Once-daily intravenous busulfan in children prior to stem cell transplantation: study of pharmacokinetics and early clinical outcomes

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We studied the pharmacokinetics and clinical outcome of a new once-daily intravenous area under the curve-targeted dosing scheme for busulfan based on body surface area. Eighteen children undergoing busulfan-based conditioning for allogeneic stem cell transplantation were enrolled. The age of the children ranged from 0.5 to 16 years. For all children, the starting dose was 80 mg/m^2. Unlimited dose adjustment was allowed to reach the target area under the curve (3800 μmol/l · min). This target area under the curve was determined on the basis of a previous study in our hospital. Pharmacokinetic studies were performed after the first dose. The median area under the curve on day 1 was 2616 (range 1781–5040) μmol/l · min at a dose of 80 mg/m^2. This resulted in a median dose increment to 114 (range 62–168) mg/m^2 to reach the target area under the curve. In only one patient, the dose was decreased. Donor engraftment was established in 14 out of 18 patients (78%). Two of the four patients were successfully retransplanted. Relapse occurred in two patients (one died, one received additional treatment). Fourteen patients survived with a median follow-up of 1.6 years (1.0–2.2 years). The disease-free survival was 66% (12 of 18 patients). Despite the high systemic peak levels, there was no new unexpected or unusual toxicity. Moderate veno-occlusive disease was seen in one patient only. We conclude that intravenous busulfan in children administered once daily is safe, convenient and feasible, and can be dosed surface-based, independent of age. There was very limited (liver) toxicity, but the rejection rate was relative high, which can be probably overcome by a higher exposure to busulfan. Future investigations should be aimed at further optimizing the target area under the curve of intravenous busulfan for specific patient groups. *Anti-Cancer Drugs* **17:1099–1105 © 2006 Lippincott Williams & Wilkins.**

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Introduction

High-dose busulfan is widely used in conditioning regimens prior to hematopoietic stem cell transplantation (HSCT). In addition to capsules for oral administration, busulfan has become available as an intravenous (i.v.) formulation [1], and studies both in adults and children have shown that this route of administration results in less variable drug exposure [2,3]. Until recently, busulfan capsules were administered four times daily to make oral intake more convenient and to reduce the risk of vomiting. Recently, there have been reports suggesting that a quadruple i.v. dose of busulfan administered once daily possibly reduces toxicity without influencing clinical outcome, as compared with that of the currently used regimen of four infusions of busulfan a day [4,5]. It was suggested that after a quadruple dose of busulfan once daily, detoxifying liver S-gluthathiontransferases may have more time to recover, as depletion of S-glutathion-transferase seems to result in liver toxicity. Obviously, a once-daily regimen of busulfan is more convenient for patients. An additional practical and logistic advantage is that busulfan infusions, which have a short shelf-life, can be prepared in the pharmacy once daily and during working hours.

Only limited data are known on the pharmacokinetics (PK) and clinical outcome after once-daily i.v. busulfan in children. In a previous pilot study, we showed that systemic exposure of busulfan in children during i.v. administration could be estimated adequately with limited blood sampling technique and a Bayesian fitting procedure from a one-compartment model [6]. In an additional study, in which we showed that i.v. busulfan can be used safely in children, it appeared that within the targeted area under the curve (AUC) no clear relationship was observed between busulfan exposure and the outcome parameters toxicity, engraftment and relapse [7]. These results suggested that a target AUC of

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950 μmol/l min is acceptable, which is slightly lower than that reported by others [1,8]. Therefore, the initial target AUC at the once-daily i.v. busulfan regimen was set at $4 \times 950 = 3800$ μmol/l · min (15600 μg/l · h)/day. In addition, recent studies suggest that a dosage corrected for body surface may be more accurate to reach the target AUC after the first dosage [4,9]. From our previous study [7], it was calculated that a dose of 80 mg/m^2 would be a safe starting dose resulting in a dose increment on day 2 in most of the children to reach a target AUC of 3800 μmol/l · min (or 15600 μg/l · h).

Therefore, in this retrospective analysis, we examined the PK, clinical outcome and toxicity of i.v. busulfan in children given as a once-daily dose, the first dose being normalized for body surface area.

