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Busulfan Exposure Target Attainment in Adults Undergoing Allogeneic Hematopoietic Cell Transplantation: A Single Day Versus a Multiple Day Therapeutic Drug Monitoring Regimen

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A B S T R A C T

Busulfan exposure has previously been linked to clinical outcomes, hence the need for therapeutic drug monitoring (TDM). Study objective was to evaluate the effect of day 1 TDM-guided dosing (regimen d1) versus days 1 + 2 TDM-guided dosing (regimen d1 + 2) on attaining adequate busulfan exposure. In this observational study, we included all adults who received an allogeneic HCT with intravenous once daily busulfan over 4 days as part of the conditioning regimen at the University Medical Centre Utrecht or between July 31, 2014 and November 12, 2021. The primary outcome was attainment of the therapeutic busulfan target (cumulative area under the curve [AUC_{cum}] 80-100 mg*h/L). Dose adjustment was based on the estimated AUC of the preceding dosing day(s). Additional TDM was performed in the event of large dose adjustments (≥25%). The choice of TDM regimen was solely based on the first day the busulfan dose was administered (regimen d1 + 2 occurred when conditioning started on a Saturday). In all patients, blood sampling was performed on day 4 for evaluation. The AUC_{cum} was estimated using a validated population pharmacokinetic model. Busulfan target exposure was compared between both TDM regimen groups using a propensity score adjusted logistic regression model. The variance in the AUC_{cum} between the TDM regimens was compared using the F-test. Patients were stratified for age (categorical). In regimen d1, 87.6% (n = 113/129) attained a therapeutic busulfan exposure, while in regimen

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d1 + 2 a proportion of 97.4% was found (n = 74/76, adjusted odds ratio for non-therapeutic AUC = 0.19, 95% confidence interval [95% CI]: 0.04-0.89). Variance of busulfan exposure in the regimen d1 group (SD = 6.8 mg*h/L) differed significantly from the variance in the regimen d1 + 2 group (SD = 3.6 mg*h/L, F-test, $P < .001$). Performing busulfan TDM on both day 1 and day 2, rather than only on day 1, improves busulfan target exposure attainment in adults undergoing HCT, provided that subsequent TDM is carried out if required.

INTRODUCTION

Busulfan is widely used as part of conditioning regimens in patients undergoing allogeneic hematopoietic cell transplantation (HCT). It is characterized by a narrow therapeutic window [1-3]. Several studies therefore advocate the use of TDM of busulfan in specific underlying disease groups, particularly if busulfan is combined with fludarabine during conditioning [1,4]. In these disease groups, primarily children, they reported graft failure and disease recurrence with busulfan underexposure, whereas overexposure has been associated with toxicity, such as veno-occlusive disease/sinusoidal obstruction syndrome [1,2]. Hence, a commonly utilized therapeutic window for busulfan exposure, expressed as a cumulative 4-day area under the concentration-time curve (AUC_{cum}), is 80-100 mg*h/L [1].

The optimal busulfan TDM sampling scheme is currently unknown, but may be important for target exposure attainment. Several studies have reported that performing TDM sampling only on the first day is not sufficient for an accurate estimation of the cumulative AUC_{CUM}, especially because of the within-patient fluctuation in clearance. Previously, we showed that in children, busulfan TDM merely on the first day, with additional TDM if needed, may be sufficient for attaining optimal target exposure (target attainment in 85.8% of included children) [1]. However, extrapolation to adults is complicated, as some studies suggested that adults might be more prone to a decrease in clearance over the course of therapy, in which case multiple day TDM may be beneficial [2-4]. As evidence on this topic is scarce, there is currently no consensus on the number of busulfan days with PK sampling, and busulfan TDM protocols therefore vary widely between transplant centers, with marked differences in the timing and frequency of measurements and utilized models to estimate AUC [5,6].

The aim of this study was to evaluate the effect of single day versus multiple day TDM sampling with additional TDM if needed, on attaining adequate busulfan target exposure in adults undergoing an allogeneic HCT.

