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SURVIVOR HEALTH AND IMMUNE RECONSTITUTION IN THE SECOND DECADE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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The growing numbers of allogeneic hematopoietic stem cell transplant (HSCT) survivors deserve a study of late effects. We analyzed 48 long term (range 10-16 years) survivors who underwent allogeneic HSCT at the NIH between 1993 and 2000. Their median age at HSCT was 35 years and the current median age is 49 years. There were 20 males and 28 females. Forty-two patients received high dose total body irradiation while the rest received reduced intensity conditioning. Underlying diagnoses were CML (30), MDS/CMMoL (7), AML (5), CLL (2), Myeloma (2), Severe Aplastic Anemia (1) and ALL (1). Currently 38 patients are alive in complete remission, 4 alive with molecular recurrence of CML but 6 have died (2 of second malignancy, one each of relapse, sepsis, CVA and multiorgan failure). Health Related Quality of Life (HRQOL) analysis using the the SF-36 scale found no significant difference in physical or mental health between long term survivors overall and the U.S. general population. Nevertheless, a subset of survivors reporting symptom distress had lower HRQOL. Since immune dysfunction underlies many late effect complications, we analyzed immune reconstitution. Quantitative immunoglobulins for survivors were in the normal range for the population as were absolute lymphocyte counts (ALC), total CD3+, CD3+CD4+, CD3+CD8+, CD19+ and NK cells. Samples from 15 long term survivors were then compared to current samples from their sibling donors and no quantitative differences were observed in absolute lymphocyte counts (ALC), total CD3+, CD3+CD4+, CD3+CD8+, CD19+ and NK cells. However there was a significant expansion in the Treg (CD25+/CD4+/FoxP3+) compartment ($p = 0.02$), accompanied by a decline in naive T cells (CD45RA+/CD27+) ($p < 0.003$) and recent thymic emigrants (TREC+) ($p < 0.05$) in survvors compared to their sibling donors. T cell receptor repertoire analysis showed that there was no significant difference in total complexity score of TCR-Vβ diversity between the patients and their donors, although TCR-Vβ subfamily spectratyping profiles showed divergence between patients and donors with both gain and loss of clonotypes. In conclusion, survivors in their second decade tend to remain vulnerable with disproportionate mortality from diverse causes. Their QOL is typically excellent but a small subset do experience persistent symptom distress. Immune parameters, even 10 years post HSCT, are not completely normal and reflect impaired thymopoiesis and repertoire divergence.

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CHRONIC GVHD SEVERITY AND SENSITIVITY TO CHANGE IN PATIENT-REPORTED QUALITY OF LIFE: RESULTS FROM THE CHRONIC GVHD CONSORTIUM

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Chronic graft-versus-host disease (GVHD) threatens patient-reported quality of life (QOL) after allogeneic hematopoietic cell transplantation. However, the sensitivity of serially assessed chronic GVHD severity to change in QOL has not been determined. We examined the sensitivity of changes in chronic GVHD severity (determined separately by NIH consensus severity criteria, physician-assessed severity, and patient-reported chronic GVHD severity) to changes in QOL as measured with the SF-36 and FACT instruments in a prospectively assembled multi-center cohort of chronic GVHD affected HCT recipients. A total of 341 individual adult (median age 52, range 19 – 79) patients (182 incident, 159 prevalent) from 6 transplant centers contributed data to an analysis encompassing 917 total visits. Chronic GVHD involvement most commonly included skin (56%), oral (53%), ocular (55%), and hepatic (39%) manifestations. On follow up, the majority had unchanged chronic GVHD severity. However, follow up visits demonstrated improvement (NIH 16%, physician 20%, patient 22%), or rather worsening (NIH 17%, physician 14%, patient 16%) in others. Subjects with complete or with missing data had similar clinical characteristics, excepting that those without missing data were more likely to have a college or post-graduate degree ($p = 0.007$). Univariable analysis accounting for repeated observations was performed to examine the relationship between change in chronic GVHD severity and change in QOL. Multivariable analysis was performed considering patient socio-demographic, disease, and transplantation covariates. Conclusions discerned in univariable analysis persisted: Change in NIH severity was not sensitive to change in QOL. Change in physician-assessed severity was sensitive to changes in SF-36 MCS (mental component summary), and FACT-TOI (trial outcome index), FACT-Total, and FACT-BMT (BMT subscale). Change in patient-reported severity was sensitive to changes in all QOL outcomes ($p < 0.001$ for each). These data demonstrate that NIH and physician determined chronic GVHD severity assessment do not capture the full symptom burden experienced by chronic GVHD affected patients. The data support the incorporation of patient-reported chronic GVHD severity in the evaluation of severity change and therapeutic response in the conduct of clinical trials as well as routine clinical practice for those affected by chronic GVHD.