Methods

Patients

Between October 2003 and March 2005 all children undergoing busulfan-based myeloablative conditioning for allogeneic HSCT in the pediatric bone marrow transplantation unit of the Leiden University Medical Center ($n = 18$) in The Netherlands were enrolled in this retrospective study. The parents of the children gave written informed consent for participation in the transplantation protocol, which was approved by the institutional ethics committee. Patient characteristics, diagnoses and stem cell sources are given in Table 1.

Preparative regimen

Busulfan (Busulfex; Orphan Medical Minnetonka, Minnesota, USA) was administered on 4 consecutive days in one single daily dose as i.v. infusion (concentration 0.6 mg/ml) in 3 h. For all children, the starting dose was 80 mg/m^2. The second dose was calculated from PK analysis targeting an AUC of 3800 ± 190 μmol/l min and given 30 h after start of the first infusion. The extra 6 h allowed for the measurement of the busulfan serum concentrations, the PK analysis, AUC and dose calculation, and preparation of further busulfan dosages. The third and fourth doses were given 24 h after the previous dose. Figure 1 shows a representative PK curve. Dose adjustment was allowed without any limit if the target AUC was not reached.

Six days of clonazepam convulsion prophylaxis (0.025 mg/kg/day, in four doses) starting 1 day before the start of i.v. busulfan was given to all patients.

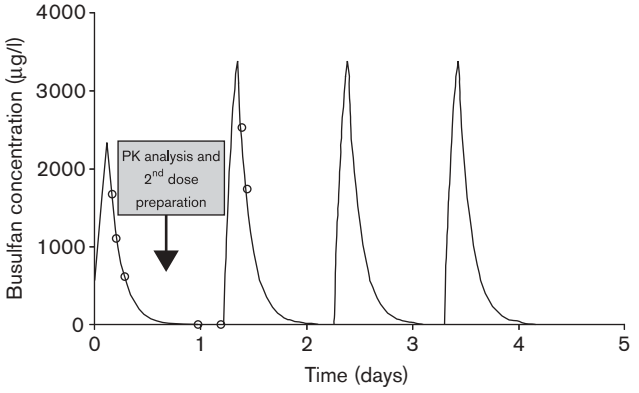
Patients received various other cytostatic drugs in combination with busulfan: cyclophosphamide (Cy) 200 mg/kg, fludarabine 150 mg/m^2 or Cy 120 mg/kg and melphalan 140 mg/m^2 (Table 1). Only one patient (no. 9) received intensive cytoreductive therapy for her leukemia

Table 1 Patients characteristics, outcome and toxicity

No.	Sex, age (years)	Diagnosis	Donor-graft T cell depletion	Conditioning Busulfan +	Outcome, chimerism (% donor)	Major treatment-related toxicity
1	M, 14	MDS/RA, PNH	U-BM/ –	Cy Mel ATG	a/w, 100%	–
2	F, 9	MDS/RA, monosomy 7	U-BM/ –	1/2Cy Mel ATG	a/w, 100%	mucositis, CsA-related encephalopathy, convulsions, Cy-related elevated liver enzymes
3	M, 3	immune deficiency	I-BM/ –	Cy	a/w, 100%	–
4	M, 11	MDS/RAEBt	U-BM/ –	Cy Mel Camp	relapse, a/w after retransplant	–
5	M, 2	JMML, arthritis, hemophagocytic syndrome	U-BM/ –	Cy Mel ATG	died of rejection	–
6	M, 6	immune deficiency	U-PB/ +	Cy Camp	a/w, 100%	–
7	M, 4	immune deficiency	I-BM/ –	Cy	a/w, 100%	mucositis
8	F, 1	JMML	U-BM/ +	Cy Mel ATG	died of relapse	–
9	M, 15	MDS/AML	U-BM/ –	Cy Mel ATG	a/w, 100%	–
10	M, 13	thalassemia	U-BM/ –	Cy Mel Camp	a/w, stable 90–100%	–
11	M, 13	MDS/RA, HLA-antibodies	U-BM/ –	Cy Mel Camp	a/w after rejection + retransplant	–
12	M, 1/2	leukodystrophy	I-BM/ –	Cy	disease progression, 50%	encephalopathy, convulsions
13	M, 13	MDS/RAEBt	I-BM/ –	Cy Mel	died, 100%	GvHD IV, sepsis
14	M, 6	thalassemia	U-BM/ –	Cy Mel	a/w after rejection + retransplant	–
15	M, 2	immune deficiency	H-PB/ +	Cy ATG	a/w, 100%	–
16	M, 8	sickle cell anemia	U-BM/ –	Cy ATG	alive after rejection, retransplant planned	CsA-related encephalopathy, convulsions
17	M, 16	MDS/RAEBt	U-BM/ –	Cy Mel Camp	early death	sepsis, GvHD III, mucositis, moderate VOD (defibrotide + supportive care)
18	M, 2	immune deficiency	H-PB/ +	Cy ATG	a/w, 100%	–