METHODS

Setting, Design, and Study Population

In this retrospective cohort study with prospectively collected data, we included all adults (≥18 years) who underwent their first allogeneic HCT with TDM-guided intravenous busulfan dosing as part of the conditioning regimen at the University Medical Centre Utrecht (UMCU) between July 31, 2014 and November 12, 2021. In our center, busulfan TDM is part of routine clinical practice in adults undergoing myeloablative conditioning. Study approval was given by the Medical Research Ethics Committee NedMec (Utrecht). The data were collected after patients provided written informed consent in accordance with the Helsinki Declaration. Captured data included demographic, HCT-related, medication-related, and laboratory data for at least six months after the start of the conditioning for the HCT. HCT and demographic variables were collected from the PROMISE database. PROMISE is a web-based database that registers and manages all HCT-related data from patients and their (potential) donors.

Busulfan Dosing and TDM Regimens

Busulfan TDM and HCT-related procedures were performed according to local UMCU treatment protocol. To prevent busulfan-induced seizures, clobazam was administered during conditioning. Drugs that possibly affected the clearance of busulfan were avoided [7]. Busulfan was administered once a day over 4 consecutive days as a 3-hour intravenous infusion. The initial busulfan dose was calculated based on actual body weight using a body weight-dependent dosing nomogram that was previously described by Bartelink et al. [8]. At each sampling day, blood sampling was performed at 5 min, 1 h, 2 h, and 3 h after the end of infusion, according to the local TDM protocol [9]. Busulfan TDM sampling was routinely performed on day 1 (regimen d1).

However, only when the first day busulfan was administered on a Saturday, samples were taken on day 1 and 2 (regimen d1 + 2). For patients with regimen d1 + 2, a trough sample was also drawn before the dose on day 2 was administered. This difference in sampling was purely for logistical reasons and not related to differences between patients or HCT procedures. Patients were divided into two groups based on their TDM regimen.

The plasma samples were analyzed with a liquid chromatography–tandem–mass spectrometry assay [10]. The analytical method was validated in accordance with the EMA guideline for bioanalytical method validation [11]. The laboratory participated in a busulfan interlaboratory comparison program. The mean interday variability of the analytical assay was 3.9%, consistent for both low and high concentrations within the linearity range. The limit of quantification (LOQ) was 50 μg/L. In case of concentrations below the LOQ, values were included and set at half the LOQ (25 μg/L).

Exposure of interest was the busulfan TDM regimen that was utilized (regimen d1 vs. regimen d1 + 2). Regimen d1 was defined as busulfan TDM on the first day of therapy with day 1 AUC-guided dose adjustment on day 2. Regimen d1 + 2 was defined as busulfan TDM on the first two days of therapy with days 1 + 2 AUC-guided dose adjustment on day 3. Dose adjustment was based on the estimated AUC of the preceding dosing day(s). Additional TDM was performed in the event of large dose adjustments in both regimens (≥25%). In all patients, blood sampling was routinely repeated on day 4 to evaluate the results of the dose adjustment on AUC_{CUM}. The TDM protocol is illustrated in Figure 1. The choice of TDM regimen was solely based on pure practical reasons, namely the first day busulfan was administered (regimen d1 + 2 occurred when conditioning started on Saturday). This allowed us to perform TDM during regular service hours in most cases. All other days, regimen d1 occurred. Patients were divided into two groups based on their TDM regimen.

Outcomes

The primary outcome was attainment of the therapeutic busulfan target exposure (AUC_{CUM} 80-100 mg*h/L, myeloablative). We estimated the AUC_{CUM} using an optimized two-compartment model that accounted for intra-individual variation in busulfan clearance (Table S1). This model was based on a previously validated model described elsewhere [12]. External validation of the model demonstrated its effectiveness in accurately describing adult data [13]. To estimate the AUC_{CUM}, we collected the following variables from the laboratory information system database: busulfan dose, time of busulfan administration, duration of infusion, sampling times, busulfan concentrations, and the busulfan dose advice from day 1 to day 4. The busulfan exposure was estimated using all available samples that were taken on days 1-4. Non-linear mixed effects modelling was applied via NONMEM (version 7.4.1, Icon, Hanover, MD, USA). MAXEVAL = 0 was used to predict the population and individual PK parameters and individual concentration-time profiles based on the model parameters.

