of reversible causes may potentially reduce or prevent this infection.

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ALTERNATING REGIMEN HYPER CVAD + IMATINIB IN PH (+) ALL PATIENT ON HIGH-FLUX DIALYSIS

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Lack of pharmacokinetic data on chemotherapy clearance in high flux hemodialysis hinders safe and effective dosing. We present a case of a 58 year old female diagnosed in September 2009 with Ph (+) ALL and a past medical history of focal segmental glomerular sclerosis on hemodialysis. The patient intially presented with worsening renal function, fevers and peripheral blasts. Upon diagnosis of Ph (+) ALL, the decision was made to treat with Hyper CVAD, a regimen of hyper fractionated cyclophosphamide, doxorubicin, vincristine and dexamethasone (odd cycle) alternating cycles with high dose methotrexate and high dose cytarabine (even cycle). High flux hemodialysis is relatively new, utilizing improved membranes that efficiently remove low molecular weight solutes and that are more effective at removing medium and high molecular weight solutes. Currently the dosing recommendations for chemotherapy are based on low flux hemodialysis. Weighing the potential for improved solute clearance and manufacturer dosing recommendations, no dose adjustments were made for the odd cycles of Hyper CVAD. Imatinib was started at 100 mg for cycle 1, titrated up to 200 mg by cycle 3 and increased to 400 mg at completion without side effects. Methotrexate is poorly removed by low flux hemodialysis and only one case report in a single patient provides pharmacokinetic information on removal by high flux hemodialysis. For even cycles of Hyper CVAD the methotrexate was initially dosed at 200 mg/m2, determined by estimating a dose cleared by 1 high flux hemodialysis session using the time averaged clearance reported in the case report by Murashima and colleagues. The methotrexate was adequately removed based on serum levels and patient tolerance. The dosage was increased to 500 mg/m2 for subsequent cycles. Further dose escalation was halted due to development of febrile neutropenia requiring hospitalization. Cytarabine was dosed at 100 mg/m2 continuous infusion for cycle 1 and increased to 200 mg/m2 base on manufacturer recommendations. The patient tolerated 8 cycles of Hyper CVAD with minimal side effects and 2 admissions for neutropenic fever. Complete remission was documented in December 2009. She remained in remission for 4 months after completion in April 2009. Recently reinduced with Hyper CVAD, peg asparaginase, and dasatinib with documented molecular remission.

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DRUG-DRUG INTERACTION BETWEEN TACROLIMUS AND AZOLE ANTIFUNGAL AGENTS, ITRACONAZOLE AND VORICONAZOLE, IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS

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Background: The blood concentration of tacrolimus (TAC) is known to be increased by concomitant administration of voriconazole (VRCZ) and itraconazole (ITCZ), azole anti-fungal agents. We investigated changes in blood concentrations of TAC before and after concomitant administration of VRCZ or ITCZ to examine the optimal timing for monitoring blood concentrations of TAC.

Patients and Methods: We studied retrospectively patients who underwent hematopoietic stem cell transplantation between April 2004 and June 2010 and started VRCZ or ITCZ use during TAC administration. In a total of 34 patients receiving concomitant administration of VRCZ (tablets, n = 27; intravenous injection, n = 7) and 11 receiving ITCZ (capsules [Cap], n = 8; oral solution [OS], n = 3), the concentration/dose (C/D) ratio of TAC was observed from 10 days before through 35 days after the initiation of VRCZ or ITCZ.

Results: In all VRCZ group patients, C/D ratios of TAC increased after initiating VRCZ as compared with those before (median, 293%; range, 131%-923%; $P < 0.001$). Median time to reach the peak C/D ratio was 8 days (range, 3-30 days). When a loading dose was applied, the peak reached earlier (median, 6 days vs. 9.5 days; $P = 0.026$). Then C/D ratios decreased from peak (median, 50%; range, 23%-98%; $P < 0.001$). In 10 patients in the ITCZ group, the C/D ratio increased after initiating ITCZ as compared with those before (median, 267%; range, 141%-828%; $P < 0.001$). Median time to reach the peak C/D ratio was 19.5 days (range, 10-32 days). Patient who applied a loading dose was none. The rates of C/D ratio increase differed significantly between Cap and OS (median, 221% [range, 38%-475%] vs. 513% [range, 440%-828%]; $P = 0.025$) and times to reach the peak C/D ratio were similar (median, 20 days vs. 19 days).

Conclusions: In the VRCZ group, since blood concentrations of TAC transiently increased and then decreased, suggesting that careful monitoring is required even after dose reduction. It is also suggested that the optimal times for careful monitoring differ depending on whether or not the loading dose is applied. In the ITCZ group, the effects tended to appear after about 1 week. Significant increases in blood concentrations of TAC were observed in patients who received ITCZ by OS.

