suggests that in the genetic absence of $CD4^+$ T cells, a CD8 regulatory population may emerge. In total, our observations support the notion that functioning host Tregs initially occupy a niche in the transplant recipient permitting lymphopenic expansion and an extended period of contribution to this compartment. Notably, this contribution reflected much greater levels than that by other lymphoid cell populations. Overall, the findings imply that host Treg cells may be important to consider with respect to eliciting anti-tumor and vaccination responses in recipients during the early period post-hematopoietic cell transplantation.

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DEVELOPMENT OF ANTIBODIES TO SELF ANTIGENS K-ALPHA-1 TUBULIN AND COLLAGEN V IN PATIENTS WITH CHRONIC GRAFT VERSUS HOST DISEASE

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Background: Chronic Graft vs. Host Disease (cGVHD) is a multisystem alloimmune and autoimmune disorder characterized by production of antibodies, immune dysregulation and impaired organ function resembling autoimmune diseases. NIH Consensus Criteria for cGVHD (Filipovich et al, BBMT 11:945, 2005) defines bronchiolitis obliterans (BO) diagnosed clinically as a distinctive feature (seen in cGVHD but insufficient alone to establish the diagnosis) and BO diagnosed by lung biopsy as a diagnostic feature of cGVHD (sufficient to establish the diagnosis). Chronic rejection following human lung transplantation is strongly associated with development of alloimmune response to donor mismatched HLA antigens. Recent studies in our laboratory and others have shown a strong correlation between development of autoimmunity to self antigens K-alpha-1 tubulin and collagen V with tissue damage and immunopathogenesis of chronic rejection characterized by BO. In this study, we analyzed the presence of antibodies to self-antigens K-alpha-1 tubulin and collagen V in patients with cGVHD. **Methods:** Serum samples from patients with cGVHD were analyzed for antibodies which bind to human recombinant purified K-alpha-1 tubulin (1 mcg/ml) and collagen V using ELISA assays. Analysis of variance was used to compare the means of different groups with $p < 0.05$ as an indicator of strong association. **Results:** Study includes 21 patients with cGVHD developing after allogeneic transplantation for hematological malignancies and 10 normal controls. 11 patients with cGVHD had lung involvement by NIH Criteria with minimal lung score of 2. Levels of K-alpha-1 tubulin antibodies were higher in patients with lung cGVHD when compared to patients without lung involvement or normal controls ($p = 0.027$). Levels of Collagen V antibodies were higher in patients with lung cGVHD when compared to normal controls ($p = 0.025$) but not when compared to patients without cGVHD of the lung. 64% of patients with lung involvement by cGVHD developed antibodies to both antigens and 82% had antibodies to at least one. **Conclusion:** In this preliminary analysis development of antibodies to K-alpha-1 tubulin and to collagen V appears to be highly associated with cGVHD and the highest titer autoantibodies are seen in those patients with lung involvement. Studies are underway to define the kinetics of these antibodies after transplantation and their incidence and titers in allogeneic stem cell recipients without clinical signs of cGVHD.

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ANDROGEN WITHDRAWAL MODULATES THYMOPOIESIS BY INDUCING THYMIC EPITHELIAL CELL PROLIFERATION AND INCREASING PRECURSOR NICHE

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Impaired thymopoiesis contributes to immune deficiency following allogeneic stem cell transplantation. Emerging clinical literature suggests that graft-versus-host disease may be exacerbated and graft-versus-leukemia effect compromised in the setting of thymic insufficiency. Data have demonstrated that the thymus is damaged following the transplant preparative regimen, with a depletion of UEA+ thymic epithelial cells. We show that castration of male mice results in thymic renewal, as demonstrated by increased thymocyte number, intrathymic T cell receptor excision circles, and the number of early thymic progenitors (ETP: Lin- CD25- c-kit hi CD44 hi) as early as eight days post-castration. These observations suggested a mechanism of enhanced thymopoieis that occurs through increased immigration of thymocyte precursors. Studies with adoptively transferred congenic marrow progenitors confirm that enhanced ETP immigration is an early event following androgen withdrawal. Data also demonstrate a significant increase in UEA+ thymic epithelial cell proliferation by BRDU+ incorporation in the initial time frame following castration, implicating thymic epithelial cell proliferation in this thymic expansion, and suggesting that there may be an increase in thymic niche regulating ETP uptake. We have further identified an increase in a stromal derived protein important for ETP uptake by Western blot in total thymus lysates consistent with a mechanism of an increased ETP niche. Preliminary data also suggest that the mRNA encoding this protein is increased in sorted thymic epithelial subsets, with the greatest increase in the UEA+ medullary TEC cells, implicating these medullary epithelial cells in ETP entry. Taken together, we show that androgen withdrawal leads to UEA+ medullary cell proliferation with augmented ETP niche and entry. Thus, we identify ETP uptake as a critical and dynamically controlled point of thymic regulation.