As a secondary outcome, we estimated the busulfan clearance on day 4 (CLday4) with the concentrations measured on day 1 (regimen d1) and the concentrations measured on days 1 + 2 (regimen d1 + 2). Here, the CLday4 that was based on the concentrations on day 4 was considered the true clearance at day 4, whereas the predicted CLday4 was based on day 1 or days 1 + 2 concentrations. When taking into account the AUC_{CUM} target of 90 mg*h/L (range 80-100 mg*h/L), a difference greater than 10% between the observed and predicted CLday4 was deemed clinically significant, as it corresponds to a 10% variation in AUC, necessitating a dose adjustment. In addition, we predicted the CLday4 in two data-subsets: one subset with the concentration-time profiles from all patients in whom the measurements were taken on day 1, a second subset from all patients in whom measurements were taken on day 2, regardless of the TDM regimen. Because samples were routinely taken on day 4, this allowed us to estimate the sampling-derived CLday4. We considered this as the "true" estimated CLday4 . We then compared the estimated CLday4 with the sampling-derived CLday4 for both TDM regimens.

Potential Confounders and/or Effect Modifiers

Biological plausibility and available literature suggest that the following determinants may influence busulfan concentrations and were therefore considered potential confounders and/or effect modifiers: age, sex, body mass index (BMI), serotherapy regimen (anti-thymocyte globulin [ATG]), and the conditioning regimen. To account for effect modification, interaction between all variables was tested.

Data Analysis

Demographic, donor, and transplant characteristics of patients were compared using the