Diagnosis: MDS, myelodysplastic syndrome; RA, refractory anemia; AML, acute myeloid leukemia; RAEBt, refractory anemia with excess of blasts in transformation; JMML, juvenile myelomonocytic leukemia.
Donor graft: U, unrelated; I, HLA-identical related; H, haploidentical related; BM, bone marrow; PB, peripheral blood.
Conditioning: Cy, cyclophosphamide; Mel, melphalan; ATG, anti-thymocyte globulin; Camp, alemtuzumab.
Outcome: a/w, alive and well.
Major treatment-related toxicity: CsA, cyclosporin A.

Fig. 1



Concentration–time curve of busulfan before and after dose adjustment on day 2 for one patient. ○, plasma concentration measurements; –, concentration–time curve as predicted by the limited sampling model. PK, pharmacokinetics.

prior to conditioning. Two other patients (nos 5 and 8) received low-dose chemotherapy to control their juvenile myelomonocytic leukemia (JMML).

End-point for evaluation of therapy

The clinical end-points of this retrospective comparison were major transplant-related toxicity, incidence and severity of veno-occlusive disease (VOD), liver toxicity, mortality, engraftment, acute graft-versus-host disease (GvHD), and disease recurrence. VOD was diagnosed according to the modified Baltimore criteria: hyperbilirubinemia (bilirubin $\geq 34\,\mu$mol/l) and at least two of three symptoms (hepatomegaly, ascites or unexplained weight gain of 5% or more from baseline) present before day 21 after HSCT when other possible causes of these clinical manifestations had been excluded. Severity of VOD was graded according to Bearman *et al.* [10]. Mild VOD was defined as clinical disease not needing intervention, moderate disease was defined as VOD needing intensive support, and severe disease was defined as VOD leading to multiple organ failure and/or death. Liver transaminase elevation was scored from grade 1 to 4 according to World Health Organization (WHO) criteria. Acute GvHD was graded according to the scale defined by Przepiorka *et al.* [11]. Engraftment was defined as neutrophil recovery to more than 0.5×10^9/l, thrombocyte recovery to more than 50×10^9/l and reticulocyte counts to more than 20×10^9/l. Donor-recipient white blood cell chimerism was determined by XY-fluorescent in-situ hybridization or variable nucleotide tandem repeat polymorphism, as described previously [12].

Pharmacokinetics and statistical analysis

From all patients, blood samples were collected through the lumen of the catheter that was not used for busulfan infusion at 4, 5 and 7 h after the start of the first infusion on day 1 of the treatment. For six patients, additional blood samples were collected at 12 and 24 h to study whether accumulation would occur. Analysis of busulfan was performed by a validated high-performance liquid chromatographic assay [7].

A validated limited sampling model was used to minimize the number of blood samples necessary to calculate the AUC [6]. Empirical Bayesian PK parameter estimates at steady state (clearance and volume of distribution) were generated for all individual children using the PK software package MwPharm, University of Groningen, The Netherlands [13]. The AUC was calculated from the expression dose/*CL*. Calculating the *P* value for the Pearson correlation coefficient tested the hypothesis that a slope was not equal to zero and $P < 0.05$ was considered significant.