LATE EFFECTS/QUALITY OF LIFE

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PROSPECTIVE NEUROCOGNITIVE FUNCTION AND RISK FACTORS AT 5 YEARS AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR HEMATOLOGIC MALIGNANCIES, COMPARED WITH CONTROLS AT 5 YEARS

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Investigators have documented significant cognitive decline after high dose treatment followed by allogeneic HCT. We have determined that partial recovery occurs by 1 year, but deficits remain in verbal capacity and motor skills. Our current aims were to determine the extent of long-term cognitive dysfunction, and risk factors for deficits at 5 years. We hypothesized improvement between 1 and 5 years, and that risk factors would include type of treatment before transplant, and duration of immunosuppressant medications. A total of 142 adults completed neuropsychological tests for verbal memory (Hopkins Verbal Learning Test; HVLT), verbal fluency (Controlled Oral Word Association Test; COWAT), information processing (Digit Symbol and Trail Making B; Trails B) and motor dexterity and speed (Grooved Pegboard), among other tests. Survivors were re-tested after 80 days, and 1 and 5 years post-transplant. A neuropsychologist traveled to test each of N = 66 5 year survivors and case-matched controls in person. Generalized estimating equations indicated significant changes over time from pretransplant to 5 years in all tests except memory ($P < .0001$; memory $P = .17$). Between 1 and 5 years, verbal fluency continued to improve ($P = .001$), as did information processing ($P < .01$); but motor dexterity and, memory did not ($P > .65$), remaining below controls ($P < .0001$ motor dexterity, $P = .060$ verbal memory). Table 1 indicates the percent impaired (t score ≤ 40) at 5 years. The only identified risk factor for poorer verbal memory at 5 years was history of intrathecal chemotherapy or cranial irradiation (95% Confidence Interval (CI) 0.71, 15.13, $P = .03$). Risk factors for impaired motor dexterity and speed at 5 years included immunosuppression longer

than 12 months (Odds Ratio (OR) 3.7, CI 1.1, 11.8, P = .03) and emotional distress pretransplant (OR 2.7, CI 1.0, 7.1, P = .05). Results indicate that neuropsychological function continued to improved from 1 to 5 years, but deficits remained for a third or more of survivors in memory and motor dexterity.

Impairment Rates at 5 Years

Test	5 Year Survivors % Impaired*	5 Year Controls % Impaired*
Motor speed and dexterity (Pegboard)	43	17
Verbal memory (HVLT)	32	20
Verbal fluency (COWAT)	20	14
Information processing (Digit Symbol/Trails B)	12/15	6/8

*T scores in normative samples would have ~15% impaired.

Scoring System

Variable	Variable Score
DLCO (% predicted): <65	1
≥65	0
AST (IU/L): >40	1
≤40	0
Albumin (g/dl): <3.5	1
≥3.5	0
Stem Cell source: Bone Marrow	1
Peripheral blood	0
Transplant: Unrelated donor	2
Related Donor	1
Autologous	0
Risk Group	Total Score
Low Risk	0, 1
Moderate Risk	2
High Risk	≥3

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A SIMPLIFIED SCORING SYSTEM TO PREDICT DAY 100 NON-RELAPSE MORTALITY AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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This study's purpose was to develop a scoring system using patient characteristics before hematopoietic stem cell transplantation (HSCT) to predict the risk of early non-relapse mortality.

