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Celiac Disease Transmitted By Unrelated Cord Blood Stem Cell Transplantation (CBST)

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Background: Celiac disease is due to intolerance to certain cereal proteins leading to immune-mediated small bowel villous atrophy and malabsorption. Specifically, the gliadin component of wheat, and the prolamin component of rye and barley are implicated in causing disease. BMT and CBST have been known to transmit immune associated diseases such as diabetes mellitus immune thrombocytopenic purpura from an affected donor to transplant recipient.

Methods & Results: We observed the occurrence of Celiac disease in a patient a year following cord blood stem cell transplantation (CBST) for acute myelogenous leukemia (AML- FAB M2) in complete second remission (CR-2). The patient had no history of celiac disease prior to CBST nor any family member. The cord donor was HLA-identical unrelated male donor with HLA types: A3, B7 (w6), DR (B1), DR (B5). The family history of the donor was unavailable for celiac disease. The CBST was complicated by grade 2 skin Graft versus Host Disease (GVHD), which responded to steroid therapy. A year post transplantation she developed persistent mucous diarrhea with tinge of blood associated with abdominal cramps. Investigations for infectious causes such as CMV enteritis were negative and colonsocopy did not reveal any evidence of GVHD. Gastrointestinal symptoms persisted and did not respond to steroid and prograf therapy. Subsequent duodenal and jejunal biopsy revealed subtotal villous atrophy with cryptic hyperplasia suggestive of celiac disease. Antigliadin IgA and IgG, reticulin IgA and Endomysial IgA andibodies were elevated. A diagnosis of post-CBST coeliac disease was made. She responded well to gluten-free diet and became symptom-free.

Discussion & Conclusion: A literature review identifies only from donor to recipient one previous example of transmission of celiac disease following HSCT. This case could be the second case of celiac disease following transplantation and the first one post CBST. An association of celiac disease with some HLA types, including DQA1.0501, and DQB1.0201, in conjunction with the haplotypes A30, B18, DR3, DRw52, and DQ2 was recently noted. The donor of this case exhibit HLA DQ A1.0501 and DQ B1.0201 alleles. The findings suggest transfer of celiac disease by cord stem cells and confirm the immune nature of the disease. In addition the propensity to develop T-cell non-Hodgkin lymphoma and transmission of celiac disease by CBST support T cell concept in celiac disease. Autoimmune enteropathy should be considered in patient with persistent diarrhea post hemopoietic stem cell transplant.

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Non-Myeloablative (NMA) Allogeneic Hematopoietic Stem Cell Transplant for the Treatment of Patients with Hematologic Malignancies Using Busulfan, Fludarabine and Total Body Irradiation (Bu/Flu/TBI) Conditioining: Results of a Phase II Trial

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Multivariate Analysis of Clinical Predictors of Overall Survival (n=92)

Characteristic	HR (95% CI)	P-Value
KPS <90	2.08 (1.10-3.92)	0.023
HCT-CI 4+	2.77 (1.44-5.32)	0.002
Not in CR	1.16 (0.59-2.32)	0.664
Age >65	1.32 (0.70-2.51)	0.393
Plt Engraftment >15 Days	2.48 (1.21-5.08)	0.013
ANC Engraftnent >14 Days	1.58 (0.84-3.00)	0.156
+ aGVHD	4.31 (1.80-10.33)	0.001
+ cGVHD	1.24 (0.53-2.95)	0.618
Risk Score: High/Very High	1.40 (0.67-2.90)	0.371

*All variables were normalized to HR=1

Introduction: Non-myeloablative (NMA) allogeneic transplant for the treatment of hematologic malignancies has become the standard of care for patients unable to tolerate myeloablative conditioning. The BuFluTBI transplant regimen was designed with the primary goal of reducing non-relapse mortality (NRM) while maximizing primary disease control in older and infirm patients.

Methods: Patients with high-risk hematologic malignancies were given an outpatient conditioning regimen of busulfan 3.2 mg/kg IV on day -5, fludarabine 30 mg/m2 IV on days -4, -3, -2, and 200 cGy of total body irradiation (TBI). Sources of hematopoietic stem cells were either from related or unrelated donors (at least 7/8 antigen match). GVHD prophylaxis was given with cyclosporine and mycophenolate mofetil. Clinical predictors of response were evaluated utilizing Cox Proportional Hazards Model.

Results: 147 patients were enrolled from 2005-2011; 86 (59%) with myeloid disease and 61 (41%) with lymphoid disease. The median age was 64, and the median comorbidity index (HCT-CI) score was 3. The overall survival (OS), with 2 years median follow-up, was 60% at 1 year and 48% at 2 years, with projected OS 37% at 5 years. Relapse rates were 29% at 1 year and 33% at 2 years, with relapse mortality of 13% at 1 year, and 20% at 2 years. NRM at 1 year was 27% and 33% at 2 years. 54% of patients developed early or late grade II-IV acute GVHD (aGVHD), and 67% of patients developed cGVHD within 2 years. On multivariate analysis, amongst 92 evaluable patients, HCT-CI score greater than 4, pre-transplant KPS <90, delayed platelet engraftment >15 days, and aGVHD were found to be independent predictors of poor survival as demonstrated in the table.

Conclusions: In an infirm elderly population with a high HCT-CI, BuFluTBI is an effective regimen with favorable OS with acceptable levels of NRM.

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What Happens Next? - Outcomes after Relapse Following Allogeneic Haematopoietic Stem Cell Transplant for Acute Leukemia in Adults

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Background: Relapse after allogeneic stem cell transplant (allo-HSCT) for acute leukaemia (AL) remains a major

challenge. Despite advances in allo-HSCT reducing risk of morbidity and mortality, relapse has not altered significantly. We performed a single institution review of relapse following allo-HSCT in patients with AL examining salvage therapy and characteristics of long term survivors.

