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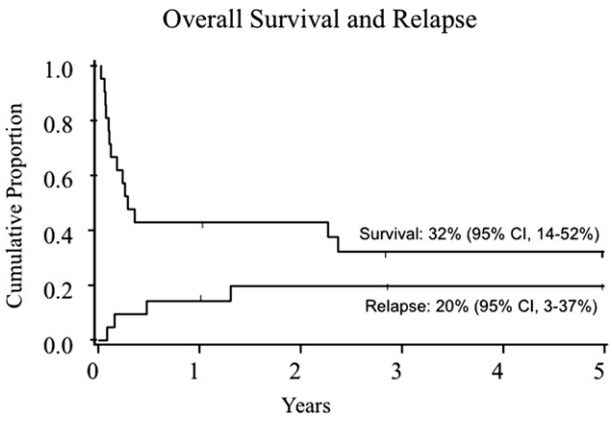
conditioning regimen consisted of Cyclophosphamide with either total body irradiation or Busulfan, with the addition of Fludarabine in 13 patients (62%). In vivo T cell depletion with Anti-Thymocyte Globulin was performed in 18 patients (85%), and 11 donor grafts underwent ex vivo T cell depletion (52%). Donor source included HLA-matched sibling (n=3), mismatched related donor (n=1), unrelated marrow (n=12) and unrelated cord blood (n=5). 58% of unrelated donors had at least 1 HLA mismatch. Neutrophil engraftment for the entire cohort was 90%, and 100% for those patients that received Fludarabine. The incidence of acute GVHD was 19% for the entire cohort. 5 year Overall Survival (OS) was 32%, with a relapse rate of 20% (Figure). Of the patients that received Fludarabine, 5 year OS was 38% with a relapse rate of 30%. For the patients with biallelic BRCA2 mutation, 5 year OS was 33% with a relapse rate of 50%



Our study provides evidence for use of HCT with a Fludarabine containing regimen for FA patients with acute leukemia or advanced MDS, who would otherwise have a dismal prognosis. The role of pre-HCT chemotherapy remains unclear, and requires further investigation. BRCA2 patients are a unique subset of FA patients and require tailored therapy to optimize HCT outcomes.

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Treosulfan for Conditioning in Children and Adolescents Before Hematopoietic Stem Cell Transplantation (HSCT)

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To identify possible dose related toxicities of treosulfan containing regimen and determine the incidence of engraftment, treatment related mortality (TRM), overall survival (OS) and event free survival (EFS) we explored 616 patients (pts) below 18 years who underwent HSCT between January 2005 and July 2010 for malignant (n= 270, 43%) or non malignant disease (n = 356, 57%). To investigate a potential non-linear association between dose and outcome, fractional polynomials were used.533 pts underwent allogeneic, 93 autologous HSCT. 513 (83%) pts received a treosulfan-based conditioning regimen during their first HSCT. 124 (20%) had a matched sibling donor (MSD). The stem cell source was bone marrow (BM) in 274 pts (44%) and peripheral blood in 264 pts (42%).In the group of pts with allogeneic HSCT, 41 were below the age of 6 months and 65 between 6-months and 1 year. 314 were between 1 and 12 years and 101 above 12 years. For allogeneic HSCT, the median treosulfan dose was 42 g/msq (12-46). 24 pts (5%) received less then 33 g/msq. 153 pts (29%) received between 33 and 39 g/msq. The majority of pts received a treosulfan dose between 39 and 45 g/msq.

