Persistence of Donor Cells and Incidence of Graft-Versus-Host Disease After Simultaneous Small Bowel and Bone Marrow Transplantation


GRAFT-versus-host disease (GVHD) has always been a concern associated with small bowel transplantation, because of the large amount of matured lymphocytes contained in the graft. In clinical organ transplantation GVHD is not a common complication; however, it is usually fatal once developed. Because there is no suitable experimental model of GVHD associated with solid organ transplantation, studies investigating the pathogenesis and treatment of this disease have been limited. We describe here a clinically relevant animal model of GVHD after fully allogeneic small bowel transplantation.

MATERIALS AND METHODS

Inbred Lewis (RT1') and ACI (RT1') rats (Harlan Sprague Dawley, Indianapolis, Ind.) were used as recipients and donors, respectively. Orthotopic small bowel transplantation (SBTX), bone marrow cell (250 × 10⁶) infusion (BMTX), and simultaneous SBTX with BMTX were performed according to the procedures previously described. FK 506 was intramuscularly administered at a daily dose of 1 mg/kg on days 0 to 13, then continued as a weekly injection at the same dose for 400 days. GVHD was clinically defined as skin rash, hyperkeratosis, and body weight loss, followed by histopathologic examination. The number of donor cells in the recipient circulation was determined by flow cytometry using monoclonal antibodies specific for donor and recipient class I MHC (MN4-91-6 and 163).

RESULTS

Under continuous FK 506 immunosuppression, graft survival was prolonged with median survivals of 270, >232, and 229 days after SBTX (n = 4), BMTX (n = 5), and SBTX + BMTX (n = 7), respectively. Clinical signs of GVHD were seen in 25% (SBTX), 80% (BMTX), and 100% (SBTX + BMTX) of these recipients with median onset time of 180, 131.5, and 89 days, respectively. Histopathologic examination of skin in these animals confirmed GVHD. Eventual animal death was not affected by rejection and caused by GVHD, infection, or surgery-related complication, such as volvulus. In SBTX recipients the number of donor cells reached 5% to 10% during the first week after transplantation. Donor cells declined with time and were no longer detected by flow cytometry 50 days after transplantation. After BMTX few, but clearly stained, donor cells (0.2% to 1.5%) persisted in the recipient blood for >200 days. However, the development of GVHD in these BMTX animals was not associated with the increase of donor cells.

When the small bowel and bone marrow were transplanted together, donor cells were easily found and accounted for 3% to 7.3% during the first 2 weeks after transplantation. The number gradually increased with time and the evolution of donor cells was generally associated with the development of skin rash and hyperkeratosis. These signs of GVHD waxed and waned under continuous FK 506 treatment, and donor cells infected between 5% and 20% of the circulating lymphocytes.

DISCUSSION

These results demonstrate that simultaneous small bowel and bone marrow cell transplantation significantly enhanced the engraftment of donor cells. However, this procedure also risks the development of GVHD, which persisted and became a chronic form for the rest of the experimental period under continuous low-dose immunosuppression. Since Monchik and Russel demonstrated that the small bowel graft was able to induce GVHD in Fl hybrid recipients, this unidirectional transplantation model has been widely used for studying GVHD. Our current understanding of the two-way paradigm in organ transplantation is based on the reciprocal host-graft immune reactions. The experimental model described here will be a useful tool to further study the pathogenesis of the disease and develop strategies for prevention or treatment of GVHD based on the two-way interactions between the graft and host.

REFERENCES