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EVALUATING PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRAVENOUS BUSULFAN IN PEDIATRIC PATIENTS RECEIVING BONE MARROW TRANSPLANTATION

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Background: Busulfan (BU) is a commonly used conditioning agent in bone marrow transplant (BMT). However, it is a narrow therapeutic index drug which has a strong correlation between area-under-curve (AUC) and both efficacy and toxicity. Studies in pediatric patients have suggested that children less than 4 years of age have a greater clearance and thus lower AUC at standard adult doses. The goal of this retrospective analysis was to evaluate any age-related pharmacokinetic and pharmacodynamic differences in pediatric patients who received BU as a conditioning agent. **Methods:** From 2001 to 2006, 21/77 pediatric patients who received BMT were reviewed. There were 15 males and 6 females with a mean age of 6 years. Diagnoses of leukemia (n = 11), HL (n = 3), MDS (n = 2), and other (n = 5) were included. 16 patients received BU + cyclophosphamide (CY) while 5 patients received BU + another agent. There were 20 allogeneic and 1 autologous transplants among which 16 were HLA matched and 5 were mismatched. **Results:** Average BU clearance in patients younger than 4 years old (n = 8) was 4.1 ± 1.0 (ml/min)/kg vs. 3.1 ± 0.7 (ml/min)/kg in patients older than 4 years old (n = 13) (p = 0.02). The corresponding averages for AUC were 998 ± 226 μM•min vs.1155 ± 183 μM•min (p = 0.12). No patients younger than 4 years old developed veno-occlusive disease (VOD) while 5 of the older patients did (p = 0.044). There were no significant differences in terms of engraftment, graft-vs-host and relapse. **Conclusion:** There were significant age-related pharmacokinetic differences in pediatric patients less than 4 years of age receiving BU for conditioning prior to BMT. There was a decrease in drug toxicity seen in these patients. Patients younger than 4 years old might not need routine pharmacokinetic monitoring.

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CEREBRAL TOXOPLASMOSIS FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR MALIGNANT LYMPHOMA: MISINTERPRETATION AS RELAPSED LYMPHOMA ON INITIAL MRI STUDIES

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Introduction: Infections are a major cause of death in allogeneic hematopoietic stem cell transplant recipients. Cerebral toxoplasmosis is a life-threatening, but fortunately rare protozoal infection even in this high risk population. Establishment of the correct diagnosis may be hindered by non-specific clinical symptoms and uncharacteristic findings in imaging studies. Here, we report the case of a 15-year-old boy with disseminated anaplastic large cell lymphoma (ALCL) and post –transplant cerebral toxoplasmosis misinterpreted as relapsed lymphoma on initial MRI. **Case Report:** The 15-year old boy received an allogeneic HSCT from a matched unrelated donor for treatment of refractory ALCL. Central nervous system involvement was excluded by normal MRI studies and the absence of lymphoma cells in cerebrospinal fluid (CSF). Complications until day +100 included acute GvHD, grade II, viral reactivations (polyomavirus, CMV and EBV) and a delayed immune system recovery. Four months post-transplant, he presented with severe headaches, fever and nausea. A cranial CT scan revealed multiple hypodense areas in both hemispheres without hemorrhage or evidence of elevated intracranial pressure. Subsequent MR imaging studies were interpreted as intracerebral relapse of lymphoma. The patient became somnolent, developed seizures and was admitted to the ICU. A diagnostic work-up was initiated including blood and CSF cultures, PCR-testing for pathogens in blood and CSF, a bone marrow aspirate and brain biopsy. Still unaware of the results, the patient was treated with broad-spectrum antibacterial drugs, acyclovir, ambisome, rituximab, dexamethasone and pyrimethamine/sulfadiazine. His condition improved rapidly; cerebral toxoplasmosis was proven by evidence of a positive PCR in CSF and detection of the pathogen in brain tissue. Another MRI two weeks later showed the characteristic findings of cerebral toxoplasmosis with numerous ring-like contrast-enhancing lesions in both hemispheres. One year later, the patient still has residual MRI findings, but without neurological abnormalities. He is kept on toxoplasmosis maintenance therapy. **Conclusion:** In hematopoietic stem cell transplant recipients, a diagnosis of cerebral toxoplasmosis should be considered in every patient with sudden onset of acute, neurological symptoms regardless of the presence of characteristic findings on initial imaging studies.

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LONG TERM FOLLOW-UP IN THREE PEDIATRIC PATIENTS WITH FARBER DISEASE, TYPE 2/3, FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM RELATED AND UNRELATED DONORS

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Introduction: Farber Disease (FD) is an autosomal-recessively inherited, lysosomal storage disorder caused by acid ceramidase deficiency. FD, type 2/3, patients lack central nervous system involvement, their clinical phenotype is dominated by the triad of a hoarse voice, subcutaneous nodules and inflammatory granuloma around the joints, resulting in severe, progressive contractures, deviation of joints and finally considerable impairment of activities of daily living or even complete immobility. Respiratory tract involvement leads to death in the third or fourth decade of life. Allogeneic hematopoietic stem cell transplantation (HSCT) has been described as a curative option for these patients. Here, we present the long term follow-up data of three children after allogeneic HSCT with encouraging results. **Patients and Methods:** The three children were transplanted between May 2001 and February 2004 at the age of 2, 3 and 4 years, respectively. The patients (female 2, male 1) received an allogeneic HSCT (MRD 2, MUD 1; stem cell source: BM 2, PBSC 1) after busulfan-based myeloablative conditioning regimens. GvHD prophylaxis consisted of CsA and short course MTX with (MUD) or without (MRD) rabbit-ATG. Transplant-related toxicities included acute GvHD, grade II (3), CMV-reactivation (1), bacterial infections (1) and CsA-associated neurotoxicity (2). No chronic GvHD has been observed. Donor cell chimerism is complete in one patient and partial in two patients. The follow-up period is in a range between three and six years. Following the first year post-transplant, all children were seen at least twice yearly by the outpatient pediatric BMT unit and once yearly by pediatric rheumatology. Pre-transplant all children had severe joint involvement with pain and considerable restriction of motility; post-transplant a rapid improvement and finally resolution of all nodules and granulomas could be observed without evidence of residual impaired function. The children's mental and motor development is normal. Routine laboratory and organ function tests, endocrinological and neurological studies have yielded normal results. The more severely affected child with CsA-associated neurotoxicity (stroke like event with seizures) has recovered completely. **Summary:** Follow-up evaluation in three children three to six years after allogeneic HSCT for Farber Disease, type 2/3, has revealed encouraging long-term results without evidence of relapse, chronic GvHD or late effects.

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BUSULFAN AND SINGLE-DOSE MELPHALAN AS PREPARATIVE THERAPY FOR INFANTS AND YOUNG CHILDREN UNDERGOING STEM CELL TRANSPLANTATION FOR LEUKEMIA: A SINGLE CENTER EXPERIENCE

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Between January, 1996 and October, 2006, we treated 29 patients under the age of 4 with ALL (n = 15), AML (n = 11), JMML (n = 2), and CML (n = 1) with a preparative regimen of Busulfan, 37.5 mg/m^2 p.o. q 6 hours for 16 doses and Melphalan 140 to 180 mg/