Results: There is no significant correlation of the time to ANC > 0.5x10e9/L with age and treosulfan-dose. Primary graft failure occurred in 2% of cases with no significant correlation with age, treosulfan dose and underlying disease in uni- and multivariate analysis. Acute graft-versus-host disease (GvHD) of grade III-IV occurred in 10% of the patients and the rate of limited and extended chronic GvHD was 13% and 6%, respectively. The most common grade 3 or 4 toxicities were diarrhoea (24%), stomatitis (22%), and SGOT elevation (25%). Veno-occlusive disease was described in 5% of all pts. There was a significant association between age and VOD-incidence, with higher VOD-rates in children below the age of 0.5 years (12%), that are exclusively children with non-malignant diseases. Treosulfan-dose has no significant impact on VOD and GVHD in both univariate and multivariate analysis. There is a border-line significant impact of age on overall survival. The 3-years pOS in children below 6 months, between 6 months and 1 year between 1-12 years and > 12 years is 75%, 84%, 70% and 60%, respectively. This difference is mainly caused by a difference in disease related mortality (DRM). TRM is not significantly different in the different age groups. With respect to dose, we did not find a significant impact on overall survival, neither in univariate nor in adjusted analysis. However, there was a better OS after first HSCT (0,74%) compared to second or third HSCT (0,51%), $P < .001$.

Conclusion: These results emphasise the low toxicity profile of treosulfan, even in heavily pre-treated children and adolescents and in patients undergoing a second HSCT. It was shown that treosulfan is highly efficient to enable engraftment without increasing the risk for severe acute or chronic GVHD.

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Reduced Toxicity Conditioning with Busulfan, Fludarabine, Alemtuzumab and Allogeneic Stem Cell Transplantation From HLA-Matched Sibling Donors in Children with High Risk Sickle Cell Disease Results in Long Term Donor Chimerism and Low Incidence of aGVHD

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Background: Myeloablative conditioning with busulfan and cyclophosphamide (200 mg/kg) (Bu/CY) followed by HLA-

matched sibling bone marrow transplantation results in approximately 85% event free survival in high-risk patients with Sickle Cell Disease (SCD) (Walters, NEJM, 2006). However, this approach is limited by 5-10% transplant-related mortality, 5-10% primary graft failure and the late effects of Bu/CY. Alternate approaches include reduced toxicity but more immunosuppressive conditioning and the use of sibling cord blood (Geyer/Cairo, BJH, 2011 and Freed/Cairo, BMT, 2012).

Objective: To determine the safety, donor chimerism and long term organ function associated with Bu 12.8-16 mg/kg, fludarabine180 mg/m^2 and alemtuzumab 54 mg/m^2 (BFA) reduced toxicity conditioning (RTC) prior to HLA-matched sibling donor transplantation in pediatric recipients with high risk SCD.

Methods: Patients ≤21 years of age with HbSS, HbSC, HbSβ^+ or HbSβ^0 were eligible if highly symptomatic (such as ≥2 vaso-occlusive crises per year requiring narcotics, acute chest syndrome, stroke, retinopathy, splenic sequestration) and with an HLA-matched sibling donor. Conditioning consisted of busulfan (4mg/kg x 4d < 4 yrs and 12.8mg/ kg x 4d > 4 yrs), fludarabine (30mg/m^2 x 6d), and alemtuzumab (2mg/m^2 x 1d, 6mg/m^2 x 2d, and 20mg/m^{2}x 2d) as we have described (Styczynski/Cairo,BMT,2011). All received tacrolimus and MMF as GVHD prophylaxis as we have described (Bhatia/Cairo, BBMT, 2010).

Results: 12 patients (11M:1F), median age 12 (2-19) with symptomatic SCD underwent sibling BM (n=10) or CB (n=2) Allogeneic Stem Cell Transplantation (AlloSCT). Median follow-up was 33 months. Median time to neutrophil and platelet engraftment for recipients of sibling BM and CB were 16 days (13-18), 18.5 days (9-43) and 39.5 days (38-41) and 74 days (73-75), respectively. The probability of grade II-IV and grade III-IV aGVHD were 16.7% and 8.3%. No patients developed cGVHD. Patients achieved mean whole-blood donor chimerism of 85, 94, 93, 93, 89 and 93% and mean erythroid (CD71) donor chimerism of 89, 89, 93, 90, 86, and 94% at days 30, 60, 100, 180, 365 and 730 post-transplant, respectively. The Kaplan-Meier probability of OS and EFS was 100% (CI_{95}: 73.5-100%). Neurological, pulmonary, vascular, and splenic function were stable to improved at 2 years.