Results

Patient characteristics and outcome

A total of 18 patients were included in the study. Outcome parameters are summarized in Table 1. Fourteen patients survived with a median follow-up of 1.6 years (range 1.0–2.2 years). The disease-free survival was 66% (12 of 18 patients). The causes of death were refractory JMML (patient 8), systemic adenovirus infection after two subsequent graft rejections (patient 5), sepsis and severe grade IV GvHD (patient 13), and a combination of sepsis, multiple organ failure, GvHD and VOD (patient 17). Relapse of myelodysplastic syndrome/refractory anemia with excess of blasts in transformation was observed in one patient (4) who received additional donor lymphocyte infusions and recently a successful second transplant. Disease progression was seen in a patient with leukodystrophy (patient 12).

Engraftment and chimerism

All patients became neutropenic following the administration of myeloablative conditioning. Donor engraftment, on the basis of peripheral blood counts and (above 95% donor) chimerism, was ascertained in 14 out of 18 patients. Early graft rejection was seen in three patients; two of these patients were polytransfused and had irregular HLA antibodies. One (patient 11) was successfully retransplanted and one had subsequent autologous recovery (patient 16), one (patient 18) rejected a mismatched cord blood transplant, but was successfully rescued with a second transplant, and one (patient 5) had autoimmune phenomena concurrent with the diagnosis of JMML, he also rejected a second graft. Decreasing donor chimerism was seen in one patient (12) at 9 months after HSCT. This patient showed neurodegenerative disease progression, he received additional donor lymphocyte infusions; which successfully reverted the decreased donor chimerism. Stable mixed donor chimerism of 95–100% was observed in one thalassemia patient (10).

Treatment-related toxicity

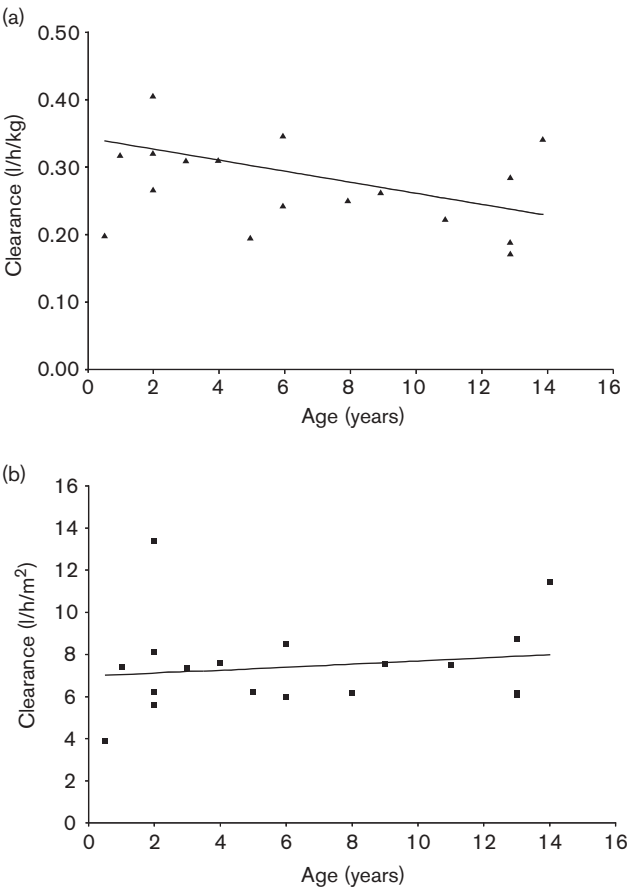
VOD was observed in one child only. This patient (17) died on day 14 post-transplant of a combination of early sepsis with multiple organ failure, GvHD grade III and moderate VOD.

