TDM monograph busulfan

Synonyms: busilvex

Summary

Indication:	Patients undergoing myeloablative allogeneic HCT with intravenous busulfan.
Sample material:	Plasma (1)
Time of sampling:	**AUC-based monitoring, Bayesian estimation:** It is advised to draw at least 4 samples after the first infusion of busulfan on day 1: • Sample 1: approximately 5 minutes after end of infusion. • Sample 2: approximately 1 hour after end of infusion. • Sample 3: approximately 2 hours after end of infusion. • Sample 4: approximately 3 hours after end of infusion. **Additional sampling** In case of a dose adjustment ≥25% or in the presence of risk factors for toxicity, TDM on the following day of treatment is advised.
Storage conditions:	The whole blood samples need to be refrigerated directly after sampling. The samples need to be centrifuged to plasma and stored at -20°C or -80°C to avoid degradation, preferably within 12 hours of collection (1,2) (1)
Interpretation:	**Target exposure** Children: 4-day cumulative AUC ($AUC_{cum\ day\ 0\text{-}4}$) 80-100 mg*h/L, with TDM-guided dose adjustment targeting an $AUC_{cum\ day\ 0\text{-}4}$ of 90 mg*h/L (3). Adults: The target exposure is most likely similar to children, but various exposures can be applied.
Evidence level:	Pediatric population: 2 Adult population: 2-3

Contents

Abbreviations:
aGVHD = acute graft-versus-host disease
ABW = actual body weight (ABW)
AIBW = adjusted ideal body weight
AML = acute myeloid leukemia
ASBMT = American Society for Blood and Marrow Transplantation
BSA =body surface area
Bu = busulfan
cGVHD = chronic graft-versus-host disease
Clo = clofarabine
Cy = cyclophosphamide
EFS = event-free survival
Eto = etoposide
Flu = fludarabine
HCT = hematopoietic cell transplantation
IBW = ideal body weight
Mel = melphalan
MDS = myelodysplastic syndromes
OS = overall survival
RIC = reduced-intensity conditioning
Q6H = four times daily dosing
Q24H = one time daily dosing
TDM = therapeutic drug monitoring
TRM = transplant-related toxicity
TT = thiotepa
VOD/SOS = veno-occlusive disease/sinusoidal obstructive syndrome

Introduction

The alkylating agent busulfan is widely used as part of conditioning regimens in children and adults undergoing allogeneic hematopoietic cell transplantation (HCT). It is characterized by a narrow therapeutic window and a high inter- and intra-patient pharmacokinetic variability. In children, underexposure has been associated with graft failure and disease recurrence, whereas overexposure has been associated with toxicity, such as veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) (3,4).
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Dosing guidelines

Myeloablative conditioning in children and adults

The busulfan dose can be based on body surface area (BSA), body weight or a mix of both (5). In most studies, the busulfan dose was calculated based on the patients weight (mg/kg) or BSA (mg/m^2).

Dosing frequency
Busulfan can be administered once daily (Q24H) or four times daily (Q6H) with similar efficacy and safety in children and adults (6–12). Intravenous busulfan Q24H dosing is preferred over Q6H dosing, because dosing Q24H reduces time and costs in patient care (13) and is more convenient due to the short shelf life (8 hours) and logistics (4 times daily preparation and administration) (14).

Myeloablative conditioning:

- Four times daily (Q6H)
  - Children: see the product information (14).
  - Adults: see the product information (14).
- Once daily (Q24H)
  - Children and adults: Bartelink *et al*. proposed a model-based body-weight dependent dosing nomogram for different busulfan exposure targets in the pediatric and adult population for once daily administration of intravenous busulfan with TDM-guided dosing (Table 1) (15).

	Myeloabalative Target AUC day 0-4 90 mg*h/L		**Non-myeloabalative** Target AUC day 0-3 60 mg*h/L		**JMML** Target AUC day 0-4 75 mg*h/L		**Other regimens** Target AUC day 0-3 75 mg*h/L	
kg	Dose (mg)	Dose (mg/kg)	Dose (mg)	Dose (mg/kg)	Dose (mg)	Dose (mg/kg)	Dose (mg)	Dose (mg/kg)
3	11	3.8	10.1	3.4	9	3.2	12	4.3
5	24	4.7	21.0	4.2	20	3.9	27	5.2
7	36	5.1	31.7	4.5	30	4.3	40	5.7
8	41	5.2	36.9	4.6	35	4.3	47	5.7
9	47	5.2	41.9	4.7	39	4.3	52	5.7
11	58	5.2	51.3	4.7	48	4.3	64	5.7
13	68	5.2	60.1	4.6	56	4.3	75	5.7

