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FLUDARABINE-BASED REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC TRANSPLANTATION IN CHILDREN WITH MALIGNANT AND NON-MALIGNANT DISEASES

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Sixty-seven pediatric patients with malignant (n=48) and non-malignant diseases (n=19) underwent seventy-three allogeneic transplantations using fludarabine-based reduced-intensity conditioning (RIC) between May 2001 and June 2006. Conditioning regimens consisted of fludarabine 30 mg/m^2/day x 5 days plus melphalan 140 mg/m^2/day x 1 day (n=25) or plus oral/iv busulphan 4 mg/Kg/day x 2 days (n=29) or plus cyclophosphamide 60 mg/kg/day x 2 days and globuline antithymocyte 2.5 mg/kg/day x 2 days (n=19). The patients were grafted with bone marrow (n=13), cord blood (n=10) or PBSC either unmanipulated (n=10) or CD34+ selection (n=34) or CD3/CD19 depletion (n=6). GVHD prophylaxis was performed with CsA+ Mtx (n=62), CsA only (n=7) and CsA + steroids (n=4). Donors were either related (n=42) or unrelated (n=31). The median number of CD34+ cells infused was 5.75×10^6/kg recipient bw (range 0.25-47.7). **Results:** All patients achieved primary engraftment. However, eight patients developed secondary graft failure. The probability of secondary graft failure was 14±5%. There were a rapid recovery of neutrophils (median 13 days; range 5-29) and platelets (median 15 days; range 5-56). The median length of hospital stay was 18 days (range 9-85). With a median follow-up of 10 months (range 3-48) the incidence of aGVHD and cGVHD were 19±5% and 13±5% respectively. The probability of TRM was 10±4%. Patients grafted with manipulated PBSC had the lowest TRM (4±3%). The relapse incidence was 23±6.5%. High number of infused CD34+ cells (p=0.066) and cGVHD (p=0.01) was associated with a lesser RI. The event-free survival was 69±7%. Fifteen patients died due to: relapse or progressive disease (n=9), aGVHD (n=2), cGVHD (n=2) and other causes(n=2). **Conclusion:** Fludarabine-based RIC provide a good alternative to "classical" myeloablative conditioning for allogeneic transplantation either malignant or non-malignant disease in children.

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SYSTEMIC VIRAL AND FUNGAL INFECTIONS ARE NOT SIGNIFICANTLY DECREASED FOLLOWING REDUCED INTENSITY ALLOGENEIC STEM CELL TRANSPLANTATION (RIALLOSCT) IN CHILDREN AND ADOLESCENT RECIPIENTS WITH MALIGNANT AND NONMALIGNANT DISEASES

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RIAlloSCT has been demonstrated to induce a high degree of mixed donor chimerism and a significant decrease in duration and nadir of neutropenia in the early post allograft period (Satwani/Cairo et al, BBMT, 2005). This reduction in duration of neutropenia has translated into a significant decrease in bacteremia during the first 30 days (Jungenhans et al, BBMT, 2002). It remains to be determined whether RIAlloSCT will also result in a decrease in systemic viral and invasive fungal infections, which are more dependent on alteration in cellular immunity. From 1/2001 to 7/2006, 58 pediatric pts with median age of 11.5 yrs (0.33-21) received RIAlloSCT for malignant (n=42) and non-malignant (n=16) diseases. RI conditioning was fludarabine based 150-180 mg/m^2 + busulfan 6.4-12.8 mg/kg (n=42), or cyclophosphamide 30-120 mg/kg (n=14) or melphalan 70 mg/m^2 (n=2) ± ATG (n=36) or alemtuzumab (n=8). Stem cell source consisted of UCB (n=29), PBSC (n=21), BM (n=8). Donor sources included HLA-match siblings (n=19), partially matched related (n=6), or unrelated (n=33). All pts received tacrolimus and MMF as GVHD prophylaxis (Osunkwo/Cairo et al, BBMT, 2004). CMV at risk recipients received ganciclovir/foscarnet (Shereck/Cairo et al, PBC, 2006) and all received antifungal prophylaxis with liposomal amphotericin B until day +100. F/U 686 ± 76 d. The median time to myeloid engraftment was 16 d and incidence of primary graft failure was 17.2%. Viral infections were present in 39 pts (67%) after a mean of 131 ± 104 d. CMV reactivation 10%, adenovirus 17%, RSV 17%, influenza (A and B) 10%, parainfluenza II and III 10%, BKV 17%, JCV 3%, HSV-1 12%, VZV 7%, HHV-6 1.7%, and Calicivirus 1.7%. Two pts died, 1of CMV pneumonitis and 1 of RSV pneumonia. Fungal infections were reported in 12 pts (20%) after a mean of 204 ± 188 d. Six pts had invasive fungal infection (aspergillus 2). Incidence of mortality secondary to viral and fungal infections was 5 and 17%, respectively. GVHD and its treatment with steroids were present in 43% and 50% of patients with viral and invasive fungal infections, respectively. The estimate 1 yr OS for all pts was 65% (CI: 52-78) and for malignant and non-malignant pts were 62% (CI: 47-78) and 73% (CI: 50-96), respectively. In summary, these results suggest that RI conditioning probably does not decrease the incidence of systemic viral and invasive fungal infections, likely secondary to GVHD, particularly following unrelated HLA disparity donor allografts.

