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Pharmacokinetics and Individualized Dose Adjustment of Intravenous Busulfan in Children with Advanced Hematologic Malignancies Undergoing Allogeneic Stem Cell Transplantation

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ABSTRACT

We investigated the pharmacokinetics (PK) of a recently approved intravenous busulfan (IVBU) formulation as a part of the preparative regimen in 20 children with advanced hematologic malignancies undergoing allogeneic hematopoietic stem cell transplantation. Seventeen patients received a thiotepa, IVBU, and cyclophosphamide–based regimen, and 3 patients received an IVBU and cyclophosphamide–based regimen. All patients received IVBU 0.8 mg/kg for the first 2 doses; thereafter, the IVBU dose was modified, if required, to achieve a final area under the concentration-time curve (AUC) at steady state of 1150 μmol/L/min per dose (range, 1000-1300 μmol/L/min per dose; SD ±13%) based on the first-dose PK determination. PK studies were repeated on subsequent doses to verify the final AUC. Initial mean IVBU clearance and half-life were 3.96 mL/min/kg and 1.98 hours, respectively. Sixteen (80%) of the 20 patients received dose adjustments: 14 patients required dose escalations, and 2 required dose reductions. Overall, thirteen (72%) of 18 available sample sets at final follow-up PK analysis showed the IVBU exposure to be within the targeted range. IVBU PK was linear, and interpatient variability was much lower than that observed with oral busulfan. IVBU was well tolerated, and no case of hepatic veno-occlusive disease was encountered. Mild and transient hyperbilirubinemia was observed in 7 patients. Thirteen of the 20 patients were alive at a median follow-up of 651 days (range, 386-1555 days). We conclude that a standardized IVBU dose of 0.8 mg/kg in children does not always result in an AUC within the reference range defined in this study. Therapeutic drug monitoring with dose adjustment based on first-dose PK can optimize the systemic busulfan exposure for children undergoing allogeneic hematopoietic stem cell transplantation.
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KEY WORDS

Intravenous busulfan • Pharmacokinetics • Stem cell transplantation • Childhood leukemia

INTRODUCTION

High-dose busulfan (BU) is an important component of many myeloablative regimens for patients undergoing hematopoietic stem cell transplantation (HSCT). Steady-state BU plasma concentrations and areas under the concentration-time curve (AUC) correlate with the incidence of graft failure, transplant-related mortality, and relapse of the primary disease [1-3]. Until recently, BU was available only in the oral formulation. When oral BU is used in a high-dose preparative regimen before transplantation in children, a number of unfavorable profiles have been described. These include delayed and variable absorptive characteristics, high variability in drug metabolism, and more rapid, age-dependent clearance of the drug [4-6]. Children up to 6 years of age have a significantly higher clearance of oral BU. Although dosing BU according to body-surface area approxi-

mates its clearance to that observed in adults, this approach does not correct interpatient differences in clearance. Additionally, the high emetogenic potential of BU, which requires empirical replacement of vomited tablets, also adds to the complexity of optimizing systemic drug exposure. Therapeutic drug monitoring (TDM) of oral BU with dosage adjustment is widely practiced, with variable results [6-8].

Advantages of administering BU intravenously (IV) include assurance of 100% bioavailability, avoidance of the first-pass effect, ease of administration, and assurance that the prescribed dose has been received. It may reduce the large variability in drug disposition while ensuring adequate systemic drug exposure. IV administration is particularly useful in children who have difficulty swallowing a large number of tablets for myeloablative regimens.

A parenteral formulation of BU (IVBU; Busulfex Injection; ESP Pharma, Edison, NJ) was approved in 1999 for clinical use in adults at a dose of 0.8 mg/kg in combination with cyclophosphamide as a preparative regimen for HSCT. Results from the phase I and II studies in adults showed that this new formulation was well tolerated and provided a more consistent pharmacokinetic (PK) profile and dosing reliability than that reported with oral BU [9,10].

Data on the use of IVBU in children are very limited. We previously reported a feasibility study of individualizing oral BU dosing on the basis of first-dose PK [6]. We showed that this approach could maximize the therapeutic effects of BU while minimizing toxicities. However, variable drug absorption and excessive vomiting remained significant problems with oral BU. In this study, we substituted IVBU for its oral formulation in transplant conditioning regimens for children with advanced hematologic malignancies. We also determined the PK parameters of IVBU and the usefulness of dose adjustment in the pediatric age group.