15	77	5.1	68.2	4.5	64	4.3	85	5.7
16	81	5.1	72.1	4.5	68	4.3	91	5.7
20	97	4.9	86.3	4.3	81	4.1	108	5.5
23	108	4.7	95.9	4.2	90	3.9	120	5.2
25	115	4.6	102	4.1	95	3.8	127	5.1
30	130	4.3	115	3.8	108	3.6	144	4.8
35	143	4.1	128	3.6	120	3.4	160	4.5
40	156	3.9	138	3.5	130	3.3	173	4.4
45	167	3.7	148	3.3	139	3.1	185	4.1
50	177	3.5	157	3.1	148	2.9	197	3.9
55	187	3.4	166	3.0	155	2.8	207	3.7
60	195	3.3	174	2.9	163	2.8	217	3.7
65	204	3.1	181	2.8	170	2.6	227	3.5
70	212	3.0	188	2.7	176	2.5	235	3.3
75	219	2.9	195	2.6	183	2.4	244	3.2
80	226	2.8	201	2.5	188	2.3	251	3.1
85	233	2.7	207	2.4	194	2.3	259	3.1
90	240	2.7	213	2.4	200	2.3	267	3.1
95	246	2.6	219	2.3	205	2.2	273	2.9
100	252	2.5	224	2.2	210	2.1	280	2.8

Table 1. Dosing nomogram for different busulfan exposure targets in the pediatric and adult population for once daily administration of intravenous busulfan. JMML = juvenile myelomonocytic leukemia.

Dosing guidelines in patients with altered pharmacokinetics

Obese patients

The current American Society for Blood and Marrow Transplantation (ASBMT) guidelines and product information both recommend calculating the initial intravenous busulfan dose based on the adjusted ideal body weight (AIBW) (14,16). The AIBW can be calculated with the equations as shown below, using the ideal body weight (IBW) and actual body weight (ABW) and a factor of 25% to account for the differences.

AIBW = IBW + 0.25 (ABW – IBW).
IBW men(kg) = 50 + 0.91 x (length in cm – 152)
IBW woman(kg) = 45 + 0.91 x (length in cm – 152)

Indications/Criteria for TDM

Busulfan meets most of the criteria for TDM. It exhibits large interindividual variability in pharmacokinetics, there is an association between busulfan exposure and outcomes (both in terms of toxicity and efficacy) with a reasonably defined exposure target in specific patient populations, particularly in children, and the pharmacological response is not readily assessable. In addition, the clearance of busulfan often decreases during the course of treatment, further necessitating repeated TDM-guided dosing (5).

Reference values

Efficacy:

- Cumulative AUC day 1-4 ($AUC_{cum\ day\ 0\text{-}4}$) of 80-100 mg*h/L, with TDM-guided dose adjustment targeting an $AUC_{cum\ day\ 0\text{-}4}$ of 90 mg*h/L (3)

Toxicity:

- $AUC_{cum\ day\ 0\text{-}4}$ >101 mg*h/L (3)

Efficacy

Myeloablative conditioning

Target exposure in children and adults
An optimal exposure target of 80-100 mg*h/L is advised in pediatric patients receiving allogeneic HCT with myeloablative conditioning. For practical reasons, an optimal $AUC_{cum\ day\ 0\text{-}4}$ of 85-95 mg*h/L is often used in clinical practice, with (repeated) TDM-guided dose adjustments, targeting an $AUC_{cum\ day\ 0\text{-}4}$ of 90 mg*h/L. In adults with myeloablative conditioning, the optimal exposure target but has not yet been clearly substantiated in the literature, but is likely similar (80-100 mg*h/L, with a target for TDM-guided dose adjustment of 90 mg*h/L). However, various targets can be applied, depending on factors such as indication and conditioning regimen.

