Voriconazole was given as prophylaxis in 44% of cases, 23% received it empirically and 33% as therapy. 14 of the 19 children treated therapeutically had aspergillosis (11 possible, 2 probable, 1 proven). Dosing was according to the summary of product characteristics. For children < 2 yrs the recommended dosage for 2-12 yrs was used. Voriconazole was prescribed for a mean period of 63 days (range 6-415). In 11% of cases the drug was stopped due to toxicity.
Therapeutic drug monitoring of voriconazole: An adequate trough level was defined as 1-5 mg/ml. First measurement of trough levels was after a median of 5 days.

Only in 8% of children < 2 years an adequate level was reached at initial dosing.

3 of 15 children between 2-7 yrs of age on recommended dosage had adequate levels at initial dosing (20%); in children aged 7-12 yrs 83% had adequate initial levels if dosage was as recommended. 14/33 patients >2 yrs on recommended dose had voriconazole levels below the limit of detection (<0.5 mg/ml). 9% of all patients had an initial trough level > 5 mg/ml.

The mean dose (range) to reach adequate trough levels for children <2 was: 365 mg oral (220-600) and 29.4 mg/kg i.v. (5.2-70). For the age group 2-7 years adequate levels were reached with a mean dose of 26.2 mg/kg i.v. (20.7-29.6). >12 years this was 17.6 mg/kg i.v. (11.9-19.6).

Intrapatient variability of levels on constant dosage was 0.7-3.5 fold.

Conclusion: We conclude that therapeutic drug monitoring is indispensable for correct dosage of voriconazole. Dosage recommendations for children need adjustment, especially in the <2 age group. Intra patient variability is also a major concern and necesittates continued level measurements. Patient characteristics that determine pharmacokinetic variability need to be identified in future studies.

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FLUDARABINE + EXPOSURE-TARGETED BUSULFAN IN CHILDREN WITH MALIGNANT AND NON-MALIGNANT DISEASES: AN EFFECTIVE AND LOW TOXIC REGIMEN

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Background: Busulfan (Bu) as myeloablative agent is used in conditioning regimens prior to HSCT. We recently found a clear association between Bu-exposure and outcomes. Comparison studies in adults showed a favorable toxicity profile for fludarabine+busulfan (FludBu) compared to the conventional BuCy regimen. We recently initiated a prospective study analysing the effectively of FluBu in myeloid malignancies and all non-malignant indications in pediatrics. We compared the outcomes with our Bu(-exposure targeted)/Cy/(Mel) from a previous cohort (2005-2008).
Methods: Fludarabine 40mg/m2 was given in 1 hour prior to a 3 hour infusion of once daily busulfan. The target area under the curve (AUC) for Bu was 75-95 mg*h/L (in total) in both groups. Bu dose targeting, based on therapeutic drug monitoring was performed before the second dose. Primary endpoint was event free survival (EFS) and survival. Secondary endpoints were acute graft-versus-host disease (aGvHD), neutropenic period and the number of erythrocytes and thrombocytes transfusions. A risk factor analysis was performed using univariable and multivariable COX regression.
Results: 100 patients were included: 65 unrelated-CBT, 22 a MSD and 13 a MUD. 52 patients were included in the FludBu group (median follow up 244 days; range 22-769) and 48 in the BuCy(Mel) group (1015 days; range 6-2085). The median exposure of busulfan was 88 (81-94) mg*h/L in FluBu and 82 (74-100) mg*h/L in BuCy(Mel). The groups were comparable regarding age, cell source, gender, indication for BMT and match-grade. The probability on EFS in FludBu and BuCy(Mel) was 74+/-6% and. 70+/-7% (NS), resp. No difference in aGvHD (≥grade 2: 20 vs.28%) was found. A trend to a lower "non-relapse mortality" was found in the FluBu group 7+/-4% vs. 19+/-6% (p = 0.08). The period of neutropenia was median 11 in the FludBu compared to 20.5 in BuCy(Mel) (HR 0.38, p = 0.05, CI95% 0.20-0.75). The median number of erythrocytes transfusion was 1 (range 1-13) in the FludBu group and 5 (0-22) in the BuCy(Mel) group (p = 0.02) and thrombocyte transfusions 4 (range 0-33) vs 10 (range 2-44; p = 0,02). Less VOD was seen in BuFlu 3% vs. 22% (p = 0.01).
Conclusion: Bu with a total target AUC of 75-95mg*h/l in combination with Flud showed to be an effective and low toxic regimen in comparison to BuCy(Mel). A shorter neutropenic period and a lower number of transfusions were needed in FludBu. FludBu as reduced toxicity regimen showed promising results.