Three patients experienced mild (WHO grade 1–2) transient transaminase elevations. In one (patient 2), after the first Cy infusion, liver enzymes increased to values greater than 5000 and 8400 IU/l for alanine aminotransferase and aspartate aminotransferase, respectively (grade 4). Other liver toxicity was not observed. Renal toxicity associated with busulfan infusion was not observed. Magnesium supplementation had to be given to all but four patients during the transplant episode. Four patients developed acute GvHD ranging from minor (grade I) in two patients to moderate (grade III) and severe (grade IV) both in one patient. Seizures were observed in the patient with leukodystrophy (patient 12) 1 day after the completion of the busulfan infusions. It remains unclear whether he was already more susceptible to neurotoxic medication. Encephalopathy associated with hypertension and cyclosporin treatment was observed in two patients, in both more than 1 week after busulfan infusion. Severe mucositis grade 3 or 4 (WHO) was observed in three patients; eight patients received parenteral feeding during the transplant course.

Busulfan pharmacokinetics and statistical analysis

The results of the PK evaluation are shown in Table 2. Figure 1 shows a representative concentration–time curve of once-daily busulfan. Accumulation was not observed as busulfan was completely eliminated by 24 h and as the trough concentrations were below the limit of detection (30 μg/l). We determined the AUC again after dose adjustment (on the second day of busulfan infusion) in 11

Fig. 2



Busulfan clearance adjusted to body weight (a) and body surface (b) in relation to age. The solid lines represent the regression lines. The correlations between clearance and age were (a) clearance/kg = 0.31 + 0.01 × age, $P = 0.04$ and (b) clearance/m^2 = 6.4 + 0.08 × age, NS.

Table 2 **Busulfan pharmacokinetics after 80 mg/m^2 once daily**

Patient no.	Body surface area (m^2)	Clearance (ml/kg/min)	Clearance (ml/m^2/min)	Volume of distribution (l/kg)	AUC after the first dose (μmol/l · min)	Dose adjustment	Adjusted dose (mg/m^2)	Total dose (mg/kg)
1	1.49	5.7	191	0.33	1781	Increase	168	18
2	1.12	4.4	125	0.83	2601	Increase	118	15
3	0.57	5.2	123	0.88	2616	Increase	114	18
4	1.4	3.7	125	0.79	2557	Increase	114	13
5	0.61	5.4	135	0.76	2461	Increase	131	19
6	0.77	4.1	100	0.84	3006	Increase	94	14
7	0.76	5.2	127	0.95	2519	Increase	118	18
8	0.5	5.3	124	0.81	2292	Increase	116	18
9	1.44	3.3	104	0.87	3252	Increase	97	12
10	1.67	2.9	103	0.73	3066	Increase	96	10
11	1.37	4.8	146	0.86	2233	Increase	124	15
12	0.37	3.3	65	0.87	5040	Decrease	62	14
13	1.43	3.1	101	0.70	3364	Increase	94	11
14	0.8	5.8	142	0.72	2150	Increase	133	19
15[a]	0.51	10.2	223	1.26	1427	Increase	196	30
16	0.85	4.2	103	0.88	3143	Increase	96	15
17	0.94	6.8	94	1.02	3460	Increase	87	25
18	0.62	4.4	103	0.92	3172	Increase	97	16
Median	–	4.4	123	0.84	2616	–	114	15
Range	–	2.9–6.8	65–191	0.33–1.02	1781–5040	–	62–168	10–25

[a]Patient excluded from the pharmacokinetic analysis.

patients. The average of the ratios of the calculated and the predicted AUCs on day 2 was 1.16 (95% confidence interval: 0.97–1.35%; NS). AUC and clearance were calculated for all 18 patients after the first dose of 80 mg/m^2. The median AUC was 2616 (range 1781–5040) μmol/l min. In all children, the busulfan dose was adjusted in order to reach the target AUC. In one patient, the dose was decreased and the other patients warranted dose increments to reach the target AUC. In one child (patient 15), the dose was adjusted to 196 mg/m^2. The data of this child were not included in the PK analysis, because this patient received maintenance treatment for previous convulsions with Phenobarbital, which is a known enzyme-inducer influencing the elimination of busulfan. The median dose was increased to 114 (range 62–168) mg/m^2 to reach the target AUC. The median elimination half-life and volume of distribution were 2.38 (range 1.44–3.07) h and 0.84 (range 0.33–1.02) l/kg, respectively. Weight-normalized clearance proved to be dependent on age, whereas surface-normalized clearance was age-independent (Fig. 2). The small number of patients did not allow us to perform a statistical correlation of exposure in relation to clinical outcome.