Children
In pediatric allogeneic HCT patients with myeloablative conditioning, busulfan exposure has been linked to clinical outcomes. Target $AUC_{cum\ day\ 0\text{-}4}$ exposures of 76.8 – 96 mg*h/L (in combination with Flu), 76.8 - 86.4 mg*h/L (in combination with Cy), and a lower limit of 57.6 mg*h/L have been proposed (17–22). In the largest study involving mostly children and young adults (N=674), Bartelink et al. compared the impact of different busulfan exposures on overall survival (OS), transplant-related mortality (TRM), relapse, and event-free survival (EFS). They defined an optimal $AUC_{cum\ day\ 0\text{-}4}$ of 78-101 mg*h/L (3). The optimal $AUC_{cum\ day\ 0\text{-}4}$ was independent of the conditioning regimen used, implicating that this target (78-101 mg*h/L) is applicable in various regimens. In a study with pediatric and adult patients that compared TDM vs. conventional dosing, the group with TDM (mean $AUC_{cum\ day\ 0\text{-}4}$ of 99 mg*h/L) had better OS and progression free survival than patients without TDM, while toxicity rates were similar in both groups (23).

Adults
The optimal busulfan exposure target in adults varies among study analyses, with a wide range being described in the current literature. Various $AUC_{cum\ day\ 0\text{-}4}$ targets have been proposed, ranging from 72.8-81.6 mg*h/L (24), 64.0-98.8 mg*h/L (25), 78-101 mg*h/L (3) and an upper limit of 88.7 mg*h/L (26). These findings are mostly in agreement with the European Society for Blood and Marrow Transplantation guidelines for HCT for inborn errors of immunity, in which a more narrow target of 85-95 mg*h/L is recommended for myeloablative conditioning in both children and adults (27).

Toxicity

Toxicity of busulfan may include mucositis, neurotoxicity (seizures), a/cGVHD, pulmonary toxicity, and VOD/SOS. In specific, a/cGVHD (3,22,28), TRM (3,29), and VOD/SOS have been associated with supratherapeutic busulfan exposure ($AUC_{cum\ day\ 0\text{-}4}$ > 101 mg*h/L (3), > 86.4 mg*h/L (29)) (Appendix 3).

Conditioning with Bu/Flu(/Clo) may result in less toxicity, as compared to Bu/Cy (in particular a lower risk for non-relapse mortality and a reduced incidence of VOD/SOS and infections), while clinical efficacy profiles of both regimens were similar (30–33).

Sampling conditions

Collection of blood samples

- Q6H and Q24H dosing: the first day and after the first dose of busulfan treatment.
  The collection of the blood samples should take place as follows:
  - The blood samples should be drawn according to the general rules for blood collection from a central venous line. It is advised not to collect the material from the lumen via which busulfan was administered. The exact times the samples were drawn should be written down.
    - Sample 1: approximately 5 minutes after end of infusion.
    - Sample 2: approximately 1 hour after end of infusion.
    - Sample 3: approximately 2 hours after end of infusion.
    - Sample 4: approximately 3 hours after end of infusion.
  - In case of TDM on therapy day 2 or 3 a through sample approximately 24h after infusion can be considered. This sample can be drawn approximate 5 minutes before the next busulfan administration.

Repeated TDM

- In patient with risk factors or in case of a dose adjustment of 25% or more, TDM on the following day of treatment is also advised.
  - Risk factors: pre-existent liver disease, drug-drug interactions, multiple-alkylator conditioning regimens, (previous) hepatotoxic medication, cachexia, concomitant acetaminophen use (due to its effect on glutathione metabolism), and/or patients with a young age.
- Although drawing of blood samples on day 4 of busulfan infusion has no consequences for dosing, this can be considered to calculate the total exposure. The total exposure can be used to assess the risk of toxicity, for example in high-risk patients prone to relapse and/or developing toxicity.

Processing of the blood samples

Busulfan is unstable at room temperature (1). For this reason, the blood samples need to be stored in the refrigerator directly after collection of each individual sample. After collection of all blood samples, the material needs to be centrifuged to plasma to avoid degradation, preferably within 12 hours of collection (2). The obtained plasma samples need to be stored at -20°C or -80°C (1). In case of shipping of the samples, dry ice packaging of the plasma samples is necessary.

Additional information concerning the interpretation of results

The $AUC_{cum\ day\ 0\text{-}4}$ should ideally be estimated using population pharmacokinetic modelling. Modelling software can be used for $AUC_{cum\ day\ 0\text{-}4}$ estimation. Various pharmacokinetic models have been developed for specific patient groups, which makes it important to select the appropriate model that matches the group to which the patient under treatment belongs (see section *Population models*).