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UNRELATED BONE MARROW TRANSPLANTATION (UBMT) FOR CHILDREN AND ADOLESCENTS WITH FANCONI ANEMIA (FA) USING CYCLOPHOPHAMIDE, FLUDARABINE AND RABBIT ATG: ANALYSIS OF 33 PATIENTS TRANSPLANTED AT A SINGLE INSTITUTION

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FA is a rare disease characterized by progressive bone marrow failure, congenital anomalies and a striking predisposition to cancer. HSCT is the only treatment able to cure the hematological complications related to this disease. In the absence of a fully matched related donor, the use of an unrelated donor is recommended but is still associated with an increased rate of rejection and GVHD. Objective: Analyze the outcome of 33 pts with FA submitted to an UBMT using CY+FLU+rATG in the conditioning regimen.
Patients and Methods: Period: 02/02 - 02/11, Age 5-18s (M: 10years) Sex: 17F/16M; Preparatory regimen: CY60mg/kg + FLU125mg/m2 + rATG 4-6mg/kg; GVHD prophylaxis: Cyclosporine and methotrexate. Stem cell source: bone marrow. All pts and donors were HLA typed at least for low-resolution class I (locus A, B, C) and high resolution DRB1. 29pts were fully compatible (8/8) and 4pts had one or two mismatches.
Results: 26 pts are alive between 8 months and 8ys days after BMT (M: 2,7ys) with an overall survival (OS) of 79% in 3 years. 32 pts survived more than 28 days and were evaluated for engraftment. 3 pts had only neutrophilic engraftment and all died between days +30 and +117 post BMT. One pt had primary graft failure (mismatch in locus C) and received a 2nd UBMT (alive and well 4.8 ys after UBMT). No late rejection occurred in this group of pts. Early complications: mucositis grade III -IV: 75%. Moderate to severe arterial hypertension: 70%. No pt developed severe hepatic sinusoidal syndrome. Hemorrhagic cystitis:7pts. Acute GVHD grade II-IV occurred in 12/31 evaluable pts while chronic GVHD occurred in 11/26 evaluable pts (limited: 6pts; extensive: 5pts). Seven pts died between 20-117 days post UBMT (M: 50 days). Cumulative incidence of TRM at 100 days was 18%. Causes of death were generally related to infection (bacterial or fungal) or GVHD complications. Pts under 10 years had an excellent survival (94%) as well as those with fully compatible donors (86%).
Conclusions: The results from UBMT in FA have improved considerably during the past few years. In this study, pts under the age of 10 had an excellent survival, equal to the one observed in pts with fully matched related donors. Early referral, the use of conditioning regimen containing fludarabine and the possibility of finding well matched unrelated donors (65% of them found in the Brazilian registry) may have contributed for the success of this protocol.

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HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR PATIENTS WITH WISKOTT ALDRICH SYNDROME (WAS): ANALYSIS OF 36 CHILDREN TRANSPLANTED IN A SINGLE INSTITUTION

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WAS is a rare X-linked disease characterized by recurrent infections, eczema, thrombocytopenia with small platelets and an increased predisposition to autoimmunity and lymphoid malignancies. HSCT is the only treatment with the possibility of cure.
Objective: Retrospective analysis of 36pts with WAS submitted to HSCT at a single institution.
Patients and Methods: 36 boys; age: 0.9-14 ys (M: 2 ys), period: 04/1992 05/2011. The majority of pts had severe manifestations of the

disease (score 3, 4 or 5). Type of donor: Related: 8pts (siblings: 5pts and other related:3pts), Unrelated: 28pts. Source of stem cells: bone marrow (BM): 12pts and umbilical cord blood (UCB):24pts (compatibility 6 / 6: 2pts, 5 / 6: 16pts, 4 / 6: 6pts). Conditioning: Cyclophosphamide120-200mg/kg + Oral Busulfan16-20mg/kg +/- rATG. Most pts received cyclosporine and methotrexate as GVHD prophylaxis.