PATIENTS AND METHODS

Patients

Children and young adults <21 years of age with recurrent or high-risk leukemia or lymphoma were eligible. Patients also met the following criteria: left ventricular ejection fraction >50%, serum creatinine and bilirubin levels no more than twice the upper limit of normal for age, serum alanine aminotransferase level no more than 3 times the upper limit of normal, human immunodeficiency virus antibody negative, and Lansky performance status >70%. Patients who received a transplant during the first or second complete remission of acute leukemia from an HLA-identical donor (related or unrelated) were considered standard risk; the rest of the patients were regarded as high risk. The transplantation protocols were approved by the Institutional Review Board of The University of Texas M.D. Anderson Cancer Center, and written informed consent was obtained from parents or guardians for all patients.

Treatment Plan

Two IVBU-based treatment regimens were used. Seventeen patients were treated on the thiotepa, BU, and cyclophosphamide regimen, which consisted of thiotepa (250 mg/m² IV over 4 hours daily on days −9, −8, and −7), BU (initial dose of 0.8 mg/kg IV every 6 hours for 2 doses; the remaining 10 doses were then dosed on the basis of first-dose AUC determination, on days −6, −5, and −4), and cyclophosphamide (60 mg/kg IV over 2 hours on days −3 and −2). Three patients were treated on the IVBU and cyclophosphamide regimen. This consisted of IVBU 0.8 mg/kg every 6 hours for 2 doses, and the remaining 14 doses were dosed on the basis of first-dose AUC determination, on days −7 to −4, followed by cyclophosphamide 60 mg/kg IV on days −3 and −2. Because all 3 patients underwent unrelated donor transplantations, they also received antithymocyte globulin 30 mg/kg IV on days −3, −2, and −1. IVBU was diluted in normal saline to a concentration of 0.5 mg/mL and was infused through a central venous catheter during 2 hours. A standard amount of IVBU, 1.7 mg (3.08 mL of drug solution), was added to the calculated dose to fill the priming volume of the IV tubing. Doses of IVBU were calculated by using the actual body weight to the nearest one hundredth of a milligram. Subsequent dosage was adjusted, as needed, to reach a targeted BU AUC of 1150 µmol/L/min per dose (range, 1000-1300 µmol/L/min per dose; SD ±13%) at steady state. The reference range of 1000 to 1300 µmol/L/min per dose was based on the median of the AUC range (1500 µmol/L/min per dose) achieved by Andersson et al. [10] in adults, with a variance of 15%.

To prevent seizures, all patients received lorazepam, which was administered from 24 hours before the first IVBU dose to 24 hours after the last IVBU dose. Lorazepam rather than phenytoin was given for seizure prophylaxis because a number of adverse events have been associated with the use of phenytoin in this setting, and it may interfere with BU metabolism [11]. Mesna 10 mg/kg IV every 4 hours was used for uroprotection during and for 24 hours after cyclophosphamide administration. Bone marrow, blood stem cells, or umbilical cord blood from related or unrelated donors was infused for hematopoietic reconstitution on day 0. No T-cell depletion was performed. Patients were monitored and received supportive care according to standard procedures in our institution. Filgrastim at a dose of 5 to 10 µg/kg/d was

given subcutaneously from day +1 until engraftment. Tacrolimus, along with methotrexate, was given for the prevention of acute graft-versus-host disease (GVHD), as previously described [12].

Study Evaluation

The modified National Cancer Institute common toxicity criteria (version 2.0) were used to score pulmonary, cardiac, hepatic, renal, gastrointestinal, bladder, and neurologic complications until day 28. The Jones criteria were used for the diagnosis of hepatic veno-occlusive disease (VOD) [13]. Engraftment was assessed by peripheral blood count recovery and marrow examination and was confirmed by conventional restriction fragment length polymorphism and cytogenetic analysis [14]. To document disease response, bone marrow aspiration was performed at 1, 3, 12, and 24 months after HSCT and additionally at any time when clinically indicated.

All patients were followed up through March 31, 2004, with a minimum follow-up of 13 months after transplantation. Actuarial estimates of treatment-related mortality and survival were calculated according to the method of Kaplan and Meier [15]. Confidence intervals were calculated with True Epistat statistical software (Epistat Services, Houston, TX). Median values were compared by using the Mann-Whitney U test [16], and the Wilcoxon signed rank test [17] was used to compare matched samples. All P values were 2 tailed, and $P < .05$ was considered significant.

