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OUTCOME OF ALLOGENEIC (ALLO) STEM CELL TRANSPLANT (SCT) AFTER FAILURE OF A PRIOR SCT: A SINGLE CENTER'S EXPERIENCE

Alluri, K.C., Paba, C.E., Nath, R. Methodist University Hospital/University of Tennessee Cancer Institute, Memphis, TN

Introduction: SCT is a curative option for patients with hematological malignancies.Treatment options for patients who relapse after a prior SCT are limited and often not curative. There is little experience of allo-SCT in this setting because of concerns of transplant related mortality.

Methodology: Retrospective review was performed of all patients who received an allo-SCT at Methodist University Hospital between february 2003 and february 2008 after failing a prior SCT. There were 12 (7 males, 5 females) patients. The median age was 45.5 range (25–75) years at the time of allo-SCT. Primary diagnosis included lymphoma -5 (4 non-hodgkin,1 hodgkin), acute leukemia -3 and multiple myeloma (MM) - 4. Median number of prior therapies was 4 range (2–7). Prior SCT was autologous (auto) in 10 patients (1 patient-3 autoSCT; 1 patient-2 autoSCT) and allogeneic in 2. Eight patients had active disease and 4 were in complete remission (CR) prior to their allo-SCT. Four patients (all with MM) had developed a secondary MDS/AML prior to their allo-SCT. SCT co-morbidity index was ≥ 3 in 8 and ≤ 2 in 4 patients. Median time from a previous SCT to allo-SCT was 11.6 range (8.6–75.3) months. Donor was a matched sibling for 8 and unrelated donor for 4 patients. Preparative regimen was Fludarabine(F) /Melphalan ($140mg/m^2$) $\pm$ antithymocyte globulin (ATG) $\pm$ Rituxan (R) in 8, F/cytoxan $\pm$ ATG $\pm$ R in 3 and Melphalan ($200mg/m^2$) in one patient. Graft versus host disease prophylaxis was tacrolimus/methotrexate in 10 patients and cyclosporine/ mycophenolate mofetil in 2 patients. All 11 evaluable patients engrafted with a median time to neutrophil engraftment of 11 range (10–16) days and a median time to platelet engraftment of 19 range (9–37) days. Nine patients achieved a CR and 2 had persistent disease after the allo-SCT. Seven patients died at a median of 151 range (7–524) days post allo SCT: 5 from tranplant related mortality (TRM) and 2 from progressive disease. Five patients are alive and disease free at 9,16, 25,42 and 66 months post allo-SCT. Two patients are off all immunosuppressive therapy.

Conclusion: Allo-SCT after failure of a prior SCT is feasible and can result in prolonged survival.

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STABLE MIXED DONOR-DONOR CHIMERISM AFTER DOUBLE CORD BLOOD TRANSPLANTATION

Gertow, J., Berglund, S., Okas, M., Ringden, O., Uhlin, M., Mattsson, J. Karolinska University Hospital, Huddinge, Stockholm, Sweden

Umbilical cord blood is increasingly used as a source of stem cells in allogeneic stem cell transplantation due to it's naïve cell content and high permissiveness for HLA-mismatch. To overcome problems of limited cell numbers, double cord blood transplantation (DCBT) has proven both safe and efficacious. Concerning chimerism analysis after DCBT, previous studies have indicated single unit predominance early after DCBT. In the present study we evaluated the chimeric pattern in T-, B- and myeloid cells using PCR based chimerism analysis in patients after DCBT. Of the seven patients included in this study, five had acute leukemia and two patients had lymphoma. Five patients received myeloablative conditioning and two patients were given reduced intensity conditioning. Interestingly, three patients showed mixed donor chimerism in all cell lineages at 100 days post-transplantation, and two of them still at 25 and 29 months after DCBT, respectively. These two patients are doing clinically well, with no infectious complications or signs of relapse, and neither of them developed acute GVHD after DCBT. All patients received high dose antithymocyte globulin (ATG) before DCBT, which could be an explanation for an increased tolerance between the cord blood units. Immunological studies revealed phenotypic differences between the two cord blood units. Among other things, antigen presenting cells and T cells of memory phenotype predominated in one cord blood unit, whereas natural killer cells were found in higher frequencies in the other unit. In conclusion, in this study donor-donor mixed chimerism was common after high dose ATG and DCBT, and in these cases phenotypical differences between the two cord blood units regarding memory phenotype were found.