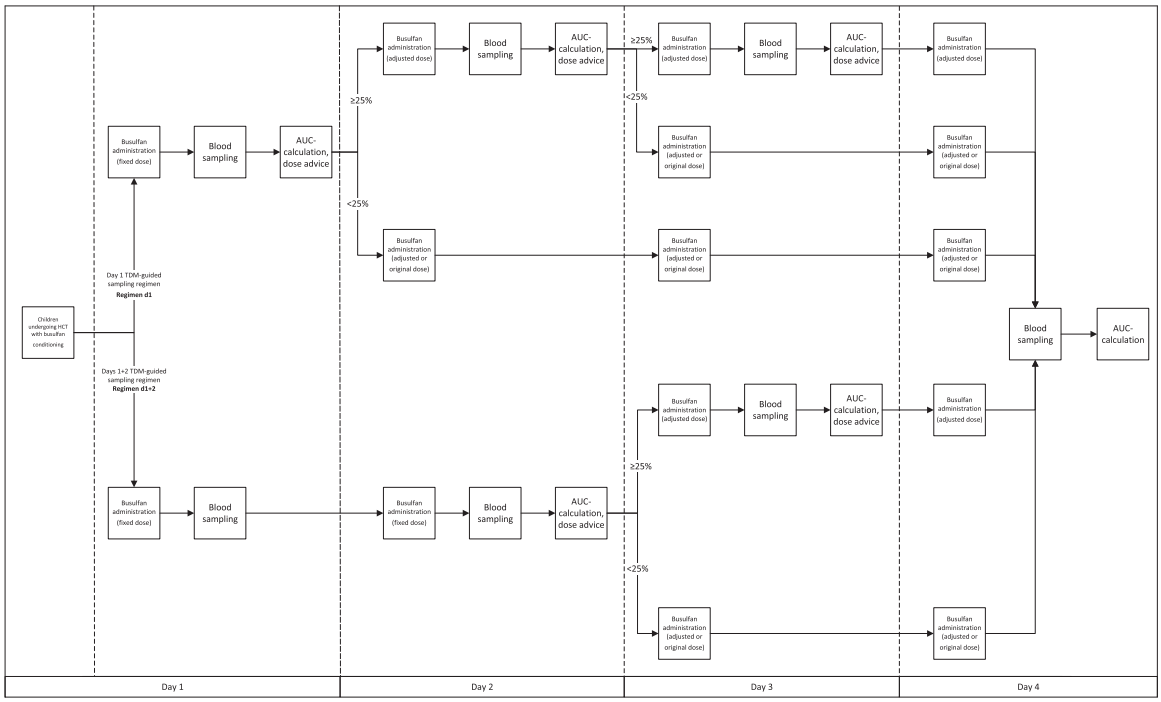

Figure 1. Two busulfan therapeutic drug monitoring (TDM) sampling strategies were applied: either blood sampling was performed on day 1 (regimen d1), with a dose adjustment based on the day 1 AUC, or blood sampling was performed on days 1 + 2 (regimen d1 + 2), with a dose adjustment based on the days 1 + 2 AUC. Additional TDM was performed in the event of large dose adjustments (≥25%). Blood was drawn at 5 min, 1 h, 2 h, and 3 h after the end of the busulfan infusion. Blood sampling was performed on day 4 to evaluate the results of the TDM-based dose adjustments. AUC = area under the curve, HCT = hematopoietic cell transplantation.

Chi-square test. Patients were stratified by age (18-40, 40-60, 60+ years) and the magnitude of busulfan dose adjustment (<25% and ≥25%), and Wald tests were used to detect statistical interaction. The target exposure attainment was calculated by stratum and in the total population. The target exposure attainment in both TDM regimens was compared using descriptive statistics and a propensity score-adjusted logistic regression model (SAS institute, version 9.4). The propensity score was calculated with the following covariates: gender, body weight, disease status (malignant/non-malignant), serotherapy regimen (anti-thymocyte globulin), and the conditioning regimen. The variance of the AUC_{CUM} between TDM regimens was compared using the F-test (SAS institute, version 9.4).

RESULTS

A total of 205 patients underwent allogeneic HCT with intravenous busulfan as part of their conditioning regimen in the study period. The median age was 58 years (range 21-74 years, Table 1). All patients were treated with busulfan/fludarabine as conditioning regimen. The majority of the patient characteristics were equally distributed between both TDM regimen groups (Table 1). In both groups, most patients were treated with ATG and primary donor source was peripheral blood, albeit this preference was most pronounced in the regimen d1 + 2 group. The results of the prediction-corrected visual predictive checks indicate that the model had an adequate predictive performance across all age and weight categories (Figures S1 and S2).

In total, 62.9% (n = 129) of patients started with regimen d1 and 37.1% of patients (n = 76) started with regimen d1 + 2. Overall, 60.5% (n = 124) of the patients received subsequent TDM (on day 2 and/or day 3) of busulfan due to a large dose adjustment (≥25%) that was based on the AUC of the previous sampling day. Within the regimen d1 cohort, 42.6% (n = 55) of the patients were monitored on day 1 only, 57.9% (n = 67) on days 1 and 2, and 5.4% (n = 7) on days 1, 2, and 3. Within the regimen d1 + 2 cohort, 34.2% (n = 26) of the patients were monitored on days 1 + 2 only, and 65.8% (n = 50) on days 1, 2, and 3. The blood of all patients was drawn on day 4, according to standard protocol. The mean number of blood samples drawn from each patient was 10.5 in the regimen d1 group and 14.6 in the regimen d1 + 2 group.

Table 1
Patient Characteristics of Both Therapeutic Drug Monitoring (TDM) Regimen Groups at the Start of Conditioning (Chi-Squared Test)