PK Studies

Heparinized blood samples (2-3 mL) were drawn in conjunction with the administration of doses 1, 5, 9, and 13 (if applicable) of IVBU immediately before drug infusion and 0.5, 1, 2, 4, 5, and 6 hours after the start of infusion (n = 7 samples). Because IVBU was administered through a central venous catheter, all blood samples for PK studies were collected from a peripheral IV catheter to avoid contamination caused by the proximity between the lumens of the catheter used for infusion. Samples were separated via centrifugation at 1500 rpm for 15 minutes in a refrigerated centrifuge at 5°C. For doses 1 and 5, plasma samples were analyzed immediately on the same day. Samples from doses 9 and 13 were cryopreserved at −70°C until analysis at a later time. Samples were subjected to processing and separation with high-pressure liquid chromatography, as previously described [6,9,18]. Parameters such as the volume of distribution of the central compartment and the elimination rate constant were estimated, and the steady-state volume of distribution, half-life, and clearance were calculated from the primary parameters. The AUC per IVBU

dose was calculated by using the following formulas, as previously described [6]:

$$\text{Initial AUC(}\mu\text{mol/L/min)} = [\text{dose(mg/kg/dose)}/\text{clearance(L/min/kg)}] \times 4.065$$

$$\text{New dose(mg/kg/dose)} = [\text{target AUC (}\mu\text{mol/L/min/dose)} \times \text{clearance(L/min/kg)}] \times 0.246$$

Dose adjustments were made at the third dose, if necessary, to target an AUC at steady state of 1150 μmol/L/min per dose (range, 1000-1300 μmol/L/min per dose). The maximum limit of IVBU dosage change was set at 50%, and the clinical status of the patient was also taken into account as to where in the therapeutic range the target with the dose adjustment would be.

PK modeling was performed with ADAPT II software, version 4.0 (BMRS, University of Southern California, Los Angeles, CA). A 1-compartment open model with a weighted least squares regression model was used to evaluate individual patient sets of concentration-time data [19]. The fifth and final IVBU AUC was calculated by using the PK parameters determined by modeling the IVBU plasma concentration versus time data of all the doses tested from each patient's data set. These 2 subsequent PK estimates were used to predict the performance of the model of first-dose data. No IVBU dose adjustments were made from these revised (fifth and final) parameter estimates derived from multiple-dose data.

RESULTS

Patient Characteristics

Between May 1999 and January 2003, a total of 20 patients met the eligibility criteria and were treated on the adjusted-dose protocols. Their clinical characteristics are described in Table 1. Median age was 5.5 years (range, 0.8-14.9 years). Median weight of the patients was 22.3 kg (range, 8.7-56.4 kg). Eleven patients were in the high-risk group, and 7 of these patients had active disease at the time of pretransplantation conditioning. Sixteen patients received HSCTs from unrelated donors, and 4 patients, from HLA-identical siblings. For the unrelated-donor group, 2 transplantations were performed with HLA-matched marrow donors, and 14 transplantations were performed with umbilical cord blood units mismatched at 0 (n = 1), 1 (n = 5), 2 (n = 6), or 3 (n = 2) HLA loci.

BU PK and Dose Adjustments

Table 2 summarizes the results of the PK analysis. All patients received the first 2 doses of IVBU at 0.8 mg/kg. The median first-dose IVBU clearance was 3.94 mL/min/kg (mean, 3.96 mL/min/kg; range, 2.25-

Table 1. *Patient Characteristics*

Characteristic	Median (range) or No. Patients
Age (y)	5.5 (0.8-14.9)
Sex (M/F)	12/8
Diagnosis	
ALL	7
AML	11
MDS	1
JMML	1
Risk category	
Standard risk	9
High risk	11
Stem cell source	
Marrow	5
Blood stem cells	1
Cord blood	14

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; JMML, juvenile myelomonocytic leukemia.

7.47 mL/min/kg). The median initial volume of distribution was 1.00 L/kg (mean, 1.50 L/kg; range, 0.21-5.83 L/kg), and the median half-life was 1.75 hours (mean, 1.98 hours; range, 1.20-3.64 hours). The median first-dose AUC was 851.5 μmol/L/min (mean, 888.5 μmol/L/min; range, 436-1437 μmol/L/min) for the entire group. On the basis of the first-dose PK analysis, 14 patients required dose escalation by 13% to 50% (median, 34%). Two patients required BU dose reduction by 8% and 21% to achieve the targeted range. Only 4 patients did not require dosage adjustment. The median final IVBU dose for the entire group was 1.04 mg/kg (mean, 0.99 mg/kg; range, 0.63-1.20 mg/kg).

