Optimization of Busulfan Dosage in Children Undergoing Bone Marrow Transplantation: A Pharmacokinetic Study of Dose Escalation

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Busulfan (BU) is a widely used myeloablative and antineoplastic agent in clinical bone marrow transplantation (BMT). The lower incidence of BU-associated toxicities and lower therapeutic effectiveness in young children given BU doses based on body weight (ie, 16 mg/kg) is associated with altered pharmacokinetics of BU; the area under the curve (AUC) of BU concentration versus time is significantly less in these patients than those observed in older children and adults. To optimize BU dosage in young BMT recipients, we developed a dosage regimen based on body surface area (BSA) and determined BU pharmacokinetics and BU-associated toxicities. Seven children (median age, 3.9 years, range, 1.1 to 5.7) undergoing allogeneic or autologous BMT for leukemia received 40 mg/m^2/dose BU every 6 hours for 16 doses; BU concentrations were measured in the plasma, and AUCs were determined for each patient after the first and 13th doses. Expressed as a function of body weight, the median BU dosage was 26.4 mg/kg (range, 24.3 to 28.2), a 60% increase over the BU dosage based on body weight. Four patients developed mucositis, and one of them also developed nonfatal hepatic veno-occlusive disease (VOD). No patients receiving 40 mg/m^2 BU developed neurotoxicity (eg, seizures) or interstitial pneumonitis. Prompt and sustained engraftment was observed in the allogeneic BMT recipients, and late graft failure was not seen. The mean BU AUCs were 1,105 μmol/L·min (range, 790 to 2,080) after the first dose and 1,022 μmol/L·min (range, 632 to 1,860) after the 13th dose of BU, comparable to the AUCs in adults given 16 mg/kg of BU. These studies suggest that, in young children, BSA-based dosing of BU (40 mg/m^2) provides drug exposures (AUCs) closer to adult values with acceptable toxicities and may improve therapeutic effects.

BUSULFAN (BU) is widely used as a component of myeloablative and antineoplastic therapy in preparation for bone marrow transplantation (BMT).[1-3] However, in young children, the incidence of BU-related toxicities (eg, mucositis and hepatic veno-occlusive disease [VOD]) appears less than that observed in older children and adults.[4-8] It has also been suggested that higher rates of graft rejection or relapse of neoplastic disease occur in younger recipients of BU-containing regimens.[3,6,7,9] These observations suggested an alteration in the disposition of BU in children. Recent studies have shown that the disposition of BU in children under age 6 years differs from that in older children or adults.[10,11] Specifically, the area under the curve (AUC) of concentration versus time for BU was significantly and consistently less in younger children.

As altered exposure to BU in children may be associated with suboptimal therapeutic effects (eg, myeloablation, antileukemic effect), albeit with minimal BU-related toxicities, we conducted a study of BU dosage based on body surface area (BSA) in children undergoing allogeneic or autologous BMT for leukemia. The dosage used (40 mg/m^2/dose for 16 doses) was designed to provide AUCs similar to adult values. In each patient, we determined plasma BU concentrations and AUC, and evaluated BU-associated toxicities.

MATERIALS AND METHODS

Patients. Seven children (median age, 3.9 years; range, 1.1 to 5.7) undergoing autologous or allogeneic BMT for leukemia were eligible for this study, which was approved by the institutional review boards of The Johns Hopkins Medical Institutions and the Duke University Medical Center. Informed consent was obtained from parents of all patients. In addition to BU, all patients received cyclophosphamide (CY; 50 mg/kg/d × 4 days) after BU; autologous or allogeneic marrow was infused 48 hours after the last dose of CY, as previously described.[1,2] At the time of enrollment on study, all patients had normal hepatic function (transaminases <50 IU/dL and bilirubin <1.5 mg/dL). BSA was calculated according to the method of Gehan and George,[12] using actual weight determined with a standard clinical scale and supine or standing height measurements with a stadiometer. All patients had indwelling central venous catheters from which blood samples were obtained. Clinical data for the seven children are listed in Table 1.

