Busulfan Pharmacokinetics Using a Single Daily High-Dose Regimen in Children With Acute Leukemia

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The pharmacokinetics of busulfan, given as a single daily dose (either 4 mg/kg or 150 mg/m^2), was determined in 22 children undergoing bone marrow transplantation for acute leukemia. The single daily dose regimen showed similar pharmacokinetics to previously reported regimens of 4 × 1 mg/kg, except for fourfold higher mean peak plasma levels and negligible trough levels. Daily systemic exposure for single dose regimens based on weight (4 mg/kg) or surface area (150 mg/m^2), respectively were very similar to regimens of (4 × 1 mg/kg) or (4 × 37.5 mg/m^2). Dose (milligrams per kilogram), peak plasma level, and area under the curve (AUC) were all higher in 12 children treated with 150 mg/m^2 busulfan than in 9 children treated with 4 mg/kg. AUC was age dependent for the 4 mg/kg dose but not for the 150 mg/m^2 dose. The use of a 150 mg/m^2 dose allows escalation of the dose above 4 mg/kg, eliminating the tendency for younger children to receive lower systemic exposure. Little toxicity was observed in this study. Clearance and distribution volume correlated negatively with age, and AUC correlated positively with dose (milligram per kilogram). Administration of busulfan as crushed rather than whole tablets reduced the delay time for appearance of busulfan in plasma but had no effect on absorption or other pharmacokinetic parameters.

SINCE THE EARLY 1980s, busulfan (Bu) and cyclophosphamide in combination (4 days busulphan followed by 4 days cyclophosphamide) has been widely used as an alternative to cyclophosphamide and total body irradiation as conditioning for patients with acute myeloid leukemia (AML) undergoing bone marrow transplantation (BMT).[1] The combination of Bu and cyclophosphamide conditioning (BuCy) has the advantage of avoiding irradiation for pediatric patients, and there is good evidence for antileukemic activity in AML, particularly with the cyclophosphamide reduced to 2 days.[2] However data on the long-term follow-up of children transplanted with BuCy is limited.[3] Almost all regimens of BuCy use Bu at a dose of 1 mg/kg administered every 6 hours (4 × 1 mg/kg) for 4 days, and pharmacokinetic analysis has been performed and reported in several of these studies.[4-9] Recent publications from two centers provide pharmacokinetic data on Bu doses of 6-hourly 37.5 mg/m^2 dose regimens (4 × 37.5 mg/m^2) in children.[10,11]

There is clinical evidence that Bu toxicity, including veno-occlusive disease (VOD)[12] and convulsions,[13] is related to higher doses of Bu and there is some pharmacokinetic evidence that VOD may be related to higher systemic exposure to Bu.[8] Two papers reported the use of BuCy in children transplanted for genetic diseases, where Bu was administered as a single daily dose of 80 mg/m^2 (equivalent to 2 mg/kg/d in a 70-kg adult of 1.73 m^2). This dose, equivalent to 2.5 to 5.25 mg/kg/d in children, was associated with minimal toxicity and a high rate of engraftment.[14,15] Thus, when our center began using BuCy for AML, a single daily 4 mg/kg dose regimen (1 × 4 mg/kg) was adopted. Because of the low toxicity encountered with this regimen,[16] but still unacceptable relapse rate in the autografted patients, we have further escalated the dose of Bu to 150 mg/m^2/d. The main advantage of a single daily dose regimen in children is the simplicity of administration, especially in very young children. However, the single daily dose regimen also allows an accurate and complete pharmacokinetic evaluation without the need to correct for the effect of previous or following doses. Circadian effects[5,17] and other within-day fluctuations that complicate pharmacokinetic analyses of qid regimens are also avoided.