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CORRELATION OF PATIENT CHARACTERISTICS INCLUDING AGE, OBESITY, GENDER AND RACE ON THE METABOLISM OF BUSULFAN

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Background: Busulfan, in myeloablative doses, is commonly used in conditioning regimens prior to hematopoietic stem cell transplantation (HSCT) and is associated with HSCT related toxicity including hepatic veno-occlusive disease (VOD). Busulfan is predominantly metabolized by conjugation with glutathione, both spontaneously and by glutathione S-transferase catalysis. Busulfan dosing is commonly adjusted using therapeutic drug monitoring (TDM) to limit toxicities. Whether patient characteristics such as race, age, obesity, gender and prior chemotherapy can influence the metabolism of busulfan remains unclear.

Methods: A retrospective chart review was conducted in 302 patients receiving intravenous busulfan between April 26th, 2001 and September 23rd, 2010. Data was obtained from an IRB approved busulfan TDM database and included gender, race, age, weight, height, BSA, BMI and elimination half-life obtained with the 1st dose of busulfan.

Results: Demographics included 172 males and 130 females, of which there were 222 Caucasians, 50 African Americans and 30 patients of other races. The mean age was 43 with 113 patients greater than 50 years old. Thirty patients weighed over 100 kg, 6 had a BMI < 18.5, 175 had a BMI of 18.5 – 29.9 and 122 had a BMI > / = 30. The mean half-life for all patients was 188 minutes (ranging 108 to 640 minutes). For the 12 patients with a BSA of 2.5 to 3.29, the mean half-life was 206 minutes (ranging 184 to 238 minutes). The half-lives for the small to large BMI groups were 186, 188 and 186 minutes. The half-life for females was 180 minutes vs. 194 minutes for males. The half-lives for Caucasians, African Americans and other races were 187, 194 and 182 minutes, respectively. Patients over 50 years old had a mean half-life of 189 minutes. For the entire group, wide variations in clearance were observed with 11% of patients having a half-life > 230 and 8% < 145 minutes. The maximum and minimum half-lives were 640 and 108 minutes.

Conclusion: Initial analysis of our data suggests that different dosing strategies based on population specific parameters may not be necessary. Pharmacists should continue to dose busulfan according to their institutional guidelines but due to the wide variations

observed in busulfan metabolism, individualized dosage adjustments should be made based on TDM.

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RETROSPECTIVE COMPARISON OF PHENYTOIN AND LEVETIRACETAM AS SEIZURE PROPHYLAXIS WITH HIGH DOSE BUSULFAN DURING ALLOGENEIC STEM CELL TRANSPLANT

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Background: Busulfan is an alkylating agent commonly used in preparative regimens for hematopoietic stem cell transplant (HSCT). Early clinical trials, prior to the use of seizure prophylaxis, revealed a high degree of neurotoxicity associated with myeloablative doses of this agent. Phenytoin has been widely used as seizure prophylaxis with busulfan. However, potential concerns with its use include the length of time to achieve a therapeutic steady state, risk of hepatotoxicity, and drug-drug interactions with busulfan and other agents used during conditioning. Alternatively, levetiracetam is highly bioavailable in both oral and intravenous forms, with a short half life it rapidly achieves steady state and is renally eliminated with limited drug interactions. The main objective of this study was to compare the incidence of seizures with phenytoin and levetiracetam. Secondary objectives were to compare VOD incidence, assess busulfan and phenytoin pharmacokinetics, and toxicity of the prophylactic agents.

Methods: All patients ≥ 18 years of age receiving busulfan in a preparative regimen prior to HSCT between 6/1/08-6/30/09 were included in this retrospective analysis. Patient information was collected from the pharmacy database and electronic medical records. Data included age, disease, preparative regimen, type of transplant, busulfan dose, busulfan AUC, survival status, incidence of relapse, and hepatic panels.

Results: 54 patients were included in this analysis with 22 receiving phenytoin and 32 receiving levetiracetam as seizure prophylaxis. Phenytoin was dosed with a 1000 mg loading dose and 300 mg daily maintenance dose. Levetiracetam was dosed at 500 mg twice daily. Of the 54 patients there were no reports of seizures in either group. There were also no reports of VOD in either group. Elevation in liver enzymes occurred in 3 (9%) patients who received levetiracetam compared to 7 (32%) patients who received phenytoin. A therapeutic steady state of phenytoin was achieved in 12 (55%) patients. Twenty patients (63%) receiving levetiracetam needed busulfan dose adjustments based on pharmacokinetic analysis versus 11 (50%) receiving phenytoin. Rates of relapse were similar in both groups.