Eighteen of 20 patient sample sets were available for final analysis and PK modeling. These analyses combined PK data available from doses 1, 5, and 9 (and dose 13 in 2 patients) and demonstrated that 72% (13 of 18) of patients achieved an AUC within the targeted exposure range of 1000 to 1300 μmol/L/min per dose for a course of therapy. When divided according to age (Figure 1), the final IVBU clearance values were higher in children younger than 6 years (n = 9; mean, 4.49 mL/min/kg; SD, 0.69 mL/min/kg) than for patients 6 years and older (n = 9; mean, 3.35 mL/min/kg; SD, 0.67 mL/min/kg; $P = .0027$ by the Student t test).

Regimen-Related Toxicities

Ten (50%) of 20 patients experienced grade 2 or 3 regimen-related toxicities. Stomatitis, esophagitis, and diarrhea were the most frequent adverse effects. Nausea and vomiting were very mild. Mild intertriginous skin hyperpigmentation and moist desquamation occurred in a third of the patients as a result of thiotepa toxicity. There were no cases of neurotoxicity. Seven (35%) patients developed hyperbilirubinemia (grade 1, n = 5;

grade 2, n = 2), but none had other features of hepatic VOD. These complications resolved without treatment within 7 days.

Engraftment, Relapse, and Survival

In this group of 20 patients with advanced hematologic malignancies, all patients survived beyond day +30. Two patients did not show signs of hematologic recovery: 1 patient had persistent leukemia, and the other patient experienced primary graft failure after a mismatched unrelated donor umbilical cord blood transplantation. All remaining patients recovered with absolute neutrophil counts exceeding 500/μL. Five of the 7 patients with active disease at the time of transplantation had achieved complete hematologic remission on the day +30 bone marrow evaluation. One patient had marrow aplasia, and another patient had persistent leukemia. As of March 31, 2004, a total of 13 patients were alive (median follow-up of the surviving patients, 651 days; range, 386 to 1555 days). Twelve (7 of 11 high-risk and 5 of 9 standard-risk) patients remain in continuous complete remission. One patient is alive with recurrent juvenile myelomonocytic leukemia. Seven patients have died: 1 death resulted from GVHD and 6 deaths from recurrent leukemia.

DISCUSSION

The therapeutic window of BU in the HSCT preparative regimen is relatively narrow. Leukemia recurrence and graft failure have both been associated with low BU exposure [1-3]. Andersson et al. [1] reported that deviation from their therapeutic window of a per-dose AUC between 950 and 1520 μmol/L/min was associated with more disease relapse, more transplantation-related mortality, more acute GVHD, and a higher day 100 mortality in adult patients with chronic myeloid leukemia. Oral administration of BU is associated with erratic absorption, resulting in unpredictable dosing bioavailability and, thus, unpredictable systemic drug exposure.

In children, age-dependent metabolism of BU further complicates the challenge of optimizing systemic drug exposure. The blood concentration and clearance might vary up to 6-fold among pediatric patients receiving oral BU [4-6]. Because of their higher clearance children require a higher dose of oral BU than adults to achieve similar exposure. TDM of oral BU has been considered an essential practice in pediatric patients undergoing HSCT. We previously showed that systemic BU exposure could be projected from the initial-dose AUC [6]. Individualized oral BU dosing reduced regimen-related toxicities while maximizing the desired drug effect. However, the inherent issue of unpredictable drug absorption cannot be resolved.