Background information [extended]

Heterogeneity of studies

Studies investigating the association between busulfan exposure and efficacy/toxicity vary greatly in endpoints, conditioning regimens, TDM regimens, busulfan exposure calculation, supportive care regimen, and baseline patient characteristics, and are mostly performed retrospectively. Due to this heterogeneity, and the lack of randomised controlled trials, studies are difficult to compare and the results need to be interpreted cautiously.

Reduced-intensity conditioning (non-myeloablative)

Data about the association between busulfan exposure and efficacy/toxicity outcomes is scarce in patients undergoing RIC (cumulative busulfan dose < 9 mg/kg) (16). In these RIC regimens, busulfan is predominantly dosed based on body weight without TDM (31,34–36). As an optimal target has not yet been established, busulfan TDM in busulfan-based RIC regimens is considered unnecessary by the ASBMT, unless the conditioning regimen was specifically developed with busulfan TDM (37).

Busulfan exposure in autologous HCT patients

Busulfan TDM has been used in patients undergoing autologous HCT with busulfan conditioning (37). In autologous HCT patients with Bu/Cy/Eto conditioning, one third would have attained suboptimal busulfan exposure if TDM was not applied (38). In this study, the busulfan target was $AUC_{cum\ day\ 0\text{-}4}$ 65.6 – 98.4 mg*h/L (38). However, a busulfan exposure target for autologous HCT has not yet been clearly defined and may differ from the exposure target used in allogenic HCT (37).

Interactions

For drug-drug interactions of busulfan, see the review of Myers *et al.* (39) and https://kennisbank.knmp.nl/

PK parameters

	Cl (L/h^{-1})	**Vd** (L/kg)	$\mathbf{t_{1/2}}$ (h^{-1})	Protein binding	Ref.
Children and young adults	2.25-2.74	0.62 – 0.85	2.8-3.9	7% (reversible) 32% (irreversible)	(4)

Population models

As various models are readily available in modelling software, it is necessary to take notice of the specific patient under treatment, and to select an appropriate externally validated population pharmacokinetic model with a population similar to the patient being treated. Various population models were externally validated and were considered to have adequate predictive value for estimating the busulfan $AUC_{cum\ day\ 0\text{-}4}$ (5,15,40–44). Across these studies, it has been shown that busulfan clearance is mainly dependent on body size (expressed as BSA, ideal body weight, or fat-free mass) and age (5). The volume of distribution is

commonly described allometrically in terms of body weight (5). The externally validated models of Bartelink *et al*. (45) and Mccune *et al.* (41) for respectively the pediatric (< 20 years) and pediatric and adult population are most commonly used in routine clinical practice for TDM-guided busulfan dosing.

Population	**Model**	**Kabs** (h^{-1}) **/ F**	**Vd** (L) **/ F**	**Kelm** (h^{-1}) **/ F**	**CL** (L/ h^{-1}) **/ F**	Ref.
Children and young adults	Bognar *et al.* (4)	N/A	0.62 – 0.85 L/kg	0.18 - 0.25	2.25-2.74 mL/min/kg	(4)

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Colophon

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Appendices

Appendix 1. Table for busulfan AUC unit conversion (37):

AUC µMolar×min Q6H dosing	AUC µMolar×min daily dosing	Css ng/ml	AUC mg/L×h Q6H dosing	AUC mg/L×h daily dosing
750	3000	513	3.08	12.3
875	3500	599	3.59	14.4
877	3508	600	3.60	14.4
900	3800	650	3.90	15.6
1000	4000	684	4.11	16.4
1023	4093	700	4.20	16.8
1096	4385	750	4.50	18.0
1125	4500	770	4.62	18.5
1169	4677	800	4.80	19.2
1243	4970	850	5.10	20.4
1250	5000	855	5.13	20.5
1316	5262	900	5.40	21.6
1375	5500	941	5.64	22.6
1389	5554	950	5.70	22.8
1462	5847	1000	6.00	24.0
1500	6000	1026	6.16	24.6
1875	7500	1283	7.70	30.8

C_{ss} = AUC divided by the dosing frequency. When the AUC is expressed in micromolar quantities the BU molecular weight (246.3 g/mol) must be used to calculate the AUC in mg/L quantities.