		TDM Regimen Day 1		TDM Regimen Days 1 + 2		
		%	*n* = 129	%	*n* = 76	*P*
Patient demographics						
Gender	Male	56.6	73	59.2	45	.71
	Female	43.4	56	40.8	31	
Age (years)	18-40	17.1	22	21.1	16	.17
	40-60	32.6	42	42.1	32	
	>60	50.4	65	36.8	28	
BMI (kg/m^2)	0-18.5	0.8	1	1.3	1	.42
	18.5-25	44.2	57	55.3	42	
	25-30	41.1	53	34.2	26	
	>30	14.0	18	9.2	7	
Donor-related characteristics						
Diagnosis	Malignant	96.9	125	93.4	71	.24
	Non-malignant	0.8	1	0.0	0	
	Missing	2.3	3	6.6	5	
Donor	Family	20.2	26	10.5	8	.07
	Unrelated	79.8	103	89.5	68	
Matching status	Matched	79.1	102	76.3	58	.65
	Mismatch	20.9	27	23.7	18	
Donor source	Bonemarrow	1.6	2	1.3	1	.03
	Peripheral blood	89.9	116	98.7	75	
	Cordblood	8.5	11	0.0	0	
Hematopoietic cell transplantation-related characteristics						
Serotherapy	None	7.0	9	0.0	0	.02
	ATG	93.0	120	100.0	76	

ATG = anti-thymocyte globuline, BMI = body mass index.

The mean number of TDM occasions was 2.6 in the regimen d1 group and 3.7 in the regimen d1 + 2 group.

Target Exposure Attainment of Busulfan

In total, 91.2% (*n* = 187) of patients attained therapeutic busulfan exposure (AUC_{CUM} 80-100 mg*h/L). For all patients, day 1 and 4 plasma levels were available. Target attainment was higher in the regimen d1+2 group (97.4%, *n* = 74) versus the d1 group (87.6%, *n* = 113; Table 2, Figure 2, Table S2). In the regimen d1 group, 12.4% (*n* = 16) of patients were underexposed or overexposed to busulfan, compared to 2.6% (*n* = 2) in the regimen d1 + 2 group (odds ratio [OR] = 0.19, 95% confidence interval [CI]: 0.04-0.89). This trend was consistant across all age groups in favour of regimen d1 + 2. Patients with BMI ≥ 30 kg/m^2 had slightly higher target attainment (12.0%) compared to those with a BMI < 30 kg/m^2 (8.3%), but this difference was not significant (*P* = .61).

Variance of the Busulfan Exposure

The busulfan AUC_{CUM} varied considerably (range 54.6-102.1 mg*h/L, mean = 90.2, standard deviation [SD] = 5.9). The variance of the AUC_{CUM} in the regimen d1 group (range 54.6-102.1 mg*h/L, mean = 90.9, SD = 6.8) differed significantly from the variance of the AUC_{CUM} in the regimen d1 + 2 group (range 76.5-100.0 mg*h/L, mean = 89.1, SD = 3.6, *P* < .001). In addition, in all age groups, the variance of the AUC_{CUM} differed significantly between TDM regimens (Figure 2).

Estimation of the Clearance on Day 4

We estimated the CLday4 in both TDM regimen groups, using the concentrations measured on day 1 (regimen d1) and the concentrations measured on days 1 + 2 (regimen d1 + 2). The estimated busulfan CLday4 and day 4 sampling-derived CLday4 varied considerably, but did not differ significantly between the regimen d1 + 2 group (mean = 2.9%, SD = 11.7%,) and the regimen d1 group (mean = 6.6%, SD = 11.9%,

Table 2
Target Exposure Attainment of Busulfan for Both Therapeutic Drug Monitoring (TDM) Regimens, Stratified for Age (18-40, 40-60, and >60 years)

			Therapeutic AUC (mg*h/L)		Non-Therapeutic AUC (mg*h/L)			
			80-100		<80 or >100			
Stratum		*N* Patients		*n*		*n*	adjOR	95% CI
Total population	Regimen day 1	129	87.6%	113	12.4%	16	Ref	
	Regimen days 1 + 2	76	97.4%	74	2.6%	2	0.19	(0.04-0.89)
18-40 (y)	Regimen day 1	22	86.4%	19	13.6%	3	Ref	
	Regimen days 1 + 2	16	100.0%	16	0.0%	0	N/A	
40-60 (y)	Regimen day 1	42	81.0%	34	19.0%	8	Ref	
	Regimen days 1 + 2	32	93.8%	30	6.3%	2	0.26	(0.05-1.42)
>60 (y)	Regimen day 1	65	92.3%	60	7.7%	5	Ref	
	Regimen days 1 + 2	28	100.0%	28	0.0%	0	N/A	

AUC = area under the curve, CI = confidence interval, adjOR = adjusted odds ratio.