Table 2. *Summary of IVBU PK in Children*

Patient No.	Sex	Age (y)	Weight (kg)	Initial Vc (L/kg)	First-Dose t$_{1/2}$ (h)	First-Dose IVBU Clearance (mL/min/kg)*	First-Dose IVBU AUC (mmol/L/min)†	% Change in Dose	New IVBU Dose (mg/kg)‡	Final IVBU Clearance (mL/min/kg)	Final IVBU AUC (mmol/L/min)†
1	M	12.5	47.8	0.25	2.70	2.25	1437	−21	0.63	2.45	1041
2	M	3.5	15.7	1.00	1.40	3.77	826	50	1.15	4.25	1098
3	M	1.0	9.7	3.12	2.12	3.58	936	25	1.03	N/A	N/A
4	F	6.0	24.6	0.70	1.64	4.17	781	31	1.05	3.32	1281
5	M	1.7	12.7	2.51	1.72	4.89	665	48	1.18	3.83	1256
6	M	2.2	11.5	2.99	2.50	3.88	839	0	0.80	4.28	910
7	F	4.4	22.0	1.09	1.68	3.55	965	0	0.84	3.39	1007
8	F	2.4	15.2	1.52	1.75	5.56	587	49	1.20	4.89	996
9	M	13.6	38.4	0.42	1.92	4.06	864	30	1.04	3.79	1187
10	M	3.0	13.7	2.83	2.94	4.01	818	42	1.14	4.73	1129
11	F	9.6	31.2	0.72	3.64	2.56	1274	−8	0.74	3.91	768
12	F	0.8	9.2	5.83	1.52	7.47	436	49	1.20	5.70	858
13	F	11.0	38.4	0.29	1.75	2.84	1146	0	0.80	2.69	1210
14	M	14.9	54.7	0.21	1.84	3.33	973	13	0.91	2.90	1123
15	M	11.5	31.1	0.39	1.33	4.25	880	31	1.06	3.94	1105
16	F	11.5	33.8	0.35	1.20	2.55	1275	0	0.80	2.79	1016
17	M	8.5	22.5	0.99	1.75	3.61	687	50	1.20	N/A	N/A
18	M	13.0	47.4	0.58	1.50	4.92	652	37	1.10	4.34	1190
19	F	5.0	13.7	2.83	2.94	4.01	915	18	0.95	5.04	929
20	M	3.5	16.5	1.29	1.78	3.99	813	31	1.05	4.26	1158
Mean ± SD		6.99 ± 4.80	25.5 ± 14.1	1.50 ± 1.44	1.98 ± 0.64	3.96 ± 1.17	909 ± 258	23.72 ± 22.15	0.99 ± 0.17	3.92 ± 0.88	1070 ± 141
Median (range)		5.5 (0.8-14.9)	22.3 (9.2-54.7)	1.00 (0.21-5.83)	1.75 (1.20-3.64)	3.94 (2.25-7.47)	872 (436-1437)	30.49 (−21.1 to 50)	1.04 (0.63-1.2)	3.92 (2.45-5.70)	1102 (768-1281)

Vc indicates volume of distribution; t$_{1/2}$, half-life; N/A, not available.

*Denotes the normalized clearance of IVBU.

†Area under the concentration-time curve for each dose.

‡Dose change was made from the third administered dose onward.
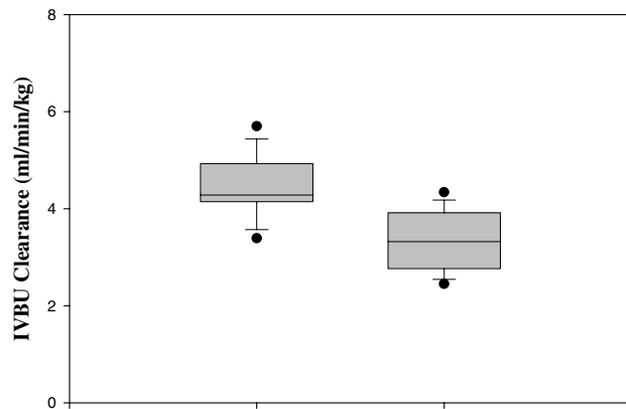
Figure I. IBVU clearance by age group. Comparison of final clearance between the 2 age groups of individuals younger than 6 years (n = 9; mean, 4.49 mL/min/kg; SD, 0.69 mL/min/kg) and those 6 years or older (n = 9; mean, 3.35 mL/min/kg; SD, 0.67 mL/min/kg). Student *t* test; *P* = .0026; *df* = 16.

Data from phase I and II studies of IVBU in adults have shown that the use of an IV preparation can ensure more standardized delivery of BU [9,10]. In those studies, IVBU was associated with significantly more consistent drug clearance, AUC, and half-life at steady state than has been seen with orally administered BU. Not only were there small interpatient variations in PK, but the IV formulation was also well tolerated. However, similar data on IVBU in children are lacking.

In this study, we sequentially determined the PK parameters of IVBU in 20 children undergoing HSCT. The optimal dose for pediatric patients has not been determined. Data from the pivotal study of IVBU in adults established that a dose of 0.8 mg/kg of adjusted body weight, infused over 2 hours, yielded PK parameters similar to those observed after an oral dose of 1 mg/kg body weight [9]. This approved IVBU dosing scheme was adopted as a starting point for this study. As in adult patients, the PK profile of this formulation is linear and highly reproducible. Age-dependent variability in metabolism is also seen in children receiving IVBU. In this population, the difference in drug clearance was up to 3-fold. A higher IVBU clearance rate in children up to 6 years of age was observed—a finding that recalled our previous experience with oral BU [6].

