Umbilical cord blood is a useful stem cell source for patients without matched donors, but the low cell dose in individual cord blood units has limited success in adults. We treated 43 patients using a reduced intensity conditioning regimen of fludarabine 30 mg/m2/day Days –8 through –3 (total dose 180 mg/m2), melphalan 100 mg/m2 Day –2 and rabbit antithymocyte globulin 1.5 mg/kg Days –7, –5, –3, –1 (total dose 6 mg/kg). Cord blood units were a 4/6 or higher HLA A, B, DR allele match with the patient and each other and achieved a minimum precryopreservation cell dose of 3.7 × 10 (7) NC/kg. Twenty-one patients received GVHD prophylaxis with cyclosporine and mycophenolate mofetil and 22 patients received tacrolimus and sirolimus. Median age was 49 years and majority of patients had acute leukemia or relapsed lymphoma. The median days to neutrophil and platelet engraftment were 20 and 41 days respectively for the cyclosporine/MMF group and 21 days and 47 days for the tacrolimus/sirolimus patients. The incidence of acute GVHD Grades II-IV and chronic GVHD in the cyclosporine/MMF group was 40% and 34% respectively and 14% and 20% respectively for the tacrolimus/sirolimus patients. Transplant related mortality was 14% in both groups. Overall survival and disease free survival were 57% and 57% at 2 years respectively for the cyclosporine/MMF patients and 73% and 51% at one year for the tacrolimus/sirolimus patients. In a multivariate analysis, age greater than 50 was the only significant predictor of poorer survival. Chimerism studies revealed that one cord unit predominates in 73% of patients. Predictors of the predominant unit include first infusion and higher CD34 and nucleated cell counts. Double cord blood transplantation can be performed safely with this reduced intensity regimen; the graft vs leukemia effect is preserved despite a low rate of graft versus host disease.

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INFECTION AND IMMUNE RECONSTITUTION AFTER HSCT: CHALLENGES AND OPPORTUNITIES

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Post-BMT immune deficiency causes significant morbidity and mortality especially in allotransplant recipients. Despite hematopoietic engraftment and recovery of marrow function, recipients have prolonged defects in generation of functional T and B lymphocytes. The clinical significance has become evident in studies utilizing high doses of pre-BMT cytotoxic therapy, donor hematopoietic stem cell (HSC) sources depleted of mature T lymphocytes, HLA-mismatched donors, and the use of potent lymphocyte depleting antibodies. Most recipients of T-cell replete matched sibling or unrelated donor HSC grafts experience late post-BMT infections, the majority of which are viral and fungal, consistent with T and B cell lymphopenia and dysfunction. A major cause of post-BMT immune deficiency is the loss of thymopoietic capacity, and impaired T cell recovery as a result of factors such as age, radiation or graft-versus-host-disease (**GVHD**). Normal thymopoiesis depends on the interaction of the thymic stroma-derived receptors and ligands. Damage to thymic epithelial cells by pre-BMT conditioning impairs the ability of the thymus to generate mature T lymphocytes after BMT. Approaches to lessen the injury or hasten the repair of or replace thymic epithelial cell or stromal elements or their products represent a promising strategy to speed peripheral T cell reconstitution and function. Common lymphoid progenitor cells (CLPs) migrate to the thymus where they receive cues for development into mature thymocytes through a series of defined maturation steps that are time-dependent. Approaches to increase the total number or homing of CLPs to the thymus or alternatively to begin the thymic maturation process ex vivo may shorten the time to peripheral T cell recovery. Such approaches may result in extrathymic T cell maturation as well. B cell deficiency post-BMT can be prolonged, especially with injuries such as GVHD and conditioning regimens that affect stromal cells and secondary lymphoid organ architecture.