P = .88, Figure 3). Overall, 34.1% of patients in the d1 regimen and 11.8% of those in the d1 + 2 regimen showed a difference greater than 10% between predicted and observed Cld4 levels (resulting in a clinically relevant dose adjustment, OR = 0.24, 95% CI: 0.11-0.54).

In addition, we also estimated the CLday4 with the concentrations from all patients with all concentrations that were taken on day 1 and all concentrations that were taken on day 2, regardless of the TDM regimen. The difference of the variation in the estimated busulfan CLday4 and day 4 sampling-derived CLday4 did not vary significantly between all patients with busulfan concentrations measured on day 1 (mean = 5.2%, SD = 12.0%) and all patients with busulfan concentrations measured on day 2 (mean = 2.1%, SD = 13.0%, *P* = .30, Figure 3, bottom rows).

Intra-Individual Variability of the Clearance

Between day 1 and day 4, 78.5% (*n* = 161) of patients exhibited a decrease in busulfan clearance, with a median decrease of 3.6%. In addition, 21.5% (*n* = 44) experienced an increase in clearance, with a median increase of 1.6%. Overall, the change in clearance varied considerably (median −2.7%, minimum −33.7%, maximum 21.2%, Figure S3).

DISCUSSION

In this study among adult HCT patients, we compared busulfan target exposure attainment (exposure target AUC_{CUM} 80-100 mg*h/L) with day 1-guided TDM (regimen d1) versus days 1 + 2-guided TDM (regimen d1 + 2). Target exposure attainment was significantly higher in the second group (97.4%) compared to the those with TDM on day 1 (87.6%, OR = 0.19, 95% CI: 0.04-0.89). This trend of better target exposure attainment with multiple TDM days was present among all age groups. In the regimen d1 + 2 group, variation in AUC_{CUM} was significantly smaller than in those in the regimen d1 group without substantially affecting prediction precision of the clearance on day 4.

Performing busulfan TDM on an additional day (TDM regimen d1 + 2) increased target exposure attainment in adults HSCT patients. This is in line with the findings of Marsit et al. and Alsultan et al. [3,4], who found that additional TDM may lead to a better control of the AUC_{CUM}. These studies suggested that due to the large intra-patient variability in clearance over time, estimates based on concentrations from samples drawn at the start of therapy may not hold true on the remaining days

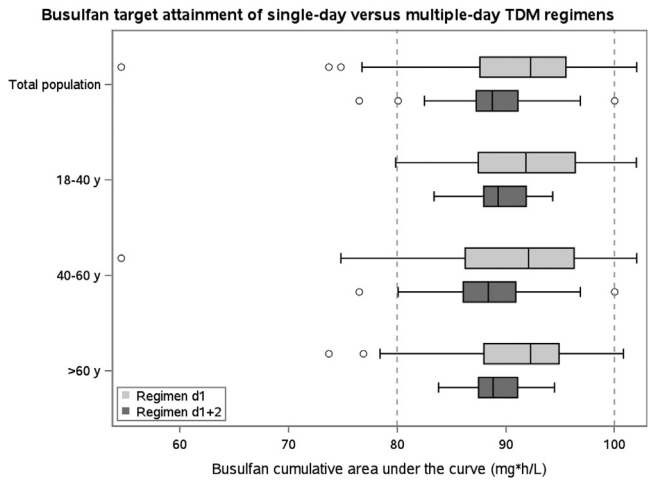

Figure 2. The cumulative area under the curve of busulfan (target cumulative area under the curve = 80-100 mg*h/L) for both therapeutic drug monitoring (TDM) regimens, stratified for age (18-40, 40-60, >60 years).

of therapy. This is supported by studies that demonstrated that busulfan metabolism involves conjugation with glutathione [14], resulting in temporary glutathione (GSH) depletion and a depletion-induced reduction clearance [2]. Consistently, during therapy, we observed a general decrease in clearance rates in most patients, though the clearance increased in some. Although the change in clearance between day 1 and 4 was generally rather small (<5%), few patients experienced significant alterations. These patients in particular may experience greater benefits from sampling on both days 1 and 2, instead of only on day 1. However, identifying which patients are susceptible to notable intrapatient variability continues to be a challenge. In children, body size predicted a decline in clearance over time [3], yet no other factors were found to anticipate the variable pharmacokinetics. The clearance only marginally decreased on day 4 relative to day 1 (median −2.7%). This is not completely in line with previous literature [3,8,12] and underlines how difficult it is to predict the change in clearance over time.