Results: 28pts is alive and well between 6 months and 17 ys after HSCT (M:4,5ys) with an overall survival(OS) of 80,3% at 5ys. 35pts survived more than 28 days and were evaluable for engraftment. Three pts had no engraftment (all received UCB).One pt died on D+34 with pulmonary aspergillosis and the other two underwent a 2nd UCBT. One is alive and well 7 years after transplant. Nine of 32 evaluable pts developed an acute-GVHD, grades II-IV (grade III-IV: 2pts). Eight of 31 evaluable pts developed C-GVHD (extensive in 3pts). There was no significant difference in OS in the univariate or multivariate analysis in relation to age less than or greater than 5 years (76% vs. 82%), type of donor, related or unrelated (87.5% vs. 75%), source of stem cells, bone marrow or cord blood (91.7% vs. 70,8%), presence or absence of acute-GVHD (78% vs 92%); or Chronic GVHD (75% vs 91%). Eight pts died between 21 to 1832 days post HSCT (M: 137 days), most deaths occurred during the first year of transplant (6pts) and were related to viral infections (4pts), fungal (1pt) and GVHD associated with bacterial infections (3pts). The cumulative incidence of TRM at 100 days was 8% and at 1 year was of 17%. Chemotherapy was well tolerated, but reactivation/acquisition of viral infections (mainly RSV) during the period of neutropenia contributed to the early death in some pts.

Conclusions: Despite the small number of pts this experince shows an excellent survival for pts transplanted for WAS. Infections complications (viral or fungal) are frequent and must be detected quickly and treated aggressively.

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EFFECTS OF BODY MASS INDEX (BMI) IN CHILDREN UNDERGOING ALLOGENEIC BONE MARROW TRANSPLANT (BMT) FOR HEMATOLOGIC MALIGNANCIES

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The rising incidence of pediatric obesity may significantly impact BMT outcomes for malignant diseases, as has been demonstrated in increased mortality in children undergoing BMT for aplastic anemia. Obesity may influence chemotherapy dosing and transplant related mortality (TRM). We analyzed 3,687 children ages 2-18, who received BMT for treatment of hematologic malignancies using either busulfan/cyclophosphamide (BuCy, N = 1,196) or Cy/total body irradiation-based (CyTBI, N = 2,495) conditioning, between 1990 and 2007. Recipients were classified according to age-adjusted BMI percentiles as underweight (<5% [UW], n = 282), at risk of underweight (6-25% [RUW], n = 509), normal (26-75%,[NW] n = 1469), at risk of overweight (76-95% [ROW], n = 987) and obese (>95%, [OB] n = 444). Total doses of chemotherapy administered to patients in the ROW and OB groups were divided by actual and ideal body weight to estimate dose adjustment practices. Median age (10-13 y) and race were similar in all groups; OB group had higher number of patients with acute lymphocytic leukemia (58%), with early disease (52%), unrelated donor recipients (56%) and from a U.S. center (61%). The table below summarizes adjusted probabilities according to BMI groups. Multivariate analysis demonstrated a higher TRM in the OB group (RR 1.32, p = 0.0075) compared to NW. Conversely, patients in the OB group had decreased risk of relapse (RR 0.72, p = 0.0037) compared to NW. There was no significant impact of UW and RUW compared to NW in any outcomes, and no differences in relapse-free and overall survival according to BMI groups. Chemotherapy adjustment assessment demonstrated that among 1,061 patients with available dose information, 171 (16%) had probable dose adjustment for conditioning. Obesity was associated with higher TRM and lower relapse in children with hematologic malignancies, likely related to higher intensity conditioning, as doses were most often calculated based on actual weight. Additionally, patients with low BMI experienced similar outcomes compared to patients with NW.