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MULTIVARIATE ANALYSIS OF PATIENT AND GRAFT SPECIFIC FACTORS AMONG 330 RECIPIENTS OF UNRELATED CORD BLOOD TRANSPLANT (UCBT) TO PREDICT RISK OF DEATH FROM OPPORTUNISTIC INFECTIONS (OI) IN THE FIRST 6 MONTHS AFTER UCBT

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Over the past 5 years we have studied the reconstitution of immunity in the immediate post-UCBT period in ~200 pediatric recipients of single unit UCB at Duke University to identify surrogate laboratory markers for those at risk for OI.

Several graft and patient-specific variables were also identified as significant factors when the laboratory measurements of dendritic and T cell reconstitution were analyzed. The overwhelming majority of OI related death occurs in the first 6 months after UCBT. To determine the impact of patient and graft-specific factors on 6-month post-UCBT OI-related mortality we reviewed all consecutive pediatric UCB recipients transplanted at Duke between June 1999 and Oct. 2005. Three hundred thirty (330) pediatric recipients of single UCB grafts were identified. Those receiving a second transplant for primary graft failure were not analyzed. Two hundred twenty (220) of the 330 patients (67%) were alive at 6 months. Of the 110 children who died by 6 months, 64 patients (58%) were identified with OI (viral, fungal, protozoal infections) implicated as a cause of death. The 46 patients who died prior to 6 months and for whom OI was not implicated as a cause of death were omitted from the study dataset, resulting in 284 patients. Of these 284 patients, 220 patients (77%) were alive at 6 months and 64 (23%) died at or before 6 months with cause of death related to OI. Twenty two (22) patients died related to adenovirus infection and twelve (12) due to CMV infection, rendering these two viruses the cause in >50% of all OI related deaths. A logistic regression model was used to investigate the impact of ten demographic and clinical characteristics on the risk of death due to OI by 6 months post UCBT. These potential predictors were gender, race, age at UCBT, CMV serology, HLA mismatches, malignancy, total body irradiation, total graft cell dose/kg, CD34+ graft cell dose/kg and CD3+ graft cell dose/kg, *In univariate analyses*, gender ($p=0.28$), race (0.12) and TBI ($p=0.80$) did not predict 6-month death due to OI. Malignancy ($p=0.07$) was marginally associated with a greater probability of 6-month death due to OI. Malignancy without TBI was also associated with a marginally higher probability of 6-month death due to OI ($p=0.04$). A significantly greater probability of 6-month OI-related death was associated with *CMV positive serology* ($p<0.0001$), *greater HLA mismatch* ($p=0.006$), and *older age* ($p=0.0009$). *Higher total graft cell dose* ($p=0.001$), CD34+ cell dose ($p=0.014$) and *CD3+ cell dose* (0.014) were associated with lower probability of death due to OI at 6 months. Since treatment with TBI was closely related to age *two multivariable models* were fit. Model 1 included; CMV ($p=0.0004$), HLA mismatch ($p=0.042$) and Age ($p=0.03$). Model 2 included; CMV ($p<0.0001$), HLA mismatch ($p=0.005$) and malignancy without TBI ($p=0.04$). Since total graft cell dose, CD34+ cell dose and CD3+ cell dose were also highly correlated, each of these variables was introduced into models 1) and 2) separately. Total graft cell dose was the strongest predictor when cell dose variables were added to Models 1 ($p=0.0097$) and 2 ($p=0.004$). CD34+ cell dose contributed less significantly to both models ($p=0.02$ for both models) while CD3+ cell dose was significant in Model 2 only ($p=0.05$). In Model 1 total graft cell dose and CD34+ cell dose replaced age because cell dose/kg inversely correlates with age. The percent concordance among these models ranged from 71-75%. Thus, in the pediatric cohort 6-month death due to OI can be predicted by the following risk factors: older age, positive CMV serology, >1 HLA mismatch, malignancy without TBI, and lower graft cell dose (total, CD34+ and CD3+). In contrast, gender, race and TBI alone do not predict 6-month death due to OI.