BU dosage and administration. Patients were given nothing by mouth for 60 minutes before the first dose of BU, then received 40 mg/m^2/dose of BU every 6 hours for a total of 16 doses. This dosage was derived by conversion of adult BU dosage based on body weight (1 mg/kg/dose) to adult BSA (1.73 m^2 for a 70-kg adult, corresponding to 70 mg/1.73 m^2/dose). Tablets of BU (2 mg; Burroughs-Wellcome, Research Triangle Park, NC) were pulverized and given to the patients in soft palatable food (eg, applesauce). All patients received phenytoin for 7 days (beginning 24 hours before the first dose of BU) as prophylaxis against BU-associated seizures.[13,14]

Pharmacokinetics studies. Heparinized samples of blood (2 to 3 mL each) were obtained before the first and 13th BU doses, and at 30, 60, 90, 120, 240, and 360 minutes after these doses. Samples were also obtained before each dose for the fifth through 16th

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Submitted March 25, 1992; accepted July 7, 1992.

Supported in part by Contract No. CM07302 from the National Cancer Institute (L.B.G.) and by Grants No. R01 CA54203 (R.J.J.), P01 CA15396 (G.W.S.), R01 CA40282 (A.M.Y.), and R01 NS24097 (A.M.Y.) from the National Institutes of Health, Department of Health and Human Services, Bethesda, MD. J.E.W., Jr is the recipient of Career Development Award No. 91-56 from the American Cancer Society.

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0006-4971/92/8009-0027$3.00/0

Table 1. Clinical Data in Children Receiving BSA-Based BU Dosing for BMT

Patient No.	Age (yr)/ Gender	Diagnosis	Type of BMT	Height (cm)/ Weight (kg)/ BSA (m^2)	BU Dosage mg/ dose	mg/ m^2	mg/ kg	Mucositis	Lowest WBC (days after BMT)	Days to ANC $>0.5 \times 10^9$/L	Maximum Bilirubin (days after BMT)	VOD
1	5.7/M	AML, CR2	Auto	111.7/16.1/0.72	28	38.9	27.8	Mild; no analgesia needed	0 (day 7)	77	1.2 (day 26)	No
2	4.4/M	JCML, AP	Allo, placental blood	95.3/15.0/0.62	25	39.5	26.1	None	0 (day 8)	39	1.9 (day 10)	No
3	3.9/F	AML, CR1	Allo, sib	100/15.9/0.67	28	41.7	28.2	None	049 (day 8)	14	1.1 (day 18)	No
4	1.1/M	AML, CR2	Allo, sib	77/10.4/0.49	18	36.7	27.7	Severe; narcotic analgesia needed	012 (day 4)	13	2.4 (day 23)	Yes
5	4.8/M	AML, CR2	Auto	103/17/0.70	28	40	26.4	Severe; narcotic analgesia needed	0 (day 3)	72	0.5 (day 23)	No
6	2.6/F	AML, CR3	Auto	87.5/14.5/0.59	22	37.3	24.3	Moderate; non-narcotic analgesia needed	0 (day 2)	25	0.4 (day 18)	No
7	1.6/M	AML, CR1	Allo, maternal	77/12.9/0.54	20	37	24.8	None	0 (day 5)	21	4.4 (day 30)	No (hepatic GVHD)

Allogeneic marrow donors were HLA-identical with the recipients, and bidirectional mixed lymphocyte cultures between donor and recipient were negative. Patients undergoing autologous BMT received marrow collected in current remission and treated ex vivo with 60 μg/mL of 4-hydroperoxycyclophosphamide.