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EXPRESSION OF p16, A BIOMARKER OF HPV INFECTION, IS ASSOCIATED WITH ESOPHAGEAL PRECANCEROUS STATE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: NEW TOOLS FOR EARLY DIAGNOSIS OF THIS FATAL DISEASE

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Introduction: Squamous cell carcinoma (SCC) of the oral cavity or esophagus is a common secondary cancer after allogeneic hematopoietic stem cell transplantation (allo-HCT). As different from oral SCC, diagnosis of esophageal carcinoma upon clinical symptoms is relatively late and mostly fatal. Thus, early detection of esophageal carcinoma is highly desired. Previous studies reported that human papillomavirus (HPV) infection is correlated with developing oral SCC after HCT. HPV infection is well documented as a causative organism of cervical or oral SCC. Besides, several studies have shown that the expression of p16 in biopsy specimens is associated with HPV infection in cervical SCC and is also found in precancerous states such as intraepithelial neoplasia, dysplasia and koilocytic change. In the gynecology field, p16 staining is commonly used for biomarkers of HPV infection.

Purpose and Methods: To clarify the correlation between expression of p16 and the development of esophageal carcinoma after allo-HCT, 48 patients who survived for at least 1 year after HCT were enrolled in this study. They were examined by endoscopy and Lugol staining. If Lugol's voiding lesion was found, biopsy and the staining for p16 were performed.

Result: The median age was 45 years, and the median duration of follow-up was 7.3 years. In one patient, a tumor found by endoscopy was diagnosed as SCC. Of the remaining 47 patients who received Lugol staining, 22 showed unstained areas and were examined by biopsy. Expression of p16 was found in 15 of the 22 patients. Among fifteen p16- positive patients, precancerous lesions such as intraepithelial neoplasia ($n = 1$), dysplasia ($n = 1$) and koilocytic changes ($n = 5$) were found. On the other hand, among seven p16-negative patients, only a koilocytic change was found in one patient. Chronic GVHD and administration of immunosuppressin at the examination were significantly related with p16 positivity.

Conclusion: The present study demonstrates that examination by endoscopy and Lugol staining is a useful tool to detect precancerous esophageal carcinoma. Although the direct correlation between expression of p16 and HPV infection in this study is still under study, it suggests that HPV may be a causative pathogen of esophageal carcinoma after allo-HCT under immunosuppressive conditions after allo-HCT.

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AZITHROMYCIN REDUCES THE SEVERITY OF NON-INFECTIOUS LUNG INJURY AFTER EXPERIMENTAL HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Non-infectious lung injury (NILI) after allogeneic (allo) hematopoetic stem cell transplantation (HSCT) significantly contributes to morbidity and mortality and can manifest as restrictive or/and obstructive pulmonary function impairment. Beneficial effects of macrolides on airway inflammation and pulmonary obstruction both after allo-HSCT and solid organ transplantation (SOT) have been described in clinical studies. We tested the role of long-term azithromycin (Azi) administration in reducing the severity of NILI following murine HSCT. Lethally (12Gy) irradiated B6D2F1 mice received 5 × 10E6 bone marrow and 6 × 10E6 splenocytes from either syngeneic (syn) (B6D2F1) or allo (C57BL/6) donors. One half of allo recipients received drinking water supplemented with Azi (1mg/ml between day +14 and day +17, 0.5mg/ml from day +18 until day +100), whereas the other half of allo and syn recipients received water only. On day +98, surviving animals were analyzed and pulmonary function tests (PFT) were performed.

All syn animals were alive and without clinical signs of graft-versus-host disease. Azi treatment in allo recipients resulted in better overall survival when compared to allo controls (53.3% vs. 29.4%), but did not relate to changes in clinical weight loss, mobility, fur and skin changes (score: 2.7 vs. 2.7). PFT, however, revealed significant improvement in both restrictive and obstructive parameters for Azi-treated animals when compared to allo controls (VC: 0.534±0.069 vs. 0.435±0.068 ml; $p = 0.034$; Cchord: 0.029±0.004 vs. 0.021±0.002 ml/cm H2O; $p = 0.0049$; FEV50: 0.446±0.06 vs. 0.369±0.039 ml; $p = 0.032$). Moreover, Cchord and FEV50 were not significantly different between AZI animals and syn controls. Neutrophil counts were assessed by myeloperoxidase (MPO) activity, with Azi-treatment resulting in its reduction. Further, CXCL1 and CXCL2 lung protein levels as well as IL-6 and TGFβ1 levels were significantly lower in the Azi allo group than in allo controls, whereas no differences were seen for TNF, IFNγ or CXCL9.