We observed that two thirds of the patient population had an initial AUC projected to be less than the reference range. Similarly, Wall et al. [20] reported that IVBU clearance was higher in young children. To reach the targeted IVBU exposure, these investigators recommended an increase in the initial IVBU dose from 0.8 mg/kg to 1 mg/kg in children 4 years and younger. Using this approach to initial dosing, Grimley et al. [21] reported that a targeted AUC was achieved in 50% of pediatric transplant recipients. In

a series of 6 children with a median age of 6 years, Cremers et al. [22] also found a relatively low AUC after an initial dose of 0.8 mg/kg, and the dosage of all patients was increased to 1 mg/kg. Conversely, Dalle et al. [23] reported that infants younger than 1 year had lower IVBU clearance, and half of the 14 patients required IVBU dose reduction.

Recently, the manufacturer of IVBU (ESP Pharma) provided the following dosing recommendation based on the patient's body weight: patients weighing 12 kg or less should receive 1.1 mg/kg per dose, and those over this weight should be given 0.8 mg/kg per dose. If we compare our data with this guideline, then the 3 children weighing 12 kg or less received a final IVBU dose of 0.8, 1.03, and 1.2 mg/kg. The median IVBU dose of the 17 heavier children was 1.05 mg/kg, and 13 of these children would have been underdosed according to the reference AUC range in this study.

Caution should be exercised in analyzing the IVBU PK data in this report and others. In addition to the different dosages used, investigators have not used a uniformly accepted AUC reference range or unit of measurement. In our study, the AUC reference range was 1000 to 1300 μmol/L/min per dose; others have expanded the therapeutic window to between 900 and 1500 μmol/L/min per dose [7,8,24]. This is an important factor to consider when analyzing the frequency of adjustment based on an individual patient's AUC. Furthermore, IVBU dosing in all the pediatric studies reported to date has been on a milligram-per-kilogram basis, and the PK data should be interpreted accordingly. Conversely, the PK profile of oral BU in children dosed on a milligram-per-square-meter basis more closely approximates the profile seen in adults [3,4,6]. This dosing approach has not yet been tested in children. Furthermore, because the PK profile of IVBU is highly consistent and reproducible over a range of dosing frequencies, IVBU has already been given on a daily basis in adults and children. These early data showed that the PK profile is linear when the total BU dose is administered in this manner [25-27].

IVBU was well tolerated in studies of adult transplant recipients. Compared with an oral BU-based preparative regimen, the incidence of hepatic VOD was lower and 100-day survival was higher [10,28]. Similarly, we observed minimal toxicity in children treated with IVBU. No neurotoxicity or hepatic VOD was observed. Mildly and transiently increased bilirubin levels were encountered in one third of the patients—an incidence similar to that reported in adults [26]. The incidence of nausea and vomiting was much lower than that observed in a previous group of children treated with oral BU on the same regimen (data not shown). This finding suggests that vomiting is mainly due to the difficulty of taking a large number of tablets or capsules during a short period. The engraft-

ment rate in this study was similar to that reported when oral BU was used in the same regimens. In our patients, IVBU did not demonstrate an adverse effect on hematologic reconstitution in HSCT, even though most patients received stem cells from unrelated donors. Considering the advanced stage of disease in the patients in this series, the disease-free survival rate is similar to that reported in other studies [6,29].

In this study, modest intrapatient variability in drug clearance was observed, and the PK determination of the first IVBU dose correlated well with that of the subsequent steady state in 72% of the patients evaluated. Given the more linear and highly reproducible absorption of this formulation, TDM of IVBU should be easier to perform. Using a more limited sampling schedule (doses 2 through 5) may be adequate to predict AUC. Alternatively, it is also possible to administer a test dose of IVBU before transplant conditioning to determine the optimal dose for the individual patient, an approach taken with oral BU [7,24]. It seems that regardless of how IVBU is dosed in children, maintaining a desired systemic exposure will continue to play an important role when using this agent in HSCT regimens [30].

We conclude that IVBU may be safely used in place of oral BU in children. The application of TDM to the new IV formulation allows for much more precision in the targeting of systemic BU exposure for individual pediatric patients on the basis of disease status, organ function, and donor source.

ACKNOWLEDGMENTS

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