Abbreviations: Allo, allogeneic; Auto, autologous; AML, acute myeloid leukemia; ANC, absolute neutrophil count; AP, accelerated phase; CR, complete remission; GVHD, graft-versus-host disease; JCML, juvenile chronic myelogenous leukemia; WBC, total white blood cell count.

doses to establish trough concentrations. BU was assayed in plasma using the previously described gas-liquid chromatographic method of Chen et al.[15]

Clinical evaluation. In the post-BMT period, patients were evaluated by clinicians (M.L.G., A.M.Y.) for evidence of BU-related toxicity such as mucositis and VOD, which was defined according to published criteria.[8] Total leukocyte counts (white blood cells), absolute neutrophil counts (ANCs), and serum bilirubin were measured every 24 to 48 hours after BMT.

Statistical analyses. AUC was calculated using a one-compartment pharmacokinetic model with zero- or first-order absorption and elimination, as previously described.[10,16] Parameter estimation was performed using nonlinear least-squares analysis (PCNONLIN, Statistical Consultants, Lexington, KY).

RESULTS

BU dosage. The median actual dosage of BU calculated from BSA was 38.9 mg/m^2 (range, 36.7 to 41.7); these variations from the ideal study dosage of 40 mg/m^2 were due to rounding off the BU dosage from the 2-mg tablet size. When BU doses were expressed as a function of body weight, the median was 26.4 mg/kg (range, 24.3 to 28.2), approximately a 60% increase over the standard BU dosage of 16 mg/kg (Table 1).

Clinical course. All patients became aplastic within 2 to 8 days after BMT. Four patients developed mucositis, which required narcotic analgesia in two. In contrast, hepatic dysfunction was less frequently observed: in five patients, bilirubin did not exceed 1.9 mg/dL in the post-BMT period. In two patients undergoing allogeneic BMT for acute myeloid leukemia (AML) in remission, bilirubin elevations were observed. In patient 4, modest hyperbilirubinemia (maximum, 2.4 mg/dL at 23 days after BMT) was associated with weight gain, ascites, and tender hepatomegaly, consistent with the diagnosis of hepatic VOD[6,8]; with fluid restriction and diuretics, symptoms resolved and bilirubin fell below 1.5 mg/dL within 7 days. In patient 7, bilirubin increased to 4.4 mg/dL 33 days after allogeneic BMT, but there was no evidence for VOD; the course was felt to be most consistent with hepatic acute graft-versus-host disease, and hyperbilirubinemia slowly resolved within 2 weeks on cyclosporine and methylprednisolone therapy. No patients developed pulmonary insufficiency or manifestations of interstitial pneumonitis (Table 1).

Pharmacokinetic data. Table 2 shows the AUC after the first and 13th doses of BU and the mean trough BU concentration (C_{min}) for each patient. The median and

Table 2. Pharmacokinetic Data in Children Receiving 40 mg/m^2/dose BU

Patient No.	AUC (μmol/L · min) After 1st Dose	AUC (μmol/L · min) After 13th Dose	Mean C_{min} (μmol/L)
1	1,138	1,860	1.46
2	2,080	1,162	1.80
3	790	923	0.67
4	818	632	0.76
5	1,262	885	1.16
6	850	670	0.96
7	800	580	0.73
Mean ± SD	1,105 ± 468	959 ± 413	1.08 ± 0.42

Abbreviations: AUC, area under the curve of BU concentration *v* time; C_{min}, minimum (trough) BU concentration.

mean BU AUC after the first dose were 850 and 1,105 μmol/L·min, respectively (range, 790 to 2,080). There was no alteration in AUC after the 13th BU dose, at which time the median and mean AUCs were 904 and 1,022 μmol/L·min, respectively (range, 632 to 1,860). These values are similar to the AUC in adults (ie, 1,200 to 1,600 μmol/L·min) that are therapeutic but not associated with increased risks of VOD or other life-threatening extramedullary toxicity.[17] The range of trough plasma BU concentrations, times to peak BU levels, and clearance rates in these patients were all similar to those previously reported in children under age 6 years receiving standard doses (1.0 mg/kg/dose) of BU.