Table.

Outcomes @ 3 years	UW (95% CI)	RUW (95% CI)	NW (95% CI)	ROW (95% CI)	OB (95% CI)	p-value
N	282	509	1467	986	443	
TRM	18 (13-22)	19 (16-22)	21 (18-22)	22 (20-25)	28 (24-32)	0.0034
Relapse	33 (28-39)	33 (29-37)	29 (26-31)	25 (23-28)	21 (17-25)	<0.0001
RFS	48 (42-54)	48 (44-53)	50 (48-53)	52 (49-56)	51 (47-56)	0.54
OS	55 (49-61)	57 (52-61)	58 (56-61)	58 (55-61)	56 (52-61)	0.81

Abbreviations: CI, confidence interval; NW, normal weight; OB, obese; OS, Overall Survival; RFS, relapse free survival; ROW, risk of overweight; RUW, risk of underweight; UW, underweight

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SINGLE CENTER EXPERIENCE OF THIOTEPA, TREOSULPHAN & FLUDARABINE BASED REGIMEN IN THALASSEMIA MAJOR

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The only curative treatment for Thalassemia major (TM) is allogenic bone marrow transplantation. The most commonly used conditioning regimen is Busulphan, Cyclophosphamide and Anti thymocyte globulin. This has high regimen related toxicities (RRT). To minimize RRT, especially in high risk TM we studied new conditioning regimen in prospective manner. Between February 2010 - September 2011, seventeen children with β-Thalassemia major underwent Allogenic Bone Marrow Transplant at BLK Super Speciality Hospital. The median age was 12 years. (Range 2-16 yrs.).

There were nine males & eight females, four patients belonged to Pesaro class II and 13 were class III. All patients received conditioning with Thiotepa 8 mg/kg on D -6, Treosulphan 14 gm/m^2/day from D-5 to D-3 & Fludarabine 40 mg/m^2/day from D-5 to D -2. Sixteen children were transplanted with bone marrow graft from HLA identical siblings (6/6 antigen) and one patient received bone marrow graft from mother (5/6 antigen). Mean cell doses given were: 6.36 $\times 10^6$ cells /kg BW for CD34+ cells (Range 2.06 – 14.02 $\times$ 10^6/kg) and 7.84 $\times$ 10 ^{8}/kg /BW for mononuclear cells (Range 2.9- 17.5 $\times 10^8$/kg). Two patients had ABO major mismatch, 4 had minor mismatch and 1 had bidirectional mismatch. Cyclosporine & Methotrexate was used as GVHD prophylaxis. No patient developed grade III - IV GVHD. None of them required TPN or parental analgesia. Sixteen out of seventeen patients achieved donor engraftment. Median neutrophil engraftment was achieved on D+15 (Range 11 – 17 day) and median platelet engraftment was achieved on D+21 (Range 9 to 34 days). One patient developed grade II gut GVHD. One patient expired on D+6 due to neutropenic enterocolitis, sepsis and intracranial hemorrhage.

Median follow-up period was 12 months (Range 1 -20 mo). Till last follow up, all the patients who achieved engraftment are alive and transfusion independent.

Conclusion: Thiotepa, Treosulphan & Fludarabine based regimen has acceptable toxicities with stable donor engraftment.

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UNRELATED CORD BLOOD TRANSPLANT (UCBT) IS ASSOCIATED LOW RATES OF LONGTERM, PERSISTENT GRAFT VERSUS HOST DISEASE (GVHD)

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Reduced rates of acute and chronic GVHD make unrelated cord blood an attractive stem cell source. Adult marrow and PBSC from unrelated donors are associated with higher rates of GVHD, persistence or progression of GVHD manifestations, need for chronic immunosuppressive therapies, reduced quality of life, infection, organ toxicities, and decreased overall survival (OS). In contrast, recent analyses from our center and others have indicated that GVHD following UCBT does not adversely impact OS (BMT 2011, 46:668-675). To better understand the longterm outcomes of