MATERIALS AND METHODS

Bu for clinical administration and for use as standards in the assay was obtained from Wellcome Australia Pty Ltd (Sydney). Most patients received initial chemotherapy according to an Australian & New Zealand Children's Cancer Study Group (ANZ CCSG) protocol for AML.[18] The study, including sampling for pharmacokinetics and dose escalation of Bu, was approved by the Children's Hospital Ethics Committee.

A total of 22 children between 1 and 14 years of age were involved in this study, 19 with AML and 3 with ALL. Table 1 gives details of the clinical data and the chemotherapy conditioning regimens for these children. Bu was given as whole or crushed tablets in a single dose on each of four mornings. A normal diet was offered on each day of Bu administration. Nine patients were given a single daily dose of Bu for 4 days at 4 mg/kg/d. Two of these patients, who were recipients of unrelated transplants, had melphalan at 140 mg/m^2 after Bu. Thirteen patients were administered a single daily dose for 4 days at 150 mg/m^2/d. Bu (±melphalan) was followed by 2 days of cyclophosphamide at 60 mg/kg/d. All patients received anticonvulsant prophylaxis. None received phenytoin; two patients already on carbamazepine continued this drug; the others all received clonazepam, 0.05 mg/kg twice daily orally from the day before to the day after Bu administration.

The Bu dose was administered during the day, before 1 PM in 19 of 21 patients with the mean starting time of 11:00 hours (range: 9:00 to 14:30 hours). Thus, the effects of diurnal variation on Bu pharmacokinetics[5,17] was minimized. Heparinized whole blood samples (1 mL) were collected from central venous lines. The first sample was collected before Bu was administered and the remainder at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after the dose. Occasionally an 18-hour sample was also collected. Plasma samples were separated by centrifugation for 10 minutes at 4°C at 3,000 rpm, then frozen and stored at −40°C until analysis.

Bu was determined in plasma samples using a modified version of a previous method[19] by conversion to the 1,4-diiodobutane derivative and measurement by Gas Chromatography with Electron Capture. An aliquot of plasma (0.2 mL) was added to acetone (0.1 mL) and 1 mol/L sodium phosphate buffer, pH 7.0 (0.1 mL), in a screw

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Table 1. Clinical Details of 22 Patients Receiving High-Dose Bu

BMT UPN	Diagnosis	Age at BMT	Donor	Chemotherapy	Bu Dose	Toxicity	Outcome (d)
84	AML	20 mos	ALLO	BuCy	4 mg/kg	—	CCR + 906
88	AML	8 yrs	AUTO	BuCy	4 mg/kg	—	Rel + 265
89	AML	14 yrs	AUTO	BuCy	4 mg/kg	—	Reel + 150
90	AML	8 yrs	ALLO	BuCy	4 mg/kg	—	CCR + 854
91	AML	15 mos	AUTO	BuCy	4 mg/kg	VOD	CCR + 733
92	AML	7 yrs	AUTO	BuCy	4 mg/kg	—	CCR + 559
98	AML	22 mos	AUTO	BuCy	4 mg/kg		Died + 2
110	AML	2 yrs	AUTO	BuCy	150 mg/m^2	—	CCR + 826
111	AML	2 yrs	ALLO	BuCy	150 mg/m^2	—	Rel + 90
114	AML	8 yrs	AUTO	BuCy	150 mg/m^2	—	CCR + 728
124	AML	13 yrs	ALLO	BuCy	150 mg/m^2	IP & ?VOD	Died GvHD + 74
129	AML	7 yrs	AUTO	BuCy	150 mg/m^2	Fit	Rel + 142
137	AML	5 yrs	ALLO	BuCy	150 mg/m^2	—	CCR + 371
141	AML	11 yrs	AUTO	BuCy	150 mg/m^2	—	CCR + 317
146	AML	5 yrs	AUTO	BuCy	150 mg/m^2	—	CCR + 307
101	AML	12 yrs	MUD	BuMlpCy	4 mg/kg	Aspgil	Died + 61
102	ALL	3 yrs	MUD	BuMlpCy	4 mg/kg	Aspgil	Died + 25
113	AML	2 yrs	AUTO	BuCy	150 mg/m^2	—	CCR + 716
126	ALL	5 yrs	ALLO	BuCy	150 mg/m^2	—	Rel + 152
154	AML	12 yrs	AUTO	BuCy	150 mg/m^2	—	CCR + 147
161	ALL	17 mos	ALLO	BuCy	150 mg/m^2	—	CCR + 63
162	AML	5 yrs	AUTO	BuCy	150 mg/m^2	—	CCR + 31