DISCUSSION

In children under age 6 years receiving a standard dosage of BU based on body weight (16 mg/kg), pharmacokinetic studies from this laboratory have shown that the mean AUC was 715 μmol/L·min.[10] Using the BSA-derived BU dosage regimen (40 mg/m^2), the AUC in our patients (1,105 μmol/L·min) was significantly higher ($P = .019$; two-tailed Student's t test) and is comparable to the target AUC in adults receiving dose-adjusted BU. Expressed as a function of body weight in this group, the BSA-based BU dosages (24.3 to 28.2 mg/kg; median, 26.4 mg/kg) are similar to those extrapolated from the studies of Shaw et al[5] and Vassal et al[14,18] in which BU dosage was based on 20 mg/m^2 or 37.5 mg/m^2, respectively. Taken together, these studies confirm that, in younger children, at least 50% higher doses of BU are needed than calculated on the basis of body weight (ie, 16 mg/kg).

These pharmacokinetic data were corroborated by the increased incidence of mucositis in these children. Interestingly, neither the severity of mucositis nor the occurrence of VOD was correlated with elevated AUC in this series; the three patients with the most severe mucositis (no. 4, 5, and 6), one of whom also had VOD, had BU AUCs below the mean. No patients in this series had neurotoxicity, as reported in children receiving 600 mg/m^2 BU,[14] but this complication may have been prevented by phenytoin prophylaxis, which we routinely administer to all patients receiving high-dose BU before BMT. Late effects that have been previously attributed to BU, such as interstitial pneumonitis, were not observed in this or other series[5,14,19] in which BU doses exceeding 1 mg/kg (or 20 mg/m^2) were used. On balance, the observed toxicities, infrequent in children given conventional doses of BU, are acceptable and manageable consequences of attainment of higher BU dosages, which may improve therapeutic effect.

It has been suggested that both allograft rejection and higher relapse rates are more frequent in young children given BMT after regimens that use standard-dose BU,[4-9] consistent with lower drug exposures to both normal stem cells and neoplastic cells. The differences in diagnoses, remission number, and types of BMT in this series preclude conclusions about improved therapeutic effectiveness in recipients of BSA-determined BU dosing. Nevertheless, donor cell engraftment was prompt in the three recipients of allogeneic marrow and one recipient of HLA-compatible allogeneic placental blood, and was complete and sustained. No episodes of late graft failure, as reported in children receiving standard-dose BU for allogeneic BMT from related donors,[3,7,19] were observed.

The reasons for altered disposition of BU in young children are unknown, but are probably multifactorial. Altered gastric pH (higher in infants and very young children), relative differences in distribution and percentages of body adipose tissue and total body water, and alterations in first-pass hepatic clearance and metabolism may all contribute to the relative underdosing of BU when the drug is administered on the basis of body weight.[20-23] These and other observations[24] suggest that BSA-based dosage of BU and other antineoplastic agents is the most rational and reliable approach in children. However, in infants under age 6 months, drug dosage based on BSA may be inaccurate,[25] and studies of adjusted BU dosage have not yet been conducted in this age group.

Although BSA-based BU dosage in children provides drug exposures closer to adult values, the wide range of AUC observed in this and other[18] studies suggests that further studies are warranted; ultimately, therapeutic monitoring of BU levels and individualized adjustment of BU dosage may be used to provide optimal drug exposures for each patient. As high AUC for BU has been associated in adults with an increased risk of VOD, which has a high case-fatality rate,[6,8,17] dose-adjustment strategies may retain or enhance the therapeutic effectiveness of high-dose BU and reduce the incidence of life-threatening drug-associated toxicities.

ACKNOWLEDGMENT

The authors thank Viki Altomonte for excellent technical assistance, Donna Burgess for manuscript preparation, and the nursing staff of the Bone Marrow Transplantation and Pediatric Oncology Units for compassionate care of these patients.

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