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### CURRENT OUTCOMES OF REDUCED-INTENSITY CONDITIONING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR PATIENTS WITH SAP DEFICIENCY AND XIAP DEFICIENCY

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Deficiencies of SAP and XIAP are both associated with X-linked lymphoproliferative disease (XLP) and are treated with allogeneic hematopoietic cell transplantation (HCT). At the current time, there is a paucity of literature concerning the use of RIC HCT for these patients. Fourteen patients with SAP (n = 9) and XIAP (n = 5) deficiencies have been treated at Cincinnati Children's Hospital using a RIC regimen consisting of fludarabine (150mg/$M^2$ if weight > 10kg, or 5mg/kg if weight < 10kg), melphalan (140mg/$M^2$ if weight > 10kg, or 4.7mg/kg if weight < 10kg), and alemtuzumab (median dose of 1 mg/kg given over days -22 to -19, -12 to -9, -11 to -8, -9 to -5, or on days -23, -12, -11). All but one pateint received methylprednisolone plus cyclosporine or tacrolimus for graft versus host disease (GVHD) prophylaxis. All patients received anti-microbial prophylaxis. Patients received 6/8, 7/8, or 8/8 HLA mismatched or matched bone marrow grafts. Median time to neutrophil recovery was 10.5 days (range 8-20). There were no transplant-related toxicities, and no cases of grades II-IV acute GVHD. Mixed chimerism (< 95% donor cells in peripheral blood) developed in 7/14 patients at a median of 48 days (range 17-118) following HCT. Three of these patients maintained greater than 50% donor chimerism without intervention. Stem cell boost and/or donor lymphocyte infusions (DLI) were utilized in 4 patients, which resulted in stable donor contribution to hematopoiesis of greater than 50%. One patient developed grade II acute GVHD related to DLI. Infectious complications included EBV viremia in 1 patient, CMV viremia in 3 patients, and adenovirus viremia in 7 patients. A lower extremity cellulitis and abscess developed in 1 patient, who later developed varicella. Significant pneumonia developed in 4 patients. One patient experienced a constellation of complications including BK viruria, adenovirus infection, diffuse alveolar hemorrhage, multiple central nervous system infections, *Klebsiella pneumoniae* pneumonia, and renal failure. Nine of 14 patients are currently surviving at a median follow-up of 907 days post-HCT. Four deaths were the result of infectious complications related to the transplant. The fifth death was the result of complications of multivisceral transplant. All survivors have a Lansky score of 100. We conclude that RIC-HCT is a viable option for patients with SAP and XIAP deficiencies.