Abbreviations: UPN, Institutional BMT number; AUTO, autologous marrow; ALLO, matched sibling donor; MUD, matched unrelated donor; CCR, continuous complete remission; Rel, relapse; GvHD, graft-versus host disease; Mlp, melphalan; Bu, busulfan; Cy, cyclophosphamide; IP, Interstitial pneumonitis; VOD, veno-occlusive disease; Aspgil, Aspergillosis.

capped 4 mL Wheaton vial with a Teflon liner. Freshly prepared 5 mol/L potassium iodide (1.6 mL) and hexane (0.5 mL) were added and the mixture was vortexed for 20 seconds then heated at 70°C for 40 minutes with brief vortexing every 10 minutes. The hexane layer was transferred to a crimp sealed autosampler vial and 5 μL was injected into the gas chromatograph. A Hewlett Packard 5730A Gas Chromatograph was used, equipped with a ^{63}Ni, model 18713A linear electron capture detector and a 0.61 m long, 2 mm internal diameter (i.d.) packed column of 2% OV101 on 100-120 mesh High Performance Chromosorb W. The carrier gas of 5% methane in argon had a flow rate of 27.3 mL/min. The instrument was operated isothermally with oven, detector, and injector port temperatures of 70°C, 250°C, and 250°C, respectively. 1,4-Diiodobutane had a retention time of 6.8 minutes.

Quantitation of plasma Bu involved the construction of a standard curve using concentrations of 2.5, 5.0, 7.5, and 10 μg/mL Bu. The standards were added in acetone (0.1 mL) to water (0.2 mL) and 1 mol/L sodium phosphate buffer pH 7.0 (0.1 mL). They were then extracted, derivatized, and analyzed by GC as described for the plasma samples. The peak height (millimeters) was plotted against Bu concentration (micrograms per milliliter) and unknown levels of Bu from plasma extracts were determined from the graph. Concentration was linear with peak height from 0.025 to at least 20 μg/mL (81.2 μmol/L) Bu. The limit of detection of the assay was 0.1 μmol/L Bu. The within-day coefficients of variation were 2.6% for a Bu concentration of 14.7 μmol/L (n = 9) and 4.8% for a Bu concentration of 6.8 μmol/L (n = 10). The between-day coefficients of variation were 5.1% for a Bu concentration of 14.7 μmol/L (n = 7) and 13.4% for a Bu concentration of 6.8 μmol/L (n = 7).

A simple one-compartment computer model was developed for pharmacokinetic analysis with simple exponential terms used for absorption and elimination. Kinetic parameters were varied until the computer-generated theoretical curve conformed on visual inspection with the plotted plasma drug measurements. The model gave a good fit of the actual data points in all cases except one patient with trisomy 21 (patient 113), whose data was excluded from the analysis. The profile of plasma Bu levels found in this patient was quite different from all other patients, suggestive of a biphasic absorption mechanism. Another patient (126) also had trisomy 21, but did not have atypical pharmacokinetics, so the cause of the atypical pharmacokinetics in patient 113 remains unknown.

Means and standard deviations were calculated for the various pharmacokinetic parameters and compared by the Wilcoxon Rank Sum test using the Statistical Package for Interactive Data Analysis (SPIDA) version 6.04 (The Statistical Computing Laboratory, Macquarie University, NSW, Australia). Pharmacokinetic parameters from literature sources were taken from the published figures and, if necessary, converted to micromoles per liter or converted to a different time unit, in order to allow direct comparisons. In some cases published data tables were used to calculate means and standard deviations, elimination and absorption constants being first converted to half-lives.