Appendix 2. Exposure-efficacy association

Primary author, year	**Dosing schedule {% IV}**	**Population (adult / pediatric)**	**Dose(s) with sampling**	**Groups**	**HR**	**CI low**	**CI high**	***p* value**
Overall survival								
Ansari, 2014 (22)	Q6H 4 days {100}	Pediatric	Dose 1[a], Dose 5[b]	AUC_6 first dose: < 3.6 mg*h/L (corresponds with AUC_{cum}=57.6 mg*h/L)	1	1	1	-
				AUC_6 first dose: > 3.6 mg*h/L (corresponds with AUC_{cum}=57.6 mg*h/L)	7.55	2.2	25.99	0.001
Benadiba, 2018 (21)	Q6H 4 days {100}	Pediatric	Dose 1	AUC_6 first dose: < 3.6 mg*h/L (corresponds with AUC_{cum}=57.6 mg*h/L)	1	1	1	-
				AUC_6 first dose: > 3.6 mg*h/L (corresponds with AUC_{cum}=57.6 mg*h/L)	5.2	1.26	21.5	0.02
Russell, 2013 (24)	Q24H {100}	Adults	Test dose	AUC_{cum}: < 62.4 mg*h/L or AUC_{cum}: > 82.0 mg*h/L	1	1	1	1
				AUC_{cum}: 62.4–82.0 mg*h/L	1.94	1.12	3.37	0.018

Seydoux, 2022 (46)	Q24H (84.3%) and Q6H (15.7%) {100}	Adults	Dose 1[a]	AUC_{cum}: < 59.1 mg*h/L	1	1	1	1
				AUC_{cum}: 62.4 – 88.7 mg*h/L	1.4	0.9	2.2	0.14
				AUC_{cum}: > 88.7 mg*h/L	1.9	1.1	3.5	0.02
Bartelink, 2016 (3)	Q24H (40%), Q6H (48%), other (12%) {100}	Pediatric / young adults	NR	AUC_{cum}: < 78 mg*h/L	1	1	1	-
				AUC_{cum}: 78–101 mg*h/L	0.71*	0.53*	0.94*	0.016
				AUC_{cum}: >101 mg*h/L	1.03*	0.63*	1.68*	0.915
Transplant-related mortality								
Bartelink, 2016 (3)	Q24H (40%), Q6H (48%), other (12%) {100}	Pediatric / young adults	NR	AUC_{cum}: < 78 mg*h/L	1	1	1	-
				AUC_{cum}: 78–101 mg*h/L	1.07	0.61	1.89	0.816
				AUC_{cum}: >101 mg*h/L	2.99	1.82	4.92	<0.001
Relapse								
Bartelink, 2016 (3)	Q24H (40%), Q6H (48%), other (12%) {100}	Pediatric / young adults	NR	AUC_{cum}: < 78 mg*h/L	1	1	1	-
				AUC_{cum}: 78–101 mg*h/L	0.57	0.39	0.84	0.004
				AUC_{cum}: >101 mg*h/L	0.41	0.14	1.17	0.094
Seydoux, 2022 (46)	Q24H (84.3%) and Q6H (15.7%) {100}	Adults	Dose 1[a]	AUC_{cum}: < 59.1 mg*h/L	1	1	1	1
				AUC_{cum}: 62.4 – 88.7 mg*h/L	0.9	0.6	1.4	0.60
				AUC_{cum}: > 88.7 mg*h/L	1.2	0.6	2.1	0.61
Non-relapse mortality								
Russell, 2013 (24)	Q24H {100}	Adults	Test dose	AUC_{cum}: < 62.4 mg*h/L or AUC_{cum}: > 82.0 mg*h/L	3.32	1.46	7.54	0.004
				AUC_{cum}: 62.4–82.0 mg*h/L	1	1	1	1
Seydoux, 2022 (46)	Q24H (84.3%) and Q6H (15.7%) {100}	Adults	Dose 1[a]	AUC_{cum}: < 59.1 mg*h/L	1	1	1	1
				AUC_{cum}: 62.4 – 88.7 mg*h/L	3.9	1.5	10.5	0.05
				AUC_{cum}: > 88.7 mg*h/L	4.8	1.6	14.7	<0.01
Disease-free survival								
Russell, 2013 (24)	Q24H {100}	Adults	Test dose	AUC_{cum}: < 62.4 mg*h/L or AUC_{cum}: >82.0 mg*h/L	1	1	1	1
				AUC_{cum}: 62.4–82.0 mg*h/L	1.81	1.09	2.99	0.021
Bartelink, 2016 (3)	Q24H (40%), Q6H (48%), other (12%) {100}	Pediatric / young adults	NR	AUC_{cum}: < 78 mg*h/L	1	1	1	1
				AUC_{cum}: 78–101 mg*h/L	0.64*	0.47*	0.87*	0.004
				AUC_{cum}: >101 mg*h/L	1.21*	0.73*	2.00*	0.454
Graft-versus-host-disease-free-survival								

