MANIFESTATIONS OF ACUTE AND CHRONIC GRAFT-VERSUS-HOST-DISEASE IN REDUCED-INTENSITY ALLOGENEIC STEM CELL TRANSPANTATION (RISCT) FOR PEDIATRIC CANCER

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Background: Allogeneic stem cell transplantation (alloSCT) plays an important role in the treatment of pediatric malignancies. Unfortunately, its success is limited by toxicities associated with myeloablative preparative regimens. We have piloted a reduced intensity alloSCT (RISCT) approach intended to reduce toxicity and to promote rapid immune recovery and enhanced Graft-Versus-Tumor (GVT) effect. The risk of increased GVT effects may coincide with increased manifestations of GVHD. Although the adult RISCT experience has shown increased GVHD, the pediatric oncology experience is limited. Here we review the unique manifestations of GVHD in pediatric patients undergoing RISCT at our institution.

Methods: We piloted a RISCT regimen in 26 pediatric patients with high-risk hematologic malignancies and sarcomas. Fludarabine-based induction chemotherapy was administered for disease control and targeted CD4 count reduction. Pre-transplant conditioning consisted of cyclophosphamide (1,200 mg/m2/day) and fludarabine (30 mg/m2/day) x 4 days plus melphalan (100 mg/m2 x 1 dose in sarcoma pts). Grafts consisted of G-CSF mobilized unmodified peripheral blood stem cells from 5-6/6 HLA-matched first-degree relatives (median CD34 dose 9.42 x106/kg; median CD3 dose 387 x106/kg). Cyclosporine was used for GVHD prophylaxis in both trials, 3 sarcoma patients also received sirolimus.

Results: Twenty-three of 26 recipients developed aGVHD: 18 with grade 1-2, 4 with grade 3, and 1 with grade 4. Twenty-one of 23 patients with >100 days follow-up developed GVHD. GVHD has been responsive in most and 6 of 11 surviving remain on treatment. Unique findings in this group include a high incidence of GVHD (91%), including high rates of bronchiolitis obliterans (BO) and rejection. Also in the adult RISCT experience has shown increased GVHD, the pediatric oncology experience is limited. Here we review the unique manifestations of GVHD in pediatric patients undergoing RISCT at our institution.

Conclusions: Despite a significant percentage of recipients experiencing acute and chronic GVHD, the transplant is overall well tolerated. Both trials however were amended to reduce the incidence of GVHD. Sirolimus was added as prophylaxis in sarcoma patients and the stem cell source for those with hematologic malignancies was changed from peripheral blood to bone marrow. With modifications aimed to control GVHD, the RISCT regimen may allow for successful application of this approach in pediatric cancers.

ROLE OF RESPIRATORY VIRAL INFECTION IN THE DEVELOPMENT OF ALLO-REACTIVE LUNG DISEASE

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Background: In lung transplants respiratory viruses (RV) are associated with bronchiolitis obliterans (BO) and idiopathic pneumonia syndrome (IPS). Both play an important role in the treatment of pediatric malignancies. Unfortunately, its success is limited by toxicities associated with myeloablative preparative regimens. We have piloted a reduced intensity alloSCT (RISCT) approach intended to reduce toxicity and to promote rapid immune recovery and enhanced Graft-Versus-Tumor (GVT) effect. The risk of increased GVT effects may coincide with increased manifestations of GVHD. Although the adult RISCT experience has shown increased GVHD, the pediatric oncology experience is limited. Here we review the unique manifestations of GVHD in pediatric patients undergoing RISCT at our institution.

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REDUCED INTENSITY CONDITIONING ALLOGRAFTING INDUCES THE GENERATION OF ANTIGEN-SPECIFIC REGULATORY T CELLS NECESSARY FOR GRAFT TOLERANCE

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Reduced intensity conditioning (RIC) regimens have been developed to assist the establishment of host-versus-graft (HvG) tolerance which is required for the subsequent use of donor lymphocyte infusions. Therefore, understanding the mechanisms of HvG tolerance is crucial for maximising the donor lymphocyte mediated graft versus leukaemia (GvL) effect. To address this question we have utilized an animal model whereby sublethally irradiated (400cGy) female recipients were transplanted with bone marrow (BM) cells from syngeneic male donors. Under these conditions, donor cells engraft and HvG tolerance specific for the male H-2 antigen is established. We observed a selective expansion of T cells with a regulatory phenotype (CD4+CD25+FoxP3+) in the peripheral blood, spleen, and bone marrow of recipient mice. Such expansion was not antigen-dependent nor it depended on the administration of donor hematopoietic cells. In fact, irradiation alone or the irradiation and infusion of female BM cells were sufficient to generate similar levels of Treg expansion. However, when we evaluated the effect of recipient chimeric spleens on H-2 specific MLR, an immunosuppressive activity was identified which was only detectable when the mice were transplanted with male but not female BM cells. Such activity was also observed in vivo: the adoptive transfer of chimeric splenocytes prevented in vivo killing of CFSE-labelled male donor cells in female hosts, and enhanced male donor BM engraftment in suboptimally conditioned (200cGy) female recipients. To confirm the role of Tregs in this suppressive activity, we depleted chimeric spleen of CD4+ or CD8+ T cells and in both cases the suppression was abolished or much reduced. The fundamental role of Tregs in HvG induced tolerance was supported by the fact that administration of anti-CD25 depleting antibodies to conditioned recipients at the time of RIC allografting and 2. the presence of the antigen during homeostatic expansion induce the generation of antigen-specific Tregs.