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Enhanced Immune Reconstitution by Sex Steroid Ablation following Allogeneic Hemopoietic Stem Cell Transplantation[1]

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Delayed immune reconstitution in adult recipients of allogeneic hemopoietic stem cell transplantations (HSCT) is related to age-induced thymic atrophy. Overcoming this paucity of T cell function is a major goal of clinical research but in the context of allogeneic transplants, any strategy must not exacerbate graft-vs-host disease (GVHD) yet ideally retain graft-vs-tumor (GVT) effects. We have shown sex steroid ablation reverses thymic atrophy and enhances T cell recovery in aged animals and in congenic bone marrow (BM) transplant but the latter does not have the complications of allogeneic T cell reactivity. We have examined whether sex steroid ablation promoted hemopoietic and T cell recovery following allogeneic HSCT and whether this benefit was negated by enhanced GVHD. BM and thymic cell numbers were significantly increased at 14 and 28 days after HSCT in castrated mice compared with sham-castrated controls. In the thymus, the numbers of donor-derived thymocytes and dendritic cells were significantly increased after HSCT and castration; donor-derived BM precursors and developing B cells were also significantly increased. Importantly, despite restoring T cell function, sex steroid inhibition did not exacerbate the development of GVHD or ameliorate GVT activity. Finally, IL-7 treatment in combination with castration had an additive effect on thymic cellularity following HSCT. These results indicate that sex steroid ablation can profoundly enhance thymic and hemopoietic recovery following allogeneic HSCT without increasing GVHD and maintaining GVT.

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[4] Abbreviations used in this paper: HSC, hemopoietic stem cell; HSCT, HSC transplantation; RTE, recent thymic emigrant; BM, bone marrow; cx, castrated; GVHD, graft-versus-host disease; GVT, graft vs tumor; DTH, delayed-type hypersensitivity; Tg, transgenic; TCD, T cell depleted; DC, dendritic cell; TN, triple negative; DP, double positive; SP, single positive; HPRT, hypoxanthine phosphoribosyltransferase; LHRH, luteinizing hormone-releasing hormone.