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Development and Validation of a Test Dose Strategy for Once-Daily i.v. Busulfan: Importance of Fixed Infusion Rate Dosing

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Intravenous (i.v.) busulfan (Bu) administered once daily in myeloablative transplant regimens is convenient, effective, and relatively well tolerated. Therapeutic drug monitoring is recommended as nonrelapse mortality increases when daily exposure, as determined by the area under the plasma concentration versus time curve (AUC), exceeds 6000 μM·min. We describe sequential studies to achieve accurate prediction of treatment doses of Bu based on the kinetics of a smaller test dose. A total of 335 patients with hematologic malignancies were given daily i.v. Bu 3.2 mg/kg × 4 and fludarabine 50 mg/m^2 × 5. Pharmacokinetic monitoring was conducted for both the test dose and first treatment dose of Bu (day −5). Three different test dose schedules were evaluated: 12 mg Bu administered over 20 minutes, 0.8 mg/kg over 3 hours, and 0.8 mg/kg infused at 80 mg/h. The 3.2 mg/kg treatment doses were infused over a fixed time of 3 hours for the first 2 test dose trials and at a fixed rate of 80 mg/h for the final protocol. All test dose infusions were on day −7. In the first 2 schedules, Bu administered over a fixed time had significantly higher clearance for the test dose compared with the treatment dose. However, when both the test and the treatment doses were administered at the same infusion rate, clearance of the drug between the 2 dosing days was equivalent. Predicted day −5 AUC (AUC$_{-5}$) showed a high linear correlation ($r^2 = 0.74$) to the actual AUC$_{-5}$. The error of these predictions was <20% in 98% of patients and <10% in 80%. In 24 individuals, the test dose predicted an AUC >5500 μM·min; therefore, the first Bu treatment dose was reduced to a desired target AUC. All adjusted doses fell within 20% of the targeted exposure. We conclude that a test dose strategy for therapeutic drug monitoring of daily i.v. Bu is accurate if the test and treatment doses are infused at the same rate. This approach allows targeting of therapeutic doses of Bu to desired levels and the potential for improved safety and efficacy.

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INTRODUCTION

Busulfan (Bu) is a bifunctional alkylating agent used in conditioning regimens for hematopoietic stem cell transplantation. An intravenous (i.v.) formulation has been developed, leading to more predictable delivery and probably improved clinical outcomes compared with oral Bu [1-12]. Even after i.v. administration, however, the exposure may vary by 3- to 4-fold. Pharmacokinetic (PK) studies with both oral and i.v. Bu have indicated that exposures above a critical level are accompanied by unacceptably high toxicity and consequent nonrelapse mortality [13,14]. Even within a commonly accepted therapeutic range, there is evidence that toxicity may increase with increasing exposures [7]. Therapeutic drug monitoring of Bu PK in individual patients with dose adjustment may therefore help to improve clinical outcomes [1]. One strategy is to check the PK of an early treatment dose and adjust subsequent doses if necessary [15]. The second is to base any necessary adjustments on the PK of a test dose given some time before the first treatment dose [16,17]. We describe the results of sequential

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studies to develop a reliable test dose regimen for once-daily i.v. Bu.

PATIENTS AND METHODS

Patients

The initial study included 99 patients with hematologic disorders undergoing allogeneic hematopoietic stem cell transplantation. The first 2 groups of 34 and 11 patients had different Bu test doses infused over a fixed time. When the optimal strategy of fixed rate infusion had been defined in the third group of 54 patients, a subsequent cohort of 236 patients was used as a validation group and included 24 for whom dose adjustments were made based on the test dose results. These patients had doses adjusted if predicted exposures were >5500 μM·min. Initially, the adjustment target in the first 3 patients was 5500 μM·min; however, in subsequent patients, the desired target was 5000 μM·min to allow for a 20% margin of error. The 212 patients without dose adjustments were included with the original 54 for a total of 266 patients given the test dose at a fixed rate without dose adjustment. Diagnoses and other details of the 4 groups are recorded in Table 1.

All patients enrolled in the study provided informed consent and met institutional guidelines for transplant eligibility. The protocol and consent forms were approved by the University of Calgary Health Research Ethics Board.

Test Dose and Treatment Regimen

With transplantation on day 0, all patients received 3.2 mg/kg Bu (based on the lower of actual or adjusted ideal body weight) once-daily i.v. on days −5 to −2 inclusive, either as a 3-hour infusion or at an infusion rate (IR) set at 80 mg/h. Fludarabine 50 mg/m^2 i.v. was given on days −6 to −2, inclusive. The first group of 34 patients was given a test dose of 12 mg Bu infused over 20 minutes, with the treatment dose infused over 3 hours. The second group of 11 patients received both the test dose of 0.8 mg/kg Bu and the treatment doses over 3 hours. The final 290 patients had a test dose of 0.8 mg/kg and all treatment doses infused at a fixed rate of 80 mg/h. This rate was approximately the median IR of our historic cohort of patients given daily i.v. Bu infused over 3 hours.

For the first 131 patients, phenytoin was given from day −12 until day −1. On the day of the first treatment dose of Bu, the phenytoin dose was adjusted if the level was outside a target range of 40 to 80 μmol/L. The final 204 patients received anticonvulsant therapy with lorazepam. The PK results of patients given different anticonvulsants were combined because there was no difference in the relationship of clearances between test and treatment doses. Discontinuation of phenytoin, when deemed necessary, was reported to the PK laboratory. No other drugs were routinely administered at the time of the test dose. Routine prophylaxis for nausea with granisitron was given during administration of Bu treatment doses. Concomitant medication was reviewed retrospectively when errors in the prediction of treatment doses >20% were observed.

Pharmacokinetic Analysis

PK samples were collected for both the test dose day and the first treatment dose of Bu. Blood samples (5 mL) were collected in heparin tubes at the end of the Bu infusion and 1, 3, 5, and 7 hours after the end of the Bu infusion. Bu concentration in plasma was determined by ultraviolet high-performance liquid chromatography,

Table 1. Diagnoses, Disease Stage, and Age Distribution of Each Group

Group	Test Dose 12 mg over 20 Minutes		Test Dose 0.8 mg/kg over 3 Hours		Test Dose 0.8 mg/kg at 80 mg/h Nonadjusted		Test Dose 0.8 mg/kg at 80 mg/h Adjusted	
Number	34		11		266		24	
Patient age (yr), median (range)	48 (18-65)		38 (19-66)		49 (18-66)		47 (19-61)	
Male	22 (65%)		6 (55%)		152 (57%)		13 (54%)	
Diagnosis	#	%	#	%	#	%	#	%
AML	14	42	5	45	117	44	11	46
ALL	2	6	2	18	42	16	7	29
CML					13	5		
CLL			2	18	18	7	3	13
NHL	2	6			21	8		
MM	6	18						
HD	2	6	1	9	3	5	1	4
MDS	3	9	1	9	24	9	2	8
MF					14	5		
Other	5	15			15	5		
Phenytoin	34	100	11	100	84	32	2	8

AML indicates acute myelogenous leukemia/granulocytic sarcoma; ALL, acute lymphoblastic/biphenotypic leukemia; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; MM, multiple myeloma; HD, Hodgkin's disease ± CLL; MDS, myelodysplasia; MF, myelofibrosis.