

## Pharmacy

phosphatase ( $r = 0.44$ ;  $P = 0.008$ ) and AST ( $r = 0.52$ ;  $P = 0.001$ ). Since liver dysfunction is relatively common after allogeneic HSCT, it was not possible to determine if elevated AST and alkaline phosphatase levels were the cause or the consequence of higher Vori levels. Based on these data, we conclude that trough Vori levels vary considerably between patients with a small proportion having potentially subtherapeutic levels on standard doses. We suggest checking serum Vori levels in patients receiving the drug for confirmed fungal infections. Additionally, patients developing elevation of AST or alkaline phosphatase on therapy should also have Vori levels monitored. Vori levels should also be checked if the drug dose is changed.

### 292

#### RESULTS OF ONCE DAILY PARENTERAL BUSULFAN (BUSULFEX®) WITH CYCLOPHOSPHAMIDE VERSUS INTERMITTENT DOSING OF BUSULFAN WITH CYCLOPHOSPHAMIDE AS A PREPARATIVE REGIMEN FOR ALLOGENEIC TRANSPLANT RECIPIENTS WITH UNDERLYING HEMATOLOGICAL MALIGNANCIES AND DISEASES

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The use of high dose oral busulfan has been a standard treatment regimen employed in the field of blood and marrow transplantation for over 30 years. The toxicity profile of high dose busulfan includes hematological, neurological and hepatic dysfunction. At doses of 16 mg/kg, the hematological toxicity requires stem cell rescue. Neurologic toxicity is mild, but has led to the routine use of phenytoin for seizure prophylaxis. The other principal toxicity of high dose busulfan is hepatic complications, primarily described as veno-occlusive disease (VOD).

Historically, high dose busulfan has been administered orally over four days in a QID dosing schedule. The rationale for this dosing interval was primarily due to the large numbers of tablets patients had to swallow for a typical dose (i.e. a 70kg person would have to swallow 560 tablets). Additional concerns due to hepatic first-pass metabolism have been associated with inter-patient variation in plasma levels.

The initial trials of a parenteral formulation of IV busulfan were designed to duplicate the oral dosing experience, and it was determined that 0.8 mg/kg every 6 hours X 16 doses was an equivalent dosing regimen. However, many transplant centers are exploring the feasibility of using once daily dosing (3.2 mg/kg daily times 4 days) versus the conventional dosing regimens.

To date, we have enrolled 13 of 20 anticipated patients on an IRB approved protocol using once daily dosing of IV busulfan. These patients will be compared to historical controls who received intermittent dosing. Pharmacokinetic monitoring is being performed using the WINNONLIN® program. The primary objectives of the study are to compare hematopoietic engraftment, incidence and severity of VOD, interstitial pneumonitis, and seizure occurrence during drug administration.

A preliminary analysis of the first 10 patients has not demonstrated any acute toxicities, and only one of the 10 patients has required a dosage adjustment.

### 293

#### ELEVATED PLASMA LEVELS OF TACROLIMUS AFTER CONCURRENT USE OF TACROLIMUS AND VORICONAZOLE IN THE BONE MARROW TRANSPLANT SETTING

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Voriconazole is a broad-spectrum triazole antifungal agent used for the prevention and treatment of invasive fungal infections in high-risk transplant recipients. Azole antifungal agents have been associated with numerous drug-drug interactions. Voriconazole is extensively metabolized through the liver via the cytochrome (CYP) P450 enzyme system. The primary isoenzymes involved are

CYP2C19, CYP2C9 and CYP3A4. Patients undergoing allogeneic stem cell transplantation at MD Anderson Cancer Center receive tacrolimus for graft versus host disease prophylaxis, dosed to achieve therapeutic plasma levels between 5-12 ng/ml. Reports in the literature have demonstrated the concurrent use of tacrolimus and voriconazole to result in supra-therapeutic tacrolimus levels in liver transplant recipients. Supra-therapeutic tacrolimus levels have been associated with adverse events such as renal failure requiring hemodialysis and seizures. The primary objective of this study was to determine the effect of voriconazole on tacrolimus levels in the bone marrow transplant setting. We performed a retrospective chart review of 30 bone marrow and stem cell transplant recipients who received concurrent therapy with voriconazole and tacrolimus. Data collected included patient demographics, diagnosis, type and date of transplant, concomitant medications, and pertinent laboratory tests (serum creatinine, blood urea nitrogen, liver function tests, and tacrolimus levels). The dose of voriconazole was as follows: 200 mg po BID (n = 18), 200 mg po QD (n = 1), 200 mg IV q12h (n = 4), and 3-4 mg/kg IV q12h (n = 7). Preliminary results reveal that 22 patients (73%) experienced an increase in plasma levels of tacrolimus, which occurred at a median of 5 days (range 2-10 days) of concomitant therapy. Over one-half of these patients had more than a 75% increase in plasma tacrolimus levels thus requiring a significant decrease in tacrolimus dose. Of the 22 patients, 7 (32%) showed mild to moderate elevations in liver function tests which may have contributed to supra-therapeutic tacrolimus levels due to the drug's extensive hepatic metabolism. While the manufacturer recommends that the tacrolimus dose be reduced to one-third of the original dose when initiating therapy with voriconazole in patients already receiving tacrolimus, our initial results suggest that some patients may require up to a 75% decrease in tacrolimus dose to avoid supra-therapeutic levels of tacrolimus and subsequent sequelae.

### 294

#### RETROSPECTIVE REVIEW OF THERAPY WITH REDUCED DOSE RASBURICASE IN ADULTS WITH HYPERURICEMIA ASSOCIATED WITH MALIGNANCY

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Here we report our institutional experience in the treatment of malignancy-related hyperuricemia with reduced dose IV rasburicase. Eight patients with various underlying diseases (AML(3), Burkitt's NHL (2), ALL (1), MDS (1), MM (1) and CLL/Richter's transformation (1)) received 9 treatments (6 mg IV over 30 minutes) of rasburicase. Rasburicase was given as a single dose except in one patient who received a second 6 mg dose early during the chemotherapy cycle for persistent elevated uric acid levels. Another patient was retreated with their subsequent cycle of chemotherapy eight days later. The 6 mg doses of rasburicase for each patient ranged from 0.05 to 0.1 mg/kg. Patient ages ranged from 46-74 years (mean 62) and patients either had developed or were deemed at high risk for developing renal dysfunction. Pre-treatment uric acid levels ranged from >21 (2 patients) to 8.7 mg/dL (mean >14.6 mg/dL) and pre-therapy serum creatinine levels ranged from 9.9 to 1.1 mg/dL (mean 3.3 mg/dL). As part of standard of care for tumor lysis, all patients received hyperhydration +/- alkalinization, prophylactic allopurinol and monitoring of uric acid levels. The single 6 mg dose rapidly reduced uric levels to normal limits (<8.3). Uric acid reductions were observed as follows: >21 to 13.0 @ 17.3h (patient then received a second dose), >21 to 5.3 @ 38.2h, 16.4 to 5.6 @ 10.3h, 15.1 to 3.3 @ 22.5 h, 15.2 to 4.0 @ 12.1h, 14.1 to 6.6 @ 23.8h, 11.1 to 0.9 @ 20.5h, 9.0 to 2.9 @ 11.5h and 8.7 to 1.2 @ 32h. We conclude, that a single 6 mg dose of rasburicase is sufficient to rapidly reduce hyperuricemia of malignancy and provides adequate and cost-effective treatment for hyperuricemia from tumor lysis in adults.