Conclusions: BFA (RTC) and HLA-matched sibling bone marrow and cord blood AlloSCT in pediatric recipients results in excellent EFS, long term donor chimerism, and stable/improved organ function.

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Post-Transplant Cyclophosphamide Is Feasible and Reduces Acute GvHD in Pediatric UCB Transplantation

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Post-transplant Cyclophosphamide (Post-Cy) has demonstrated to decrease the occurrence of aGVHD in preclinical and haploidentical studies. Nevertheless, Post-Cy increases time to neutrophil recovery, an issue that is of utmost importance for UCB transplant related mortality (TRM). We postulated that despite UCB lower cellular doses, the use of Post-Cy decreases graft vs host and host vs graft reactions, enhancing engraftment, and improving clinical outcomes. So we explore the feasibility of using Post-Cy in the setting of UCB transplantation in children. In June/2010, our group decided to include post-Cy for UCB transplantation. A single 50 mg/kg/dose of Cy was added on day +3. CSA and MMF was started day +4, as well as G-CSF. Post-Cy was used both in RIC and myeloablative transplants. Rabbit ATG or Alemtuzumab was used only for RIC transplants. The group that received Cy-Post (21 cases) was compared with our previous UCB transplantation cases (35 cases) where Post-Cy was not used. Multivariate logistic regression models were used to evaluate the independence of the relationship between Cy-Post and aGvHD, of other covariates such as, age, gender, RIC, HLA match, CMV receptor status, pre-freezing TNC and CD34. Attached table compares characteristics of patients with and without Post-Cy. No significant differences were identified among the 2 groups. The groups with and without Post-Cy were infused with 7.1 vs 6.4x10^7 TNC/kg, and 2.84 vs 2.81x10^5 CD34+cells/kg, respectively. 100-day (25% vs 26%) and 1-year (25% vs 31%) TRM and overall survival (60% vs 57%) were not different among the groups. Median time to neutrophil and platelet engraftment with and without Post-Cy was 24 vs 16 days ($P < .01$), and 43 vs 35 days (P=0.02), respectively. Forty-nine (87.5%) patients were evaluable for aGvHD, 49% were classified as grades II-IV. In the group with Post-Cy grades II-IV aGvHD was 32% compared with 68% in the group without Post-Cy. OR was 0.31 (95%CI:0.1, 1.0), and adjusted OR was 0.16 (95%CI: 0.03, 0.78), $P = .02$. No documented cases of grade IV aGvHD in the Post-Cy group. In conclusion, we found an important effect of Post-Cy over the occurrence of aGVHD, independently of HLA match, and of other relevant variables. Neither, we find an effect over early TRM, and is uncertain its impact over long term mortality. We hypothesize that usage of Post-Cy in UCB transplantation in children, can allow the use of UCB units with greater HLA mismatch, and thus, increasing the potential pool of grafts available for transplantation. This could be especially useful for ethnic minorities.

Patient Characteristics by Post-Cy Group

Characteristics	Post-Transplant Cyclophosphamide				*P*- value*
	Yes		No		
	n = 21	%	n = 35	%	
Age group (years)					
0.1-9.9	17	81	26	74	.75
10.0-19	4	19	9	26	
F. donor / M receptor	6	29	8	23	.90
Double cord	3	14	3	9	.66
Diagnoses					
Acute leukemias	12	57	17	49	
SAA	3	14	8	23	.58
Others	6	29	10	29	
RIC	7	33	16	46	.41
TBI	12	57	22	63	.78
ATG or Alemtuzumb	6	29	17	49	.17
HLA match (n=52)					
6/6	1	5	6	19	
5/6	9	50	11	34	.31
4/6	10	45	15	47	
Receptor CMV (+)	21	100	30	86	.14
CMV viremia	13	62	19	54	.78
Invasive mycosis	4	19	6	17	.99

* Fisher's exact two sided test.

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Haploidentical BMT Using Fully Myeloablative Conditioning, T Cell Replete Grafts, and Post-Transplant Cyclophosphamide (PT/Cy) Has Limited Toxicity and Promising Efficacy in Pediatric Patients with High Risk Hematologic Malignanices

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