RESULTS

A semi-logarithmic plot of the disposition of Bu from a single daily oral dose of Bu administered at 4 mg/kg or 150 mg/m^2 is shown in Fig 1. Mean plasma Bu levels and 95% confidence intervals for the two groups of patients are shown for a 24-hour period. There was a short delay time after the dose was administered before Bu appeared in the plasma. Bu reached a peak in plasma after about 2 hours and was almost completely eliminated by 24 hours as 17 of 21 patients had 24-hour trough-levels below the 0.1 μmol/L limit of detection and the remaining 4 were below 0.4 μmol/L. None of the patients vomited on the day that Bu pharmacokinetics was performed.

In 9 of 21 patients a 4 mg/kg single dose per day regimen was used and the remaining 12 patients had a 150 mg/m^2

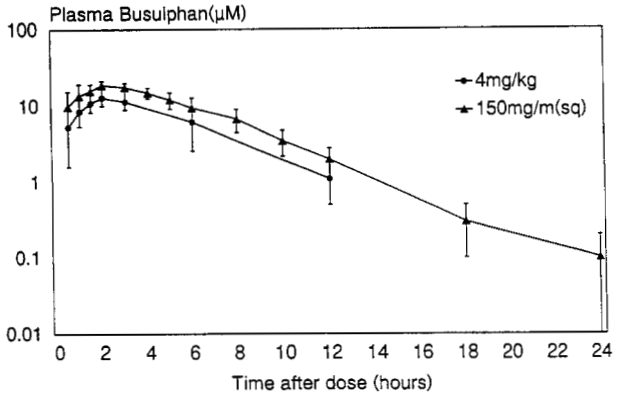

Fig 1. Semi-logarithmic plot of the mean disposition of busulfan in children on the 4 mg/kg and 150 mg/m² dosing regimens.

single dose per day regimen. The pharmacokinetics of these two groups are compared in Table 2. There were no significant differences between the two groups in age, absorption, elimination, delay time, clearance, volume of distribution, or time when the plasma peak occurred. For the 150 mg/m²

Table 2. Dosing Regimen Effects

Parameter (units)	150 mg/m²/d Dose (n = 12)	4 mg/kg/d Dose (n = 9)	P Value
Age (mos)			
Median	65.7	86	
Range	17-162	15.5-156.5	
Dose (mg/kg)			
Mean ± SD	5.8 ± 0.9	4.3 ± 0.3	<.0005
AUC (μmol/L. h)			
Mean ± SD	124 ± 35	76 ± 16	.001
Peak Bu Conc. (μmol/L)			
Mean ± SD	20.9 ± 4.7	14.0 ± 3.1	<.0005
K (abs) (h^{-1})			
Mean ± SD	1.11 ± 0.54	1.10 ± 0.37	NS
T/2 (abs) (min)			
Mean ± SD	49 ± 32	42 ± 14	NS
K (elim) (h^{-1})			
Mean ± SD	0.29 ± 0.07	0.31 ± 0.04	NS
T/2 (elim) (min)			
Mean ± SD	149 ± 31	138 ± 18	NS
Delay (h)			
Mean ± SD	0.38 ± 0.38	0.46 ± 0.50	NS
Time peak Bu (h)			
Mean ± SD	2.04 ± 0.81	2.08 ± 0.70	NS
Cl/F (mL/min/kg)			
Mean ± SD	3.44 ± 1.13	3.96 ± 0.97	NS
VD/F (L/kg)			
Mean ± SD	0.70 ± 0.10	0.78 ± 0.19	NS

Abbreviations: P, level of significance when the differences are analyzed using the Wilcoxon Rank Sum test; NS, not significant; n, number of children on the 150 mg/m²/d or 4 mg/kg/d dosing regimens; K (elim), elimination constant; T/2 (elim), elimination half-life; K (abs), absorption constant; T/2 (abs), absorption half-life; AUC, area under the curve; Cl/F, total clearance rate corrected for bioavailability; F, bioavailability; VD/F, apparent volume of distribution corrected for bioavailability; Conc., concentration.

