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Post Transplantation High-dose Cyclophosphamide (PTCy) to Promote Immune Tolerance After Reconstructive Transplantation

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Background

The life-long use of immunosuppressants and their associated toxicities remains one of the primary obstacles that curtail the wider use of VCAs for reconstruction. In this study we therefore investigated if the combination of bone marrow transplantation and high dose cyclophosphamide induces a state of long term allograft acceptance in the setting of full thickness skin transplantation and orthotopic hind limb transplantation in a mouse model.

Methods

Full thickness skin transplantation and orthotopic hind limb transplantation were performed across a full MHC mismatch barrier. Animals were treated with a non-myeloablative dose of total body irradiation and anti-Thy1.2 monoclonal antibody 24 hours prior to transplantation. In interventional groups, a total of $3 \times 10^7$ unfractionated bone marrow cells and $2.5 \times 10^7$ splenocytes were injected at the day of transplantation. Three days post transplantation a high dose of cyclophosphamide was administered. Peripheral blood chimerism levels and Vβ-T cell receptor staining was performed in selected animals secondary full thickness skin transplants using donor matched and third party grafts were performed.

Results

Full thickness skin graft survival was increased by the treatment protocol alone, compared to controls, however, animals receiving additional donor bone marrow show graft survival of greater 250 d. VCA recipients the addition of donor bone marrow showed no difference in graft survival and currently records greater than 250 d. Mixed donor chimerism is evident during post operative survival in all animals receiving a VCA or a skin graft plus donor bone marrow infusion. Vβ-T cell receptor staining shows decreased expression of Vβ 5.1/5.1 and Vβ 8.1/8.2 in animals receiving the full induction regimen. Donormatched secondary skin grafts were accepted.

Conclusion

The results of this study demonstrate that a non-myeloablative conditioning regimen combined with pre-transplant T cell depletion and post transplant cyclophosphamide induces long-term allograft survival in a fully MHC mismatched murine skin and VCA model. Results further underline the crucial role of concomitant donor BM and splenocytes transfusion for long-term graft acceptance in this model. Results of mechanistic studies indicate thymic engraftment of donor derived cells and a selective state of donor specific tolerance.