107 to 270 d). The unavailability for consent to retrieve cadaveric donor BM resulted in the accrual of three patients with a mean age of 3.3 ± 4.1 years who were monitored as contemporaneous controls. Following transplantation, all patients were maintained on routine IS with Tacrolimus and steroids with azathioprine and OKT3 being reserved for the treatment of steroid-resistant rejection. Prophylactic therapy with gancyclovir and Cytogam was restricted to cytomegalovirus (CMV)-negative recipients of allografts from CMV-positive donors. To monitor rejection, protocol endoscopic biopsies of the intestinal allografts were performed weekly in the first month and monthly thereafter.

Bone Marrow Cell Isolation and In Vitro Studies

BM cells were isolated from the vertebral bodies of the cadaveric donor by a method described elsewhere.[2] Pre and serially post transplant (every other month) *in vitro* studies were performed using the peripheral blood mononuclear cells (PMBC) 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.[2]

RESULTS AND DISCUSSION

The infusion of BM was uneventful with no complications uniquely attributable to concomitant donor cell infusion. None of the augmented patients exhibited any evidence of graft vs host disease (GVHD). Two patients in the study group died on POD 19 and 60 due to respiratory and multi-system organ failure, respectively. One BM-augmented recipient also lost his graft to intractable rejection and enterectomy on POD 19. Of the remaining four study patients, three have had total parenteral nutrition (TPN) discontinued and are home bound. One BM and multivisceral recipient remains hospitalized with partial TPN support. All of the three control patients are alive, two being TPN-free and home bound. Additionally, the incidence and severity of rejection was comparable in both groups.

When tested for chimerism, donor cells were detected in

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Aided by Project Grant No. DK 29961 from the National Institute of Health, Bethesda, Maryland.

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0041-1345/96/$3.00/+0

the PBMC of all five BM-augmented and three control patients at the last sample tested; however, the levels were much higher in the study as compared to that in the control patients. Due to short post operative follow-up, results of serial immune monitoring were inconclusive. From these observations we conclude that adjuvant BM infusion in intestinal allograft recipients is safe and is not associated with an increased incidence of GVHD and/or rejection. We are accruing more patients in this study and hope that a longer follow-up in a larger cohort of recipients may elucidate the beneficial effects of augmented chimerism following adjuvant BM infusion.

REFERENCES

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