Our results suggest that additional TDM on day 2 can improve busulfan target exposure attainment and reduces variability between patients. Interestingly, in children, performing TDM on an additional day (regimen days 1 and 2, with subsequent TDM if required) did not significantly increase target exposure attainment, partly because initial target exposure attainment was already near optimal, leaving little room for improvement [1]. Moreover, adults may be more susceptible to GSH depletion [2], which makes this population more prone to a change in

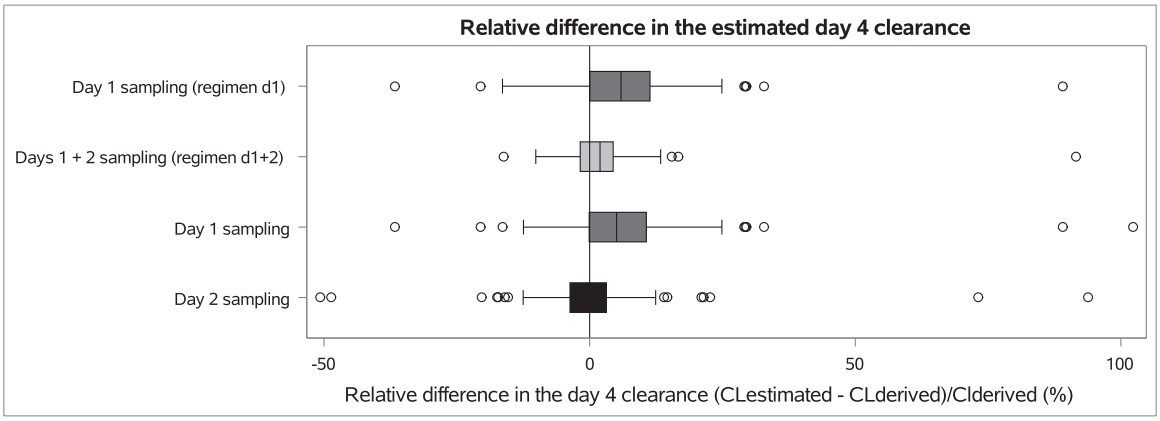

Figure 3. The agreement between the estimated and derived day 4 busulfan clearance (CLday4) for both TDM regimens and concentrations that were measured on day 1 and day 2. In regimen d1, the CLday4 was estimated based on the concentrations that were measured on day 1, whereas in regimen d1 + 2 regimen, the CLday4 was estimated based on the concentrations measured on days 1 and 2. The CLday4 was also estimated using the day 1 or day 2 concentrations, regardless of the TDM regimen. The derived CLday4 was calculated using the concentrations that were measured on day 4.

clearance on the remaing days of busulfan treatment. Studies showed that older age was associated with decreased GSH synthesis [15,16], resulting in lower intracellular GSH concentrations. Subsequently, lower GSH reserves lead to faster depletion, impacting clearance rates more profoundly, which can result in increased intrapatient variability. Consistent with this, a pharmacokinetic model was proposed that accounts for GSH depletion over time, with patients aged > 40 years being more prone to GSH depletion [2]. This may have some implications for busulfan TDM, particularly in elderly patients. First, in these patients, combining busulfan day 2 concentrations, which capture the decrease in clearance, with concentrations from day 1 could provide a more accurate estimate of the total clearance. Second, day 2 concentrations in particular may be more predictive for estimating the total exposure of busulfan. Although the effect was rather modest, we found a trend towards day 2 concentrations being more predictive for the clearance on day 4 than the day 1 concentrations (Figure 3). Furthermore, concentrations from days 1 and 2 were more predictive of the day 4 clearance than the day 1 concentration alone, emphasizing the importance of day 2 concentrations in estimating AUC_{CUM}.