GVH/GVL

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TARGETING OF HLA CLASS II RESTRICTED ANTIGENS IN GRAFT VERSUS LEUKEMIA REACTIVITY

Falkenburg, J.H.F., Stumpf, A., Rutten, C.E., van der Meijden, E.D., Luxemburg-Heijs, S.A.P., van Bergen, C.A.M., Willemze, R., Griffioen, M. Leiden University Medical Center, Leiden, Netherlands

The beneficial effect of allogeneic HLA matched stem cell transplantation (SCT) can be attributed to T cells recognizing minor histocompatibility antigens (mHag) expressed on hematopoietic cells of recipient origin. T cells recognizing HLA class I restricted mHag selectively expressed on hematopoietic cells have been shown to be capable of inducing Graft versus Leukemia/lymphoma (GVL) reactivity without significant Graft versus Host Disease (GVHD). Since HLA class II is predominantly expressed on hematopoietic cells, we characterized the role of HLA class II directed T cell responses in GVL reactivity. Since the HLA class II locus consists on HLA-DR, HLA-DQ and HLA-DP we identified whether all different class II molecules could be involved in GVL reactivity. First, we identified the role of CD4 T cells in a patient successfully treated with donor lymphocyte infusion (DLI) for relapsed leukemia after HLA matched SCT who experienced only mild GVHD of the skin. 5 HLA class II restricted mHag were molecularly identified including a HLA-DQ restricted mHag were encoded by PI4K2B, and four HLA-DR restricted mHag. These newly identified autosomal HLA-DR restricted mHag were encoded by a NADP+ dependent dehydrogenase gene (restricted by DRB1*0301), a C-type lectin receptor gene (DRB1*1301), a protein tyrosine kinase gene (DRB3*0101), and a non-classical MHC class I gene (DRB3*0202). These genes show selective or predominant expression in cells of hematopoietic origin and the immunogenic variants have balanced population frequencies of 25–70%. All T cell clones recognized high HLA class II-expressing patient-derived B-cells, mature dendritic cells and in vitro cultured leukemic cells with antigen-presenting phenotype. From a patient with a B cell leukemia successfully treated with DLI resulting in GVL reactivity without GVHD we identified an exclusive T cell response targeting only HLA-DP expressed on hematopoietic cells of recipient origen. We demonstrated that in the absence of inflammatory cytokines none of the HLA class II restricted T cells recognized non-hematopoietic cells. Only after profound upregulation of HLA class II on non-hematopoietic cells, some of the T cell clones could recognize non-hematopoietic tissues. In conclusion, we demonstrate that HLA class II restricted alloreactive T cells contribute to GVL reactivity in the absence of GVHD, and may be sufficient to elicit anti-tumor reactivity in HLA class II expressing hematological malignancies.

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PREVENTION OF ACUTE GVHD DURING HAPLO-BMT: EVALUATING THE EFFICACY OF T-CELL COSTIMULATION BLOCKADE USING A NOVEL RHESUS MACAQUE TRANSPLANT MODEL

Miller, W.P.[1], Wheeler, C.E.[1], Panoskaltsis-Mortari, A.[2], Kirk, A.D.[1], Larsen, C.P.[1], Blazar, B.R.[2], Kean, L.S.[1] [1] Emory University, Atlanta, GA; [2] University of Minnesota, Minneapolis, MN

We have developed a fully pedigreed and MHC-typed Rhesus macaque BMT model, with which to study GvHD and its prevention. For the current study, we have concentrated on MHC haplo-identical BMT, and determined the effect of T cell costimulation blockade on GvHD prophylaxis. Our preparative regimen consists of TBI (8 Gy with lung shielding to 6 Gy). GvHD is graded using standard clinical grading scales. Here we report on the first experimental cohort. The first animal served as a control for TBI-based preparation, and, as expected exhibited profound pancytopenia. The second animal was transplanted with haploidentical hematopoietic stem cells (4.47×10^8 total nucleated cells/kg and 1.10×10^8 CD3+ T cells/kg) and was treated with only rapamycin for immunosuppression. He exhibited profuse diarrhea and necrotic skin changes within 8 days of transplant, coincident with early engraftment, and was sacrificed at day 14. A diagnosis of Grade IV skin GvHD was rendered on