Methods: Patients undergoing their first HSCT at the University of Rochester from 1995 to 2004 were eligible. Non-relapse mortality at 100 days (Day100NRM) was the primary outcome. Sex, race, age, smoking status, body mass index, diagnosis, year, transplant type, cell source, conditioning regimen, dose of nucleated cells, diffusion capacity of the lung for carbon monoxide (DLCO), forced expiratory volume at one second, forced vital capacity, creatinine, BUN, bilirubin, serum aspartate aminotransferase (AST), left ventricular ejection fraction, and albumin were evaluated as independent variables. The study population was randomly divided into two samples: an exploratory sample to construct a prediction model with risk factors for Day100NRM and a validation sample to test this model. **Results:** Data regarding patient characteristics were available on 677 (95%) patients. 507 subjects (75%) were randomly selected to form the exploratory sample. Using logistic regression, related and unrelated allogeneic (versus autologous) transplant, stem cells from bone marrow (versus peripheral blood), low DLCO, low albumin, and high AST were identified as statistically significant predictors of Day100NRM in the exploratory sample (c-statistic = 0.856). This model was successfully validated (c-statistic = 0.819) on the remaining 170 subjects (validation sample) and on three random sub-samples of the exploratory sample. Next, receiver operating characteristic curves and classification tables were used to identify optimal cut-off points to dichotomize DLCO (<65, ≥65% predicted, corrected for hemoglobin), AST (>40, ≤40 IU/L)) and albumin (<3.5, ≥3.5 g/dl) to construct a scoring system for clinical use. This prediction model was used to categorize patients into three groups- low, moderate, or high risk of Day100NRM (see Table). There was an incremental increase in risk of Day100NRM (2%, 13%, 39%) across the risk groups. **Conclusions:** Type of transplant, stem cell source, DLCO, AST, and albumin were predictive of Day100NRM, and were used to construct a simplified scoring system. This pre-transplant risk scoring system may be used for prognostication, and perhaps to institute risk based targeted therapies. External validation is necessary to determine its generalizability to other populations.

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RURAL-URBAN DISPARITIES IN SURVIVAL OUTCOME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES

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Background: We evaluated whether a patient's area of primary residence is an independent risk factor for overall survival (OS) after HLA-identical sibling or autologous hematopoietic stem cell transplantation (HSCT). **Patients and Methods:** This is a retrospective study that included patients who received autologous HSCT (n = 1739) for lymphoma and multiple myeloma (MM) or HLA-identical sibling (n = 267) HSCT for leukemias between 1983 and 2004 at the University of Nebraska Medical Center. Primary area of residence using the patient's zip code was categorized as either urban or rural according to the Rural Urban Commuting Area Codes classifications. Association between area of primary residence and OS was examined using Cox Proportional Hazards regression analysis to adjust for other prognostic variables. The role of distance from transplant center and average income were also explored. **Results:** Patients coming from rural areas were more likely to be: older, Caucasians, live at least 100 miles away, and have an average income lower than $50K compared to patients coming from urban areas. More rural patients are transplanted for MM, otherwise distribution of diseases and disease stages were similar between the two areas. The number of transplants performed in patients coming from rural areas increased in the recent years. In the univariate analysis the following were associated with increased risk of death: patients from rural areas, patients living more than 100 miles away, and patients with income lower than $50K In multivariate analysis, among recipients of autologous HSCT, patients from rural areas had an increased risk of death (RR 1.18, P = 0.016) compared to patients from urban areas after adjusting for age, disease stage and time period of transplant. The effect of distance and income dissipated. Survival rates between rural and urban locations are: at 1 year (73% vs. 78%, P = 0.04) and at 5 years (48% vs. 54%, P 0.012). We failed to detect a significant difference in the risk of death according to area of residence in the HLA-identical sibling HSCT cohort, although this may be due to lack of statistical power. **Conclusion:** The primary location of a patient's residence may be an independent risk factor for survival after HSCT. Specific issues regarding the coordination of follow-up care of patients from rural areas, as well as their health behavior and medical utilization patterns post-HSCT should be studied prospectively.