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**Autologous Stem Cell Collection for the Treatment of Malignant Diseases in Pediatric Patients: The Use of the Power Hickman**

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**Background:** Dual-use catheters for chemotherapy and hematopoietic progenitor cell collection are increasingly used in the pediatric autologous transplant population. Published data for benefits and complications with these lines is limited. We evaluated the use of various collection line strategies before and after an institutional change to the Power Hickman dual-use line to determine advantages and disadvantages.

**Methods:** We reviewed 65 collection episodes over a 5 year period comparing 3 groups: Power Hickman, Muhurkar dialysis catheter, and peripheral IV. We assessed variables in the categories of efficiency, complications, and cost.

**Results:** The Power Hickman was found to be more efficient than the Muhurkar for several variables including need for second anesthesia for line placement and number of collection days. No differences were found among the groups for complications. A cost advantage was suggested for the Power Hickman and PIV over the Muhurkar.

**Discussion:** A dialysis catheter may still be required for some patients due to their size and other variables. However, for other groups, our data indicate that dual-use catheters are a safe and efficient option.

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**Outcomes After Second Allogeneic Transplants in Pediatric Patients With Relapsed Hematological Malignancies**

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Recurrence of hematological malignancies is one of the most common indications for a second hematopoietic stem cell transplant (HSCT). However there are limited outcomes data after second HSCT in pediatric patients. We report the results of second HSCT in 42 patients with relapsed lymphoid (n=12) or myeloid (n=30) malignancies after first HSCT performed at our institution between 2000-2012. The median age at the time of the second transplant was 7 years (range: 2-19 years). 20/42 patients had active disease at the time of second transplant. The median time to relapse after a first transplant was 242 days (range: 138d-731d) for lymphoid malignancies and 202.5days (range: 50d-1687d) for myeloid malignancies. 20/42 received a haplo-identical donor (haplo), 19/42 received a matched or mismatched unrelated donor (MUD/MMUD) and 3/42 received a matched or mismatched related donor (MRD/MMRD). 16 patients had myeloablative conditioning and 26 reduced intensity

conditioning. Overall survival and disease free survival (DFS) were 30% (13/42) and 26% (11/42), respectively with a median follow up of 1496 days (range: 37d-3434d). 5/16 of these survivors had received myeloablative conditioning versus 6/26 who received reduced intensity conditioning. The DFS by disease type was 16% (2/12) for lymphoid and 30% (9/30) for myeloid malignancies (MDS/AML, n=6/10; AML, n=2/17; biphenotypic, n=1/1), respectively. Patients with MDS/AML had better outcome than patients with AML alone. Survival also varied according to donor type (7/20 haplo, 4/19 MUD/MMUD, and 0/3 MRD/MMRD). Of the 11 disease free survivors, 8 were in remission at the time of the second transplant and 9 had relapsed >240 days post transplant. Overall median survival was 4.6 years (range: 0.2-9.7 years). The primary cause of death was relapse/persistent disease in 24/42 or infection/ GVHD in 7/42. Additionally, 7 of these patients underwent a third HSCT for relapsed disease after second HSCT and all 7 had active disease at time of third transplant. No patients survived after a third transplant. Hence 26% of relapsed patients may be long term disease free survivors after a second HSCT from a haploidentical or unrelated donor. Patients transplanted in full remission with relapse >240 days after first HSCT and a diagnosis of MDS/AML are likely to be favorable prognostic factors.

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**Outcomes in Pediatric Patients With Engraftment Failure After Allogeneic Transplants**

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Graft failure is an uncommon but serious complication after allogeneic haematopoietic stem cell transplantation (HSCT) and is an indication for a 2<sup>nd</sup> HSCT. However, there are limited outcomes data for pediatric patients who undergo such therapy. We now report on 44 pediatric patients who had a 2<sup>nd</sup> HSCT after graft failure following HSCT for malignant (n=14) or non-malignant diseases (n=30) at our institution between 2000-2012. Primary graft failure was defined as failure to achieve ANC >0.5x10<sup>9</sup>/L for 3 consecutive days by day +30 (day +42 for cord donors) or donor chimerism <5% (n=22) and secondary graft failure was defined as loss of chimerism to <5% after having achieved >5%, or ANC persistently below 0.5x10<sup>9</sup>/L or platelet count <20 x10<sup>9</sup>/L (n=23). The median age at first transplant was 6 yrs (range 1month to 21 years), 18 pts were transplanted from a matched or mismatched unrelated donor (MUD/MMUD); 16pts from haplo-identical donor (haplo), and 10 from a matched or mismatched related donor (MRD/MMRD). Donor stem cell products were: marrow for 26 patients; peripheral blood (PB) for 17 patients and a cord blood unit (CBU) for 1 patient. 26 patients received myeloablative conditioning (MAC); 17 reduced-intensity conditioning (RIC) and 1 patient received no conditioning. The median time between 1<sup>st</sup> and 2<sup>nd</sup> HSCT was 55 days (range: 30d-2587d) for patients with malignancies and 66 days (range: 33d-1846d) for patients with non-malignant disorders. The donor was the same for both the 1<sup>st</sup> and 2<sup>nd</sup> transplant for 34 pts. More patients received PB stem cell products for their second transplant (marrow product=17,

PB=25, CBU=2). At the time of 2<sup>nd</sup> HSCT, 24 had RIC, 8 had MAC and 12 had no conditioning. 31 patients engrafted after the 2<sup>nd</sup> HSCT. The overall survival for patients who underwent a 2<sup>nd</sup> HSCT was 61% (27/44) with a median overall survival of 3.8 years (range: 0.2yrs to >10 yrs) and better survival for patients with non-malignant (21/30) versus malignant disease (6/14). There was no difference in survival between patients with primary versus secondary graft failures. Infection was the primary cause of death (9/17). For 13 patients who failed to engraft after 2<sup>nd</sup> HSCT, 3 patients died and 10 patients received a 3<sup>rd</sup> HSCT of whom 5 patients survive. Thus 61% of pediatric patients can achieve graft salvage from a second transplant, and half of the continuing graft failures can be rescued by a third HSCT.