Our data experimentally confirm the beneficial effects of Azi on pulmonary function impairment in allo-HSCT recipients as being at least partially mediated through altered chemo- and cytokine expression and decreased neutrophil recruitment to the lung. They strengthen the concept of Azi as a well-tolerated, inexpensive but yet efficient drug in the treatment of NILI following allo-HSCT and SOT.

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ENDOCRINE COMPLICATIONS FOLLOWING PEDIATRIC BONE MARROW TRANSPLANTATION

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Background: Pediatric bone marrow transplantation (BMT) for various diseases can lead to endocrine system dysfunction due to the common preparative regimens involving chemotherapy and radiation therapy.

Objective: The primary objective of this study was to assess the prevalence of post BMT endocrine complications in children treated at the Alberta Children's Hospital from 1991-2001. The secondary objectives were to characterize the time of onset of endocrine dysfunction, underlying disease processes, chemotherapy, radiation therapy, and age at the time of BMT.

Methods: A retrospective cohort study design was used. Subjects were included if they were less than 18 years of age at the time of their BMT (allogeneic or autologous) at the Alberta Children's Hospital, the BMT was performed between January 1, 1991 and December 31, 2001, the subject had follow-up through the Alberta Children's Hospital for at least one year post BMT, and their charts were available for review. Subjects were excluded if they had a pre-existing diagnosis of an endocrine condition under evaluation prior to their bone marrow transplant.

Results: A total of 194 pediatric BMT procedures were performed at the Alberta Children's Hospital from January 1, 1991 to December 31, 2002. Of these, 150 complete charts were available for review. Sixty five subjects received follow up care at other centers and were not included in this study. Therefore, a total of 85 subjects were included in this review. The prevalences of endocrine complications identified were: primary hypothyroidism 1.2%, compensated hypothyroidism 7.0%, hyperthyroidism 2.4%, hypergonadotrophic hypogonadism 22.4%, abnormal bone density 2.4%, and secondary diabetes mellitus 1.2%.

Conclusions: These findings emphasize the need to screen for endocrine system dysfunction, particularly hypergonadotrophic hypogonadism in children who have undergone BMT. Children need to be followed long term so that endocrine complications can be diagnosed and treated promptly.

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VARIATION IN MANAGEMENT OF IMMUNE SUPPRESSION AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION: RESULTS OF A NATIONAL SURVEY OF ASBMT TRANSPLANT PHYSICIANS

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Practice variation in immune suppression (IS) liberation after allogeneic hematopoietic cell transplantation (HCT) is anticipated to have important consequences, but has not been characterized to date. We conducted a survey of transplant physician members of the American Society for Blood and Marrow Transplantation to discern variation in IS management and attitudes toward this practice, characterize the burden of GVHD in the setting of IS taper, and to describe the proportion of HCT recipients who successfully liberate from IS by 2 and 5 years. From 1,100 eligible physicians, 225 (21%) completed the electronic survey. Practice varied according to reported time of initiation of IS taper post-HCT, sequence of agents tapered, frequency of changes, and strategy utilized; 25% reported no consistent strategy. In the presence of post-HCT relapse, 71% of respondents recommended stopping all IS agents, and 50% utilized donor lymphocyte infusion. Confidence in therapeutic decision making was limited: Most reported no consistent practice guidelines, 41% reported that their current IS liberation strategy is not adequate, and 26% reported being either uncomfortable or very uncomfortable with making decisions on IS management. The majority indicated that they could not predict who would develop GVHD on taper of IS, and reported a resultant burden of GVHD emerging or recurring in the setting of IS taper. In the setting of recurrent GVHD following IS taper, therapeutic approaches differed: 44% resumed the original IS agents; 73% started 1-2mg/kg of steroids; and 16% both started 1-2mg/kg steroids and added an additional systemic IS agent. The potential adverse consequence of GVHD emerging or recurring in the setting of IS taper was highlighted by HCT physicians' self-report of the proportion of these cases that are not successfully treated to resolution. Projected rates of IS liberation increased from 2 to 5 years post-HCT, and differed significantly according to donor relation and stem cell source utilized ($p < 0.05$). The marked variation in practice, burden of GVHD emerging in the setting of IS taper, and limited confidence in therapeutic decision making all highlight shortcomings in an essential component of HCT physicians' scope of practice. These findings argue for both more rigorous study of IS liberation post-HCT and development of evidence-based practice guidelines.