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