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### Optimizing Cyclosporine Dosing Regimen to Achieve Therapeutic Levels at the Time of Allogeneic Bone Marrow Transplantation: A Pediatric Quality Improvement Intervention

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Several studies have demonstrated that a therapeutic Cyclosporine (CsA) concentration within one week following graft infusion correlates with a reduced risk of grade III-IV acute graft versus host disease (aGVHD). Therefore, to begin a quality improvement (QI) project we performed a retrospective chart analysis to determine when, using our standard approach to initial CsA dosing, our allogeneic bone marrow transplant patients first achieved therapeutic CsA levels (Trough=150-250ng/ml). Fifty three allogeneic transplants were performed during the period assessed, of which 47 were eligible for evaluation. Patients were excluded from analysis due to alternate GVH prophylaxis or major drug interactions. In this historical cohort, CsA prophylaxis was initiated as follows: loading with Cyclosporine, 2mg/kg/dose IV Q 12 hrs for two days (day -2 and day-1) then decreasing to 1.5mg/kg/dose IV Q 12 hrs. Using this approach, 34% of patients had therapeutic levels within the first 3 days following transplant. Following this baseline analysis, we initiated a QI intervention aimed at achieving a therapeutic trough CsA level in at least 80% of patients by Day +3. To accomplish this, the following new CsA regimen was instituted. Patients 5 years or older received Cyclosporine at 2.5mg/kg/dose IV Q 12 hrs beginning on day -3, and patients less than 5 years of age received Cyclosporine at 2.5mg/kg/dose IV Q 8 beginning on day -3. If the trough level was subtherapeutic (below 100 NG/ML) on day 0, we gave an extra 2mg/kg/loading dose IV, then increased the basal dose by 20%. If the level was between 100 and 149, we increased the basal dose by 20% without an additional loading dose. The impact of this intervention on the percentage of patients

achieving therapeutic CsA levels between Day 0 and Day +3 was then assessed. To date, we have performed 28 transplants under the new CsA regimen. Of these, 23 patients were evaluable. Five patients were excluded per the previous criteria. Using the new dosing guidelines, 87% of patients achieved therapeutic CsA levels in the Day 0 to Day +3 window. This represent a statistically significant improvement over our previous dosing regimen in which 34% of patients achieved therapeutic CsA levels by Day +3 ( $P < .0003$ ). No patients had suprathreshold CsA levels, defined as greater than 400 ng/ml within the first 3 days post transplant. One patient did exhibit nephrotoxicity, defined as a persistent doubling of the serum creatinine by Day +10. This patient also had Adeno and BK viruria at Day 0 which confounds assessment of causation. Overall, the revised dosing regimen is both well tolerated and more effective in achieving the targeted CsA level in  $\geq 80\%$  of cases (95% confidence interval, 68-95%). Following completion of this project, we plan further analyses to determine whether this practice change has impacted rates of aGVHD in our patient population.

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### The Risk Factors Associated with Liver Injury and the Impact of Liver Injury on Transplant Related Mortality in Pediatric Recipients of Allogeneic Hematopoietic Stem Cell Transplantation

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In adults, hepatic complications following allogeneic hematopoietic stem cell transplantation (AlloHSCT) are associated with significant morbidity and transplant related mortality (TRM). However, there is a paucity of parallel data on the incidence of, and risk factors for, liver injury (LI) and the impact of LI on TRM in pediatric AlloHSCT recipients.

**Methods:** We compared total bilirubin, direct bilirubin and alanine aminotransferase values pre-AlloHSCT and at 1month, day +100 and 12 months post-AlloHSCT in 248 patients following myeloablative conditioning (MAC) or reduced toxicity/reduced intensity conditioning (RTC/RIC). Liver injury was defined as  $\geq$  Grade 2 toxicities according to the NCI CTCAE 3.0/4.0 or total bilirubin 1.95mg/dL (1.5 times above upper limit of normal). Univariate and multivariate logistic regression models were used to identify risk factors for the incidences of LI and TRM.

**Results:** 248 eligible patients received MAC (n=109) or RTC/RIC AlloHSCT (n=139). The incidence of LI at 1 month post-AlloSCT was significantly higher in MAC vs. RTC/RIC AlloHSCT based on total bilirubin levels (21.9% vs. 7.8%;  $P = .0067$ ). There was no significant difference in LI pre-AlloHSCT, LI at day +100 and 12 months post-AlloHSCT between the two groups. The TRM among patients with LI at 1 month post-AlloHSCT was as 64.2% (CI<sub>95</sub> 49%, 79.4%)