Conclusion: Levetiracetam is a safe and effective alternative to phenytoin for busulfan seizure prophylaxis. With low hepatoxicity, no pharmacokinetic monitoring, and limited drug-drug interactions it is an attractive option in the HSCT population.

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WEIGHT-BASED DOSING OF VALGANCICLOVIR IN PEDIATRIC HSCT RECIPIENTS

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Background: IV ganciclovir is the standard therapy to prevent CMV infection in HSCT recipients at Texas Children's Hospital. In 2001, the FDA approved valganciclovir (VGC) for treatment of CMV retinitis in AIDS patients. This oral preparation increased the oral bioavailability of ganciclovir from 5% to 60% and demonstrated a well established safety profile. The oral route of administration avoids the need for a central line and markedly decreases the added costs associated with IV therapy. Unfortunately, data as to the efficacy of VGC to prevent CMV infection in pediatric HSCT recipients is limited. In 2004, our institution reported positive experience in liver transplant patients using 15–18 mg/kg/dose. Encouraged by this result, the HSCT program began using a similar dosing strategy for patients unable to receive IV ganciclovir. This report evaluates the efficacy and safety of weight-based dosing of VGC for CMV prophylaxis in pediatric HSCT recipients.

Methods: Thus far, we have evaluated thirty-two patients (2-20 years old) for this retrospective study. The inclusion criteria were: allogeneic HSCT recipients, CMV seropositive (donor and/or recipient) prior to transplantation, received VGC ≥ 7 days. Exclusion criteria were: ANC < 500 and renal dysfunction. Efficacy was defined as no incidence of CMV reactivation during therapy based upon the development of CMV antigenemia or the presence of CMV by quantitative PCR (qPCR). ANC served as a marker for safety. The dosing was as follows: 15-18 mg/kg/dose (max 900 mg) twice daily for 14 days, then once daily thereafter.

Results: The duration of therapy ranged 7 days to 2 years. The average dose for patients < 60 kg was 15.2 mg/kg/dose (8.2 – 22.5 mg/kg/dose.) Patients ≥ 60 kg received a maximum 900 mg per dose. CMV reactivation was not observed in 30 of 32 patients. Therapy was discontinued in 4 patients due to declining ANC. Four patients required filgrastim intermittently to maintain ANC > 500. Effect on ANC cannot be assessed for one patient due to concurrent treatment with hydroxyurea. Most importantly, no patient developed CMV pneumonitis.

Conclusion: Our data demonstrate that valganciclovir 15 – 18 mg/kg/dose is effective and safe as a CMV prophylactic regimen in pediatric HSCT patients. However, frequent monitoring, including CMV qPCR and hematologic profile, is necessary with VGC therapy.

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USE OF HEPATITIS B IMMUNE GLOBULIN AND ADEFOVIR IN A CORD BLOOD TRANSPLANT RECIPIENT

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A 52-year old female with acute myelogenous leukemia in remission presented for a matched unrelated donor hematopoeitic stem cell transplant, testing negative for Hepatitis B surface antigen. The recipient underwent HPCT conditioning using the Slavin regimen. The patient's human leukocyte antigen (HLA) typing matched with a cord blood donation from a twin birth where the mother was found to be Hepatitis B surface antigen positive; the HBsAg status of the twin donors was unknown at the time of hematopoeitic stem cell transplantation.

As a precaution against the recipient developing a Hepatitis B infection, Hepatitis B Immune Globulin and Adefovir was administered as chemoprophylaxis. Dosing of Hepatitis B Immune Globulin was derived from the liver transplant literature. Hepatitis B Immune Globulin 20,000 international units was given intravenously on transplant day zero and repeated on transplant days 1 through 7. Additional doses were scheduled for every two weeks to begin on transplant day +14. Adefovir 10 mg was ordered to be administered by mouth daily beginning on transplant day negative 2.

On transplant day +19 the HBsAg status of the twin donors was discovered to be negative. Hepatitis B chemoprophylaxis was discontinued at that time with no additional doses administered to the recipient.

Hepatitis B Immune Globulin is used in the liver transplantation population to prevent hepatitis B virus recurrence in HBsAg-positive recipients after transplantation. Adefovir is used to treat chronic hepatitis B infections.

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DECLINE IN BONE MINERAL DENSITY IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: IMPACT OF MYELOABLATIVE VERSUS REDUCED INTENSITY CONDITIONING REGIMENS

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Background: Compared with myeloablative (MA) regimens, reduced intensity conditioning (RIC) regimens have shown a lower incidence of some complications (veno-occlusive disease, pre-engraftment infections, bronchiolitis obliterans); however, the incidence is similar for others (chronic kidney disease, hypothyroidism). The incidence of osteoporosis and osteopenia has not been compared.