While the added value of routine TDM of busulfan has been established in children [17], this is less clear in the adult population. Although among adults, various studies have linked busulfan exposure to clinical outcomes [7,9,17,18], this association varies depending on the conditioning regimen and indication, and is not observed in some conditioning regimens [7]. While TDM is advised in a number of studies, various targets have been proposed, ranging from 72.8-81.6 mg*h/L [19], 64.0-98.8 mg*h/L [20], 78-101 mg*h/L [17], and an upper limit of 88.7 mg*h/L [21]. Given the limited evidence for TDM, it can be debated that target exposure attainment is less relevant in the adult population. However, considering the narrow therapeutic range of busulfan and the notable intra- and interpatient pharmacokinetic variability as previously discussed, there is a likely risk of overexposure and TDM with or without a second day sampling scheme may seem as a sensible strategy.

Finally, some limitations need to be considered. First, McCune et al. have shown that plasma metabolomics are associated with busulfan clearance [22]. Thus, the variations in target exposure attainment among patients could be introduced due to differences in these metabolomics. In an attempt to mitigate not having an on-site laboratory available, plasma metabolomics may serve as a proxy, although its comparative effectiveness should be evaluated in future research. Unfortunately, we did not have data on these metabolomic profiles. Second, serotherapy regimen and donor source varied considerably between TDM regimen groups, but we don't expect this to affect busulfan clearance directly. However, differences in comedication, which can vary by conditioning regimen and donor source, may have affected busulfan clearance and, consequently, target exposure attainment between groups. Unfortunately, we did not collect data on medication co-administered during busulfan therapy. Nevertheless, our study provides valuable insights into the differences between two TDM regimens across a large patient group, potentially assisting clinicians and clinical pharmacists in performing and optimalisation of busulfan TDM. Third, donor source and serotherapy patient characteristics were not equally distributed between both TDM regimen groups, which may have introduced bias. However, we do not expect this to impact the results significantly, as the number of patients causing this difference is relatively small.

Our results suggest that, drawing samples on days 1 and 2 instead of day 1 may seem like a sensible strategy to optimize busulfan exposure. This may provide some additional challenges for centers due to additional PK-sampling outside office hours, but places minimal additional burden on the patient, healthcare providers and overall treatment costs. In a meta study that also included studies with repeated TDM, busulfan TDM has proven to be cost-effective [23]. Moreover, one could argue that drawing additional samples on day 2 has minimal impact on costs, as these samples can be analyzed in bulk. However, some centers send samples out to external laboratories for analysis, which logistically complicates performing additional TDM on the subsequent dosing day (s). Our TDM strategy may therefore not be feasible to implement in these particular centers.

Performing busulfan TDM is further complicated by inaccuracies. Large variation between centers in laboratory busulfan quantitation, AUC calculation/estimation, and heterogeneity in the timing of blood sampling, was also demonstrated previously [5,17,24]. A consensus statement on standardization of busulfan drug quantitation and dose recommendation methods might be beneficial.

In conclusion, this study suggests that performing busulfan TDM on both day 1 and day 2, rather

than only on day 1, improves busulfan target exposure attainment in adults undergoing HCT. This approach is effective when using a reliable pharmacometric model and "as needed" TDM on subsequent days, guided by prior pharmacokinetic data.

AUTHOR CONTRIBUTIONS

TB, IHB, JSK, KCME, EHS, CAL, ACGE, JK, MAW, AHMV, and AL designed the research and participated in the manuscript. TB, KCME, JSK, and CL collected the data. IHB performed the pharmacometric analysis of the data. TB, ACGE, and AL performed the statistical analysis. TB, JSK, KCME, ACGE, IHB, and AL wrote the manuscript. All authors read and approved the manuscript.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, TB, upon reasonable request.

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Conflict of interest statement: The authors have no conflicts of interest to declare.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2024.07.015.

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