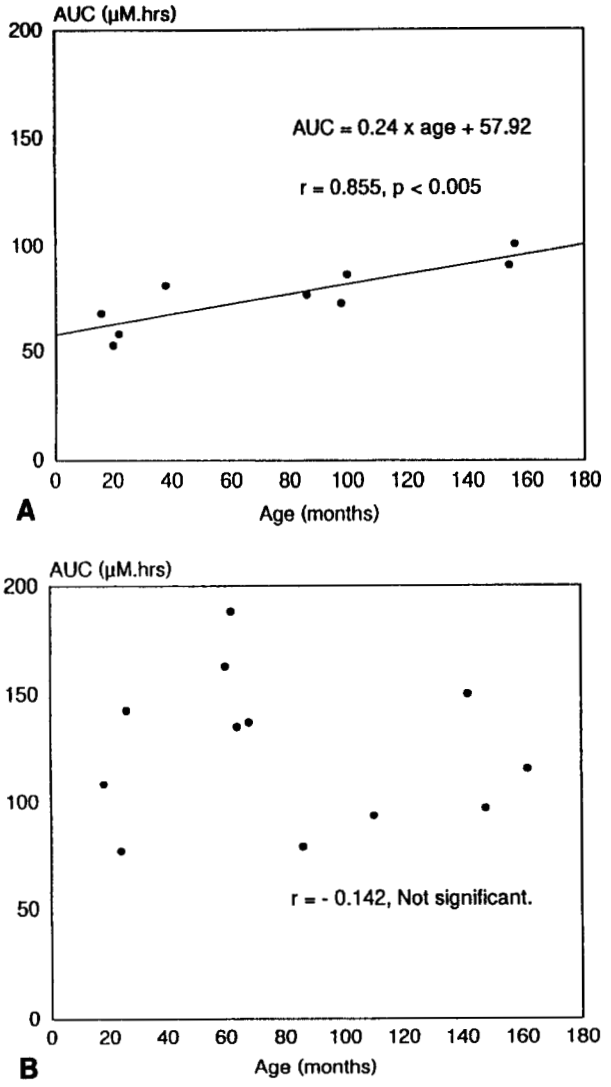

Fig 2. AUC and age correlations obtained for the 9 children on the 4 mg/kg/d dose (A) and the 12 children on the 150 mg/m²/d dose (B).

dose regimen mean values for dose (milligrams per kilogram), area under the curve (AUC) and peak Bu concentration were significantly higher, being, respectively, 35%, 63%, and 49% higher than the 4 mg/kg dose regimen. The systemic exposure to Bu was higher for the 150 mg/m² single dose regimen than the 4 mg/kg regimen (Fig 1).

We found a positive correlation between AUC and age in the group of 9 children taking a single daily Bu dose of 4 mg/kg (Fig 2A). This shows that younger children have a lower systemic exposure to Bu than older children on the same weight-based dose regimen. There was no correlation between AUC and age for the 150 mg/m² regimen (Fig 2B), demonstrating that younger children had equivalent exposure to Bu as the older children when the surface area based dose was used. Bu pharmacokinetics in more children less than 5 years of age will confirm this finding.