Discussion

This study shows that once-daily i.v. busulfan is safe, convenient and effective in conditioning before hematopoietic transplantation in children and that the first dose can be dosed on the basis of body surface area, independent of age. Dose optimization is important for achieving the best transplant outcome. Overdosing can lead to potentially severe toxicity, such as VOD [14], whereas underdosing can lead to nonengraftment and relapse [8]. Previously, we developed a limited sampling model to estimate systemic exposure to intravenously administered busulfan in children [6]. Using this model in a large group of children, we observed that after administering busulfan four times daily, outcome and toxicity were in accordance with data from other groups despite the relative low average AUC of busulfan that was reached [7]. On the basis of these findings, in the present study the safety and efficacy of once-daily busulfan in children were studied, aiming at a target AUC after the first dose of busulfan of 3800 μmol/l · min, with unlimited dose adjustment. The limited-sampling model applied was originally developed and validated for a busulfan dosage regimen of 1 mg/kg i.v. four times daily. Cremers *et al.* [6] proved that a combination of two sampling time-points was sufficient to estimate the AUC adequately. In this study, we added one (and in some case three) time-point to improve the estimation of the AUC. The AUC after the first dose ranged between 1781 and 5040 μmol/l · min. After the first infusion of busulfan, individual dose adjustments were made using a Bayesian fitting procedure to reach the target AUC in all patients. With respect to clinical outcome, early graft rejection was observed in 25% of the patients, whereas (moderate) VOD was seen in only one patient. Despite the high systemic peak levels of the drug, there was no new unexpected or unusual toxicity in our patients.

This study is one of the first reports describing the PK, clinical outcome and toxicity of once-daily i.v. busulfan in a considerable group of children. PK parameters such as clearance and volume of distribution are in the same range as observed in our previous study in which busulfan was administered four times daily [7]. Furthermore, we observed that the increment of the first dose in the present study (median increase 3.6) resulted in an almost linear increment of the AUC (median increase 3.4). In addition, linearity of the kinetics of busulfan was tested and demonstrated by plotting all available concentrations, normalized for dosage vs. time after the start of infusion for the two regimens. No significant difference exists between dose-normalized plasma levels of either dosage regimen. Linearity could not be tested within the same patient; however, our findings are in accordance with others because linearity and first-order kinetics of busulfan had been reported previously [5,15,16]. Furthermore, no accumulation was observed, which is also in accordance with previous findings [4]. As 1.0 was included in the confidence interval of the mean ratio of the calculated and predicted AUC on day 2, it is likely that there is no substantial change in PK of the drug during treatment.

Previous studies [8,17] reported that clearance of busulfan normalized for weight is age-dependent and therefore suggest age-dependent dosing. We showed that clearance normalized to body surface area in children was independent of age, which was also found by others [4,9,18]. Our observation enables a fixed first dose based on body surface and reduces the chance of failure in dosage calculation. Nguyen *et al.* [18], however, preferred dosing using a scheme based on a weight-based nomogram, as estimation of the body surface area in children might be difficult. Still, our results show that interindividual variance in PK was rather high (± 20%), which suggests that PK monitoring remains necessary to maximize outcome, as also illustrated by the very wide range in the total dose of busulfan (corrected for weight ranging from 10 to 25 mg/kg). Several factors exist that may influence the metabolism of busulfan, i.e. the etiology of the disease and drug interactions with busulfan. Previously, we failed to find any correlation between busulfan metabolism and the use of acetaminophen and itraconazol, which are both known inhibitors of busulfan metabolism [7]. One of our patients (15) was using hepatic enzyme-inducing anticonvulsants resulting in much greater busulfan clearance. Intravenous busulfan, however, shows more predictable behavior than oral busulfan, and this route of administration is more convenient for patients and easier to handle for the

nursing staff. The stability of busulfan in solution is rather short (12 h). Therefore, dosing once daily makes the i.v. route of administration also more practical for the pharmacy because the preparation of the infusions can be carried out once daily during working hours.

