HCoV infection developed LRI. BAL was performed in 38 (18%) patients, 6 of whom had HRhV detection in upper respiratory samples. Two of these BALs tested positive for HRhV.

Conclusion: This prospective study is the first to describe the natural history of HCoV and HRhV infections during the first 100 days after HCT. HRhV and HCoV infections were common and prolonged shedding may occur. While HRhV frequently caused symptomatic URI and occasionally LRI, there was no apparent association with either URI or LRI in patients infected with HCoV in this study group. However, this study does not exclude the possibility that HCoV is a rare cause of lower tract disease. Studies are on-going to further investigate this.

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TACROLIMUS AND SIROLIMUS AS GVHD PROPHYLAXIS FOR SIBLING DONOR HEMATOPOIETIC STEM CELL TRANSPLANT (HCT) USING THREE CONDITIONING REGIMENS; FLUDARABINE-MELPHALAN, FTBI-VP16, AND BUSULFAN-CYCLOPHOSPHAMIDE

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Based on encouraging phase II data, we prospectively tested the combination of tacrolimus and sirolimus (tacro/siro) as GVHD prophylaxis in patients undergoing HLA-matched sibling donor HCT. Eighty-five patients were stratified according to conditioning regimen as follows: fludarabine-melphalan (FluMel: n = 46); FTBI-VP16 (TBI: n = 28), and busulfan-cyclophosphamide (BuCy: n = 11). The median age was 47 years (range: 10–67). The patient diagnoses were AML (33), ALL (18), NHL/HD (11/3), MDS (6), CML (5), myeloma (3), MPD (3), and CLL (1). A majority of patients received a PBSC graft except for five who received a BM graft with the overall median CD34+ cell dose of 5.1 $\times$ 10^6/kg (range: 1.7–10.5). All patients engrafted (median neutrophil engraftment: 15 days). Fifty five of 85 patients are alive after a median follow up of 26 months (range: 14–37). Twenty-two patients died of relapse while eight were due to non-relapse causes including acute/chronic GVHD (3), multi-organ failure (1), mucormycosis (1), leukoencephalopathy (1), and respiratory failure (1). The probabilities of overall survival (OS), disease-free survival (DFS), and relapse at 2 years were 66% (CI: 59–72), 58% (CI: 52–64), and 34% (CI: 28–42), respectively. The day 100 and 2 year transplant-related mortality (TRM) was 3.6% (CI: 2–12) and 10.2% (CI: 7–20), respectively. Conditioning regimen was not significantly associated with OS, DFS, relapse, or TRM. The cumulative incidence of acute GVHD grade II-IV and III-IV was 40% (CI: 37–50) and 16% (CI: 12–27), respectively. Fourteen of 21 patients with grade II GVHD had upper GI involvement only. There was a trend for higher probability of acute GVHD in patients conditioned with BuCy compared with TBI and FluMel (64%, 49% and 34%, respectively)($p = 0.12$). The probability of chronic GVHD was 45% (limited: 14%, extensive: 31%). Thrombotic microangiopathy (TMA) was a major complication which developed in 19% of patients, significantly associated with BuCy (55%) compared with TBI (25%) and FluMel (6.5%)($p = 0.005$). TMA was reversible in all cases, managed by holding tacro and/or siro except for two who required plasma exchange/hemodialysis. In summary, the combination of tacro/siro is associated with a low TRM rate over 2 years. The encouraging results on acute GVHD in our study support the ongoing phase III trial comparing tacro/siro versus tacro/MTX (CTN 0402). However, TMA was frequently observed and the risk was significantly greater with BuCy conditioning.

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PREDICTION OF VOD USING BIOMARKERS OF ENDOTHELIAL INJURY

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Clinical risk factors for VOD are well known, however, predicting the occurrence of VOD in individuals remains challenging. Since the primary mechanism of injury in VOD is conditioning-related damage to hepatic sinusoidal endothelial cells and hepatocytes, we measured soluble biomarkers of endothelial injury in the peri-stem cell transplant (SCT) period to determine if they correlated with the occurrence of VOD.