We have observed a very clear correlation between AUC and dose (milligrams per kilogram) on the whole group of

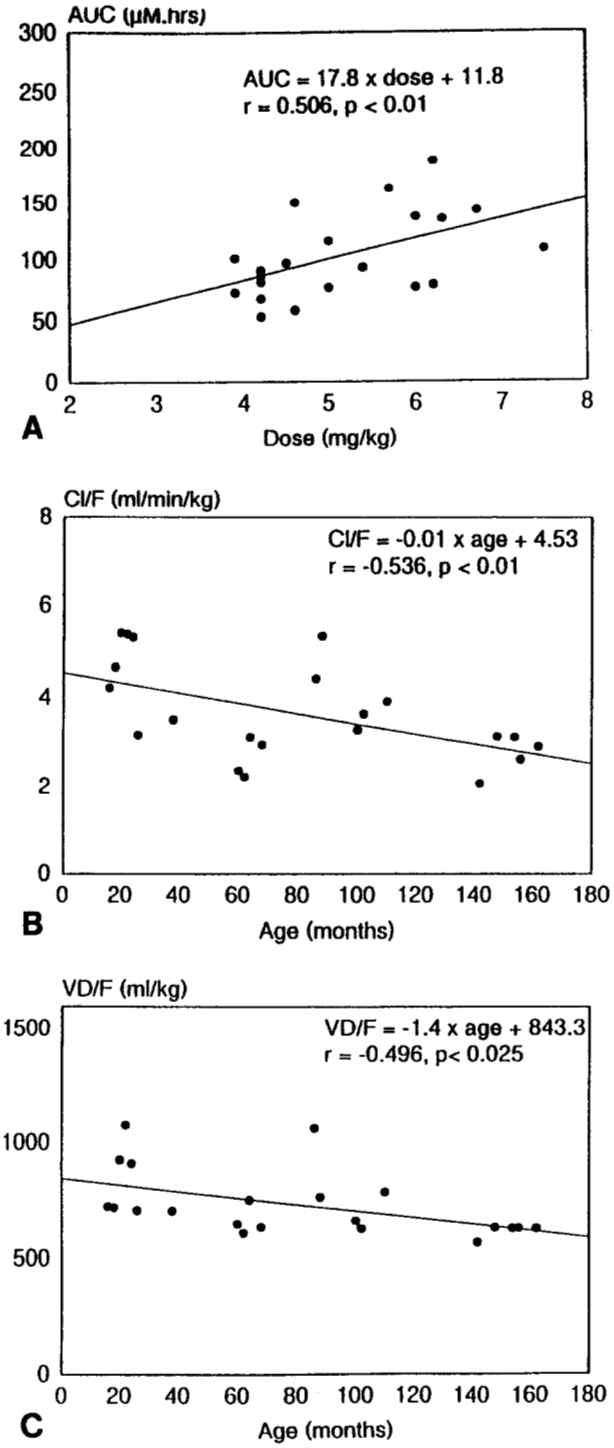

Fig 3. Correlations obtained for various pharmacokinetic parameters in the whole group of 21 children. (A) Positive correlation of AUC and dose (milligrams per kilogram). (B) Negative correlation of clearance and age. (C) Negative correlation of distribution volume and age.

21 patients with a dose range from 3.9 to 7.25 mg/kg (Fig 3A). A recent report demonstrated a good correlation between AUC and dose (mg/kg) with a dose range from 0.9 to 2.6 mg/kg where 26/40 patients received Bu twice daily and the remainder four times per day.[7] We found a negative correlation between clearance and age in the whole group of 21 patients (Fig 3B), showing that younger children had higher Bu clearance. A previous study also showed that clearance was significantly higher in younger children.[5] There was also a negative correlation between volume of distribution and age (Fig 3C), indicating that younger children in our study had higher distribution volumes than older children.

Younger children in the study were given crushed tablets of Bu whereas the older children were given whole tablets. Patients taking crushed tablets had a significantly shorter delay time (Table 3), but there was no significant difference in absorption, elimination, AUC, or dose (milligram per kilogram). The mean delay time was 40 minutes for whole tablets compared with 8 minutes for crushed tablets. The possibility was previously raised[6] that the form of drug administration (crushed tablets or capsule) may affect absorption, but we have shown that the form of drug administered affects delay time rather than absorption.