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### MAXIMALLY TOLERATED BUSULFAN AREA UNDER THE CONCENTRATION-TIME CURVE (AUC) IN COMBINATION WITH FLUDARABINE AS CONDITIONING PRIOR TO ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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Intravenous busulfan (IV Bu) dosing in hematopoietic cell transplantation (HCT) has been based largely on bioequivalence studies done with the oral dosage form. As systemic exposure to Bu has been correlated with efficacy and toxicity, we used area under the concentration-time curve (AUC) to prospectively determine the maximally tolerated systemic exposure to IV Bu when given daily in combination with fludarabine. 3 AUC levels were planned: 6000, 7500, and 9000 micromole*min/L, in cohorts of 20 patients (pts) each, with an additional 10 pts to be enrolled at the maximally tolerated AUC. Pts had be 16-65 years old and have a hematologic malignancy, an HLA A, B, C, DRB1 8/8 or 7/8 matched donor, Karnofsky performance status 70-100%, and adequate organ function. The initial dose of IV Bu was 170mg/$m^2$/day on day -6 and day -5; day -4 and day -3 doses were adjusted based on pharmacokinetic modeling after the first dose to achieve an average daily AUC of 6000. First doses for the subsequent cohorts were based on the linear correlation between AUC and dose in the previous cohort: 180mg/$m^2$/day for AUC 7500 and 220mg/$m^2$/day for AUC 9000, with dose adjustment on days -4 and -3 as described. Pharmacokinetic analysis was done after the last dose to verify the accuracy of the dose adjustments. The first 20 pts in the AUC 6000 cohort (DL1) were coenrolled onto a randomized trial of GVHD prophylaxis and were analyzed separately from a second cohort of 20 pts receiving AUC 6000 (DL1A) and standard prophylaxis. 20 pts were then enrolled onto AUC 7500 (DL2), followed by 3 pts on AUC 9000 (DL3). All DL3 pts had dose limiting toxicity so accrual to that level was stopped. An additional 9 pts have been treated on DL2; 2 are < 100 days posttransplant and are not evaluable for toxicity or GVHD. The dose-limiting toxicity seen at DL3 was hepatic venoocclusive disease (VOD) which developed in all 3 pts; 2 pts died. There was no difference between the dose levels in cumulative incidence of relapse (p = 0.58) or event-free survival (p = 0.5). Nonrelapse mortality at 6 months was significantly different: DL1 20%, DL1A 0%, DL2 18.8% and DL3 67% (p = 0.02). Overall survival at 6 months was DL1 75%, DL1A 90%, DL2 78%, and DL3 33% (p = 0.06). We conclude that 7500 micromole*min/L is the maximally tolerated AUC based on protocol-defined criteria but exceeding an AUC of 6000 may not provide any benefit due to the increase in nonrelapse mortality.

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### FEATURES OF FRAILTY ARE SURPRISINGLY COMMON IN ADULTS 50 YEARS AND OLDER UNDERGOING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) IN THE MODERN ERA

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**Introduction:** The rapid growth in HCT for adults 50 years and older demands better measures of age related impairments to determine eligibility and tolerance.

**Methods:** We performed a prospective comprehensive geriatric assessment (CGA) incorporating measures of frailty before HCT for consecutive adults 50 years and older between 2005 and 2010. All diseases and conditioning regimens were acceptable. To assess frailty, we employed the 5 point Fried criteria. This includes three self-report domains of unintentional weight loss, feeling of exhaustion and low physical activity and two performance based measures of walking speed and hand-grip strength. A score of 0 is normal; 1-2 and 3-5 reflect pre-frail and frail, respectively.

**Results:** Among 146 pts who underwent CGA, 95 had complete frailty data in all 5 domains. Missing information arose from incomplete questionnaires and/or performance based tests. Among the 95 with complete frailty data, scores of 0 and 1 were found in 18.9% and 31.6%, respectively. Another 24.2% had 2 features of frailty and 25.2% met full frailty criteria (i.e., 3 or more). Higher frailty scores showed no association with greater comorbidity by HCT-CI (P = .3). Age did not impact frailty; two or more frailty features occurred in 45% of those 60 and older and 54% for those 50-59 years (P = .82). However, more frailty domains were strongly associated with active disease at HCT (P = .008) and worse performance status (P = .004). Pts exhibiting 2 or more frailty domains demonstrated higher day 180 cumulative incidence of relapse at 27% compared to only 4.5% for less frail patients (P = .014). When restricting the analysis to pts in partial or complete remission, similar but non-significant relapse differences were found of 19% for 2 or more frailty features versus 3.5% without (P = .22). Higher frailty scores had no impact on non-relapse mortality, acute GVHD (P = .23) or overall survival (P = .32)

**Conclusion:** We demonstrate for the first time the high prevalence of a frailty phenotype in older adults immediately prior to HCT with 81% meeting at least pre-frail criteria and 24% being frail. The association of frailty with advanced pre-HCT disease and relapse but not greater age intimates prior treatment before HCT conditioning results in a significant loss of reserve and a phenotype of accelerated aging. These data suggest the traditional notion that older patients undergoing HCT are selected for robust health, at least in the modern era of reduced intensity conditioning, may be spurious.