Methods: All adult patients who proceeded to an allo-HSCT for AL from 1998-2012 (n=100) were reviewed. 24 relapsed following allo-HSCT and a detailed review of salvage treatments and outcomes was made. Probability of overall survival (POS) and 95% confidence interval (CI) were calculated by actuarial method.

Results: The 5 year POS of the 100 patients with AL proceeding to allo-HSCT was 71 % (CI 61-80%). Of 24 relapsing after allo-HSCT, 17 had initial diagnosis AML, and 7 ALL. The AML group median age was 49y (range 22-65), 53% male. Ten patients received sibling donors, 6 unrelated donors and 1 patient a related haplo-identical donor. Relapses were mostly systemic (14) and extra medullary (EM) 3 of the 17 cases. Median time to relapse was 13 months (3-57). Salvage treatments were: second allo-HSCT +/- chemotherapy (chemo) (n=5); donor lymphocyte infusion (DLI) +/- chemo (n=5); chemo +/- withdrawal of immunosuppression (WI) (n=4); or palliative/supportive care (n=3). Ten patients (57%) achieved complete response (CR), and CR was maintained by 8 patients (47%), with a median follow up 34 months (range 8-66). All deaths (n=9) were due to disease. All 3 patients with EM relapse are in ongoing remission.

In the ALL group (n=7) median age was 22y (range 19-52), 57% of male. 3 were sibling donor transplants, 3 unrelated and 1 patient received a double cord. Relapse was systemic in 5 patients, and EM in 2. Median time to relapse was 13 months (range 3-57). Salvage treatments comprised: chemo +/- WI (n=3), second allo-HSCT +/- salvage chemo (n=2), DLI +/- salvage chemo (n=1), with 1 patient receiving novel monoclonal antibody therapy. Three patients achieved a CR, however, all died, 2 of disease progression. Two patients remain alive in PR with ongoing salvage treatment to be determined.

Conclusions: Despite advances in allo-HSCT, long term survival outcomes for patients with ALL who relapse after allo-HSCT remain poor. However, in contrast, for patients with AML who relapse, durable long-term remissions can be achieved with salvage therapy (with and without second allo-HSCT) with almost half of our patients (47%) in ongoing CR at a median of 34 months (range 8-66). As shown in other studies EM relapse, may be salvaged with good long term results.

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Impact of Invasive Fungal Infections on Mortality, Length of Hospital Stay, and Costs in Allogeneic Hematopoietic Stem Cell Transplant Patients

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Background: Over the last decade, unrelated donors have become a vital resource for hematopoietic stem cell transplantation (HSCT) and the number of allogeneic HSCT (allo-HSCT) has increased significantly. While invasive fungal infections (IFIs) remain major concerns in these patients, data regarding impact of these infections on mortality, length of hospital stay, and hospital charge are limited in the United States at a national level. Additionally, with many updates in transplant practice, risk factors for IFIs in these patients may have changed.

Methods: To assess risk factors and impact of IFIs on mortality, length of hospital stay, and hospital charges, a quantitative and cross-sectional design was used to analyze secondary data from the 2010 Healthcare Cost and Utilization Project - Nationwide Inpatient Sample (HCUP NIS) database. Chi-square test, Mann-Whitney test, and multiple logistic regression were used for statistical analyses.

Results: A total of 5,753 weighted hospital records of allo-HSCT were identified with a mean age of 44.8 $\pm$ 19.1 years. The IFI rate was 7.8% (451), with aspergillosis (30.6%) and candidiasis (9.6%) as the two most common IFIs. Compared to patients without IFIs, patients with IFIs had nearly 5 times higher mortality (25.1% vs. 5.1%), longer hospital stays, and higher hospital charges ($p < .01$). Multiple regression analyses on risk factors confirmed presence of graft-versus-host disease as a recognized risk factor for IFIs. However, younger age, female gender, and related donors were also identified as risk factors for IFIs in this analysis. The underlying reasons for these unexpected findings will be explored.

Conclusions: An analysis of a large U.S. inpatient database confirmed that allo-HSCT patients with IFIs have higher mortality and higher health care costs. The risk factors for IFIs have been identified that could enable better management and control of these infections.

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The Impact of ABO Incompatibility in Allogeneic Stem Cell Transplant (ALLOSCT): A Retrospective Single Center's Analysis

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Background: ABO typing is not readily available within donor databases. ABO incompatibility between donor and recipient is not considered a hurdle to an allogeneic hematopoietic stem cell transplantation (ALLOSCT). Conflicting data still exist as to its influence on graft-versus-host disease (GVHD), relapse, and survival.

Method: We retrospectively examined the impact of ABO compatibility on outcomes of 109 patients who underwent matched unrelated donor (MUD), matched related (REL) and cord blood (CBU) ALLOSCT at our institution since 01/01/2010.

Results: Median age was 58 years (range, 19.9- 83.6); 33 (30%) were female; 64 (59%) patients had a myeloid, 34 (31%) lymhoid, 8 (7%) plasma cell and 3 (3%) had other disorder; 57 (52%) patients received myeloablative, 25 (23%) non-myeloablative and 27 (25%) received reduced intensity conditioning. The stem cell sources were represented by 78 (72%) MUDs, 15 (14%) RELs and 16 (15%) CBUs. 80 (86%) of the MUD and REL transplants were 10/10, 11 (13%) were 9/10, 1