Methods: 59 patients who underwent HLA-matched donor SCT received conditioning with cyclophosphamide (1800 mg/m^2 x 2) and TBI (14 Gy) and tacrolimus with sirolimus or methotrexate as GVHD prophylaxis are included in this analysis. They are stratified based on the occurrence of VOD (VOD+ n = 18, VOD- n = 41), diagnosed by clinical, radiologic and pathologic criteria. Banked samples collected after conditioning but prior to SCT (day -1) and weekly after SCT (day 7, 14, 21) were thawed and analyzed using commercial ELISA kits and quantified using a VersaMax plate reader. Von Willebrand Factor (vWF) and thrombomodulin (TM) were assayed in plasma; E-selectin and soluble intercellular adhesion molecule-1 (ICAM) were assayed in serum. Assays were performed in duplicate and the mean of two assays were analyzed. Not all patients had every time point analyzed due to missing specimens. The within-sample results were compared using the 2-sided Wilcoxon rank-sum test using the Bonferroni method to adjust for multiple comparisons.

Results: Among patients who received sirolimus, levels of vWF, TM and ICAM were significantly different between VOD+ and VOD- groups on day -1 ($p \leq 0.04$), day+7 ($p \leq 0.0001$) and day+14 ($p \leq 0.004$). E-selectin was only predictive on day+7 ($p = 0.009$). Using pre-defined thresholds, vWF (>1400 IU/ml) and TM (>100 ng/ml) levels on day +7 were 100% sensitive and 100% specific in predicting the occurrence of VOD. Biomarkers could not reliably predict VOD among patients not treated with sirolimus. There were no differences in biomarkers among VOD- patients, suggesting that in the absence of VOD, markers of endothelial injury are not elevated, even when sirolimus is used.

Conclusions: Plasma vWF and TM and serum ICAM elevations before and early after SCT can be used to predict the occurrence of VOD in patients receiving sirolimus. This analysis demonstrates the contribution of sirolimus to endothelial injury and VOD after SCT, and may help select patients in whom prophylactic or pre-emptive strategies against endothelial damage and VOD may be useful.

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CYTOMEGALOVIRUS (CMV) REACTIVATION IN RECIPIENTS OF UMBILICAL CORD BLOOD (UCB): RISK FACTORS AND OUTCOMES

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Pre-transplant CMV serostatus has been shown to be an adverse risk factor in allo-HCT recipients. The consequences of CMV reactivation after transplantation have not been extensively described in the UCB setting. We analyzed the impact of pre-transplant CMV seropositivity and CMV reactivation on UCBT outcomes. Between 1994 and 2007, 332 patients with malignancies underwent UCBT at the University of Minnesota and 54% were CMV seropositive. All UCB units were considered seronegative. While there was a trend to greater day 100 TRM ($p = 0.07$), CMV seropositivity was not associated with survival ($p = 0.55$) or relapse ($p = 0.78$). For the 180 CMV seropositive patients, the median age at UCBT was 51 years (range 6–68). Myeloablative conditioning consisting of cyclophosphamide (CY) and TBI 13.2 Gy, with ATG (n = 31, 25%) or fludarabine (FLU, n = 91, 75%). Myeloablative conditioning was followed by single (n = 56, 46%) or double (n = 66, 54%) UCBT. Reduced intensity conditioning (RIC) consisted of CY, FLU and TBI 2 Gy and was followed by double UCBT in all 58 patients. GVHD prophylaxis consisted of cyclosporine/methylprednisone (17%) or cyclosporine/mycophenolate mofetil (83%). All patients had weekly screening for CMV reactivation (by pp65 antigenemia or PCR) and received acyclovir prophylaxis until day 100. The incidence of CMV reactivation was 51% (92/180) with no difference in recipients of a myeloablative vs. RIC ($p = 0.33$). Among recipients of myeloablative conditioning, CMV reactivation was similar regardless of GVHD prophylaxis regimen ($p = 0.8$). In univariate analysis, the only variables associated with CMV reactivation were older age