Overall toxicity was relatively low in our patients. Former studies on the correlation of busulfan PK (AUC and C_{ss}) and either VOD or engraftment have been mainly performed in children receiving busulfan four times daily either intravenously or orally. After regimens in which busulfan was administered four times daily, VOD rates as high as 20–30% were reported [7,19]. Comparing outcome parameters after a single dose a day with a regimen of four doses of busulfan a day, the engraftment rate was lower after the once-daily regimen. This was accompanied by an overall lower toxicity, whereas the estimated total exposure (sums of the AUCs after 4 days) was equal in both groups [7]. It is important to note that these groups of children were studied separately and patient characteristics were comparable, but not the same. Our findings on toxicity are in agreement with others who administered busulfan to children once daily and also observed only single cases of VOD [9,16]. The median AUC in these children was more than 6000 μmol/l min, which is considerably higher than that in our patients. In 50% of these patients, however, general hepatic toxicity was experienced, as compared with approximately 20% in our patients. Data from evaluations of busulfan once daily in adults are heterogeneous. Both high [20] and low [4,5,21] risk of VOD is reported. After our once-daily regimen, in 25% of patients early graft rejection was observed. This suggests that the efficacy of our regimen is somewhat lower than previously reported [7,9,22–24]. A direct comparison in a randomized study of busulfan once daily vs. busulfan four times a day is, however, needed to resolve this issue.

In our previous study, we administered i.v. busulfan every 6 h to 31 children according to the initial dosing guidelines of the manufacturer: 1.0 mg/kg for patients younger than 4 years and 0.8 mg/kg for patients 4 years or older with dose adjustment to a maximum dose of 1.0 mg/kg [1]. This regimen resulted in a mean AUC of 950 ($\pm$ 260) μmol/l · min. As we could not find any correlation between busulfan exposure and transplant outcome measure, the target for the single quadruple dose in our present study was set to 3800 μmol/l · min. The present findings, however, suggest that an AUC of busulfan obtained after one quadruple dose does not yield the same efficacy and toxicity rates as the same dose divided into four over the day. Several explanations have been mentioned for the different efficacies of busulfan at transplantation outcomes after i.v. vs. oral administration, i.e. circumvention of the first-pass hepatic effect. The decreased efficacy and toxicity observed after busulfan once daily compared with busulfan four times a day, both after i.v. administration, however, needs another clarification. A better recovery of the enzymes glutathione-S-reductase and glutathione-S-transferase after a single dose of busulfan could explain the decreased toxicity after busulfan once daily. These enzymes are responsible for the hepatic conjugation of busulfan. Srivastava *et al.* [25] found that glutathione-S-transferase M1 polymorphism is a risk factor for hepatic VOD in bone marrow transplantation, suggesting that capacity of the enzymes to detoxify busulfan is an important factor for the toxicity of busulfan. Literature is not yet conclusive as to which AUC is the most optimal AUC for once-daily dosing in children in the various conditioning regimens. The optimal AUC may be rather different between, for instance, busulfan–Cy and busulfan–Cy–melphalan-based regimens. We suggest that PK-directed and individualized dosing should at least be continued until a clear exposure interval with an optimized safety and efficacy profile is defined for i.v. busulfan.

In summary, this study demonstrates that a conditioning regimen in children containing four single daily doses of busulfan was safe. The heterogeneity of the underlying diseases in our patients limits the conclusions that can be drawn concerning the efficacy of the once-daily busulfan regimen. The first dose of busulfan can be dosed independent of age and adjusted to body surface area. In the future, a clear interval for the target AUC in children should be defined to maximize efficacy with an acceptable toxicity. Probably, this ideal target AUC will be dependent on several parameters such as underlying disease, other agents used in the pretransplant conditioning, genetic profile with respect to busulfan metabolism or type of donor. Routine PK monitoring is probably not necessary anymore in certain patients groups (adults) and standard regimens as interindividual differences are predictable and acceptable. For the time being PK-directed dosing in children, however, will be necessary to optimize the busulfan containing conditioning regimens in the future.

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