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RISK ADAPTED ALLOGENEIC STEM CELL TRANSPLANTATION (ALLOSCT) FOR ACQUIRED SEVERE APLASTIC ANEMIA (SAA) IN PEDIATRIC RECIPIENTS

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AlloSCT from a HLA matched sibling donor is the preferred treatment in children with acquired SAA in children. Alternative donor HSCT gives inferior results, and has been reserved for patients lacking matched family donors and unresponsive to medical therapy. However, given the poor outcome of medical therapy in subsets of patients with SAA, the advent less toxic fludarabine (FLU)-based non-myeloablative (NMA) regimens (Chan et al, BMT, 2001), and our recent experience with UCBT (Styczynski/Cairo et al, BMT, 2004), we investigated a risk-adapted AlloSCT approach to 17 consecutive children with SAA with matched related or unrelated donors between 01/2001 and 08/2006. There were 11 males and 6 females with median age of 11 years (range 4-16). Patients with fewer than 10 transfusions underwent NMA AlloSCT with FLU 180 mg/m^2, cyclophosphamide (CY) 60 mg/kg, and ATG 8 mg/kg (n=8) or FLU 180 mg/m^2, busulfan (BU) 12.8 mg/kg, and alemtuzumab 54 mg/m^2 (n=2). The remainder underwent myeloablative (MA) AlloSCT with FLU 180 mg/m^2, CY 200mg/kg and ATG 8mg/kg (n=6) or CY 200 mg/kg and ATG 8 mg/kg (n=1). Stem cell sources were BM (n=12) from 6/6- (n=9) or 5/6- (n=2) matched family donors or 9/10-matched unrelated donor (MUD) (n=1), or UCB (n=5), either 6/6- (n=1), 5/6- (n=2), or 4/6-matched (n=2). All patients received tacrolimus and mycophenolate mofetil as GVHD prophylaxis as we previously described (Osunkwo/Cairo et al, BBMT, 2004). The median time to myeloid and platelet engraftment were 14 (9-30) and 40.5 (12-161) days, respectively. 15 pts (88.2%) engrafted and 2 (11.8%) had secondary graft failure. Acute GVHD grade II-IV was observed in 35.3% of pts, whereas only 5.9 % developed chronic GVHD. 1 patient developed PTLD. 6 pts (35.3 %) died, multiorgan failure (n=3), extensive AGVHD (n=1), fungal infection (n=1) and thrombotic microangiopathy (n=1). The probability of overall survival (OS) for all patients was 60.9% (CI 95: 36.4-86.5). We did not observe differences in OS according to donor type (related vs. unrelated), intensity of conditioning regimen (MA vs. NMA), or CMV status of donor and recipient. However, we found a significant difference in OS by degree of match (6/6 or 9/10 vs. <6/6) 77.8 % (CI 95: 50.6-100) vs. 33.3 % (CI 95: 0-71.1) (P<0.05). In conclusion, risk-adapted AlloSCT is feasible in children with newly diagnosed acquired SAA and further investigation of this approach is warranted.