Toxicity and outcome are summarized in Table 1. One patient suffered a brief convulsion after the third dose of Bu. She was on carbamazepine and after loading with oral clonazepam the fourth dose of Bu was given uneventfully. Definite VOD occurred in one patient at the 4 mg/kg dose and another had possible VOD with the 150 mg/m^2 dose (124), but this is uncertain as she also had skin, gut, and liver graft-versus-host disease. Interstitial pneumonitis of unknown etiology requiring ventilator support also occurred in this patient. The pharmacokinetic profiles of the patients who developed VOD or pneumonitis did not differ from the rest of the group, but the numbers are small.

DISCUSSION

High-dose therapy with Bu has customarily been based on body weight as a dose of 1 mg/kg four times daily. We have used a single daily dose of 4 mg/kg and found the

Table 3. Crushed or Whole-Tablet Dose Effects

Parameter (units)	Whole Tablets (n = 11)	Crushed Tablets (n = 10)	*P* Value
Age (mo)			
Median	109	34.6	
Range	67.5-162	15.5-64	
Delay (min)			
Mean ± SD	40 ± 24	8 ± 13	.005
Time peak Bu (min)			
Mean ± SD	138 ± 51	108 ± 31	NS
K (abs) (h^{-1})			
Mean ± SD	1.12 ± 0.49	1.09 ± 0.46	NS
T/2 (abs) (min)			
Mean ± SD	48 ± 33	44 ± 16	NS
K (elim) (h^{-1})			
Mean ± SD	0.30 ± 0.05	0.30 ± 0.06	NS
T/2 (elim) (min)			
Mean ± SD	145 ± 24	144 ± 30	NS
AUC (μmol/L, h)			
Mean ± SD	100 ± 25	107 ± 48	NS
Dose (mg/kg)			
Mean ± SD	4.8 ± 0.8	5.6 ± 1.2	NS

Table 4. Comparison With Previous Pharmacokinetic Studies on Children

Parameter (units)	This Study		Vassal et al 1989[4]	Vassal et al. 1992[10]	Yeager et al 1992[11]	Hassan et al 1991[5]	Grochow et al 1990[6]
	Dose/kg	Dose/m^2					
Age (yrs)	1-13	1-12	4-14	2-14	1-6	1-13	0-4
Number	9	12	11	27	7	9	14
Dose							
(mg/kg)	4	—	1	—	—	1	2
(mg/m^2)	—	150	—	37.5	38.9	—	—
T/2 (abs) (min)							
Mean	52	49	—	—	—	—	45
SD	34	32	—	—	—	—	27
T/2 (elim) (min)							
Mean	152	149	140	176	—	148	129
SD	31	31	31	84	—	28	74
AUC (μmol/L, h)							
Mean	76	124	15.9	26	18.4	17.6	11.9
SD	16	35	4.8	10	7.8	9.1	4.0
Peak Bu Conc (μmol/L)							
Mean	14.0	20.9	3.3	5.1	—	5.4	—
SD	3.1	4.4	0.9	1.5	—	2.1	—
Time to peak Bu (min)							
Mean	125	122	156	94	—	72	—
SD	42	49	53	40	—	42	—
Delay time (min)							
Mean	28	23	25	—	—	—	—
SD	30	23	17	—	—	—	—
Cl/F (mL/min/kg)							
Mean	3.96	3.44	—	4.5	—	4.9	—
SD	0.97	1.13	—	1.4	—	2.2	—
VD/F (l/kg)							
Mean	0.78	0.70	—	1.04	—	—	1.42
SD	0.19	0.10	—	0.38	—	—	0.83

regimen well tolerated, with little toxicity. As our regimen of 4 mg/kg/d was well tolerated but associated with an appreciable relapse rate following autologous BMT, it was logical to consider dose escalation. One approach was to use a dosing regimen based on body surface area. Pharmacokinetic studies showed that a surface-area based single dose of 150 mg/m^2 Bu in children was on average 35% higher than the weight-based 4 mg/kg dose and produced a 63% increase in the AUC indicating considerably higher systemic exposure was achieved. This higher dose was also well tolerated with little toxicity.

A comparison between our results for the 4 mg/kg and 150 mg/m^2 regimens with previously reported Bu pharmacokinetics is shown in Table 4. The values we obtained for mean delay time, absorption half-life, elimination half-life, clearance, distribution volume, and time to peak Bu compared well with the results obtained by other centers.[4-6,10] The mean peak plasma level for our 4 mg/kg dose was found to be 14.0 μmol/L, which was 4.2-fold higher than the value reported by Vassal et al,[4] although only 2.6-fold higher than the value reported by Hassan et al,[5] both using 1 mg/kg doses. The mean peak plasma level for our 150 mg/m^2 dose was 20.9 μmol/L, which was 4.1-fold higher than that reported by Vassal et al[10] for a 37.5 mg/m^2 dose. It was clear that peak plasma levels are about 4-fold higher, when the 4-fold higher oral dose was used. The mean AUC we observed after a dose of 4 mg/kg (mean: 4.3 mg/kg) was 4.8-fold higher than that found by Vassal et al[4] using a 1 mg/kg dose. In contrast to the mean peak level above, the mean AUC was 4.3-fold higher than Hassan et al[5] for a 1 mg/kg dose. For our 150 mg/m^2 group we found a 4.8-fold higher mean AUC than that found by Vassal et al[10] using a 37.5 mg/m^2 dose and a 6.7-fold higher mean AUC than that found by Yeager et al[11] in children on a 38.9 mg/m^2 dose. The comparisons show that systemic exposure on a single daily dose weight-based regimen (1 $\times$ 4 mg/kg) is equivalent to a qid regimen (4 $\times$ 1 mg/kg) and that the systemic exposure for a single daily dose surface-area based regimen (1 $\times$ 150 mg/m^2) is the same or greater than qid (4 $\times$ 37.5 mg/m^2 or 4 $\times$ 38.9 mg/m^2) regimens.

We observed that AUC increased with age for a weight-based regimen confirming that younger children have a relatively reduced systemic exposure to Bu on this commonly used regimen. Younger children received equivalent systemic exposure to the older children when the dose was based on surface area.[10,11] The relatively high relapse rate in autologous BMT patients,[16] and past data[5,6,10] suggested that children achieved lower systemic exposure than adults. We have now confirmed this by our observation that systemic exposure to Bu changes with age and is lowest in the younger patients when the dose is based on body weight. It has been proposed that higher clearances[10] and larger volumes of distribution[6,10] may lower systemic exposure in younger children. The higher clearance and larger volume of distribution

in younger children observed in this study and in a previous study[5] may be the cause of the relatively lower systemic exposure in younger children.

When considering escalation of the dose of Bu, our hypothesis was that escalation of a single daily dose may provide additional antileukemic activity without a prohibitive increase in toxicity, through avoiding prolonged high trough levels. It is still too early for us to comment on the toxicity of the higher dose of Bu. The incidence of VOD was too low in this series of patients for us to determine whether a relationship exists between VOD and AUC or peak Bu levels. Convulsions have not been a problem with clonazepam prophylaxis. Because of the low toxicity encountered in our patients, we cannot comment on any possible relationship between Bu pharmacokinetics and the complications of therapy or the relapse rate. However, continued pharmacokinetic monitoring of patients in trials designed to establish a target AUC may give us this information in the future. Our experience to date would confirm the appropriateness of increasing the dose of Bu in children to produce dosing equivalent to that used in adults. We are continuing to recruit patients at the 150 mg/m^2/d dose before we consider further intensification of therapy.

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