Seydoux, 2022 (46)	Q24H (84.3%) and Q6H (15.7%) {100}	Adults	Dose 1[a]	AUC_{cum}: < 59.1 mg*h/L	1	1	1	1
				AUC_{cum}: 62.4 – 88.7 mg*h/L	1.2	0.9	1.7	0.14
				AUC_{cum}: > 88.7 mg*h/L	1.5	0.9	2.2	0.09
Bartelink, 2016 (3)	Q24H (40%), Q6H (48%), other (12%) {100}	Pediatric / young adults	NR	AUC_{cum}: < 78 mg*h/L	1	1	1	1
				AUC_{cum}: 78–101 mg*h/L	0.57*	0.44*	0.73*	<0.001
				AUC_{cum}: >101 mg*h/L	1.38*	0.90*	2.12*	0.139

Table 3 (5). A summary of the studies that investigated the association between busulfan exposure and clinical outcomes. *HR = 1 – HR. AUC_{cum} cumulative exposure measured by the area under the concentration versus time curve, AUC_6 = AUC during the first 6 hours, Q24H = once daily, Q12H = twice daily, Q6H = four times daily, Bu = busulfan, CI = confidence interval, Cy = cyclophosphamide, Flu = fludarabine, HR = hazard ratio, IV = intravenous, NR = not recorded, OR = odds ratio, RR = relative risk. [a]All patients, [b]Some patients, [c]Increased due to graft failure.

Appendix 3. Exposure-toxicity association (VOD/SOS)

Primary author, year	**Dosing schedule {% IV}**	**Population (adult/pediatric)**	**Dose(s) with sampling**	**Groups**	**HR**	**CI low**	**CI high**	***p* value**
Ansari M, 2013 (28)	Q6H 4 days {100}	Pediatric	Dose 1	GSTA1*B*B + and *B1*B1 + (all patients)	5.3	1.3	21.5	0.009
				GSTA1*B*B + and *B1*B1 + (females only)	9.6	2	45.1	0.001
				GSTM1*0 (null)	3.8	1.1	13.7	0.03
Ansari M, 2017 (29)	Q6H 4 days {100}	Pediatric	Dose 1	GSTA1 group four (slow metabolizer)	7.1	2.5	20.4	0.0005
Bartelink, 2008 (13)	IV: Q24H 4 days {50} PO: Q6H 4 days	Pediatric	Dose 1[a], Repeated[b]	IV Bu dose targeted	OR 3.76	NR	NR	0.044
				PO Bu no exposure monitoring	OR 1.0	-	-	-
Bartelink, 2014 (33)	Q24H 4 days {100}	Pediatric	Dose 1, Dose 4[b]	AUC_{cum} (Bu/Cy/(Mel)): 78 mg*h/L [range 65–110]	1	1	1	-
				$AUCc_{um}$ (Bu/Flu): 91 mg*h/L [range 74–113]	0.05	0	0.4	0.005
Gokcebay, 2015 (47)	Q24H 4 days {100}	Pediatric	NR	Age-based dosing	1	1	1	-
				Weight-based dosing	9.46	NR	NR	0.009
Huezo-Diaz, 2018 (48)	Q24H 4 days {100}	Pediatric	Dose 5	CTH c.1364 TT genotype	21.82	3.59	132.65	0.000002
				CTH c.1364 TT genotype and/or GSTA1*B	19.56	4.91	90.34	0.0001
				CTH c.1364 TT genotype and GSTA1*B	9.24	1.032	82.68	0.01
Philippe, 2018 (49)	Q6H 4 days (96.3%) Q12H 4 days (0.4%) Q24H 4 days	Pediatric	Dose 1	C_{max} > 1.88 ng/mL	RR 6	NR	NR	<0.001
				Percentage time spent > 1300 ng/mL	OR 2.05	NR	NR	0.003
				Age < 1 years	OR 2.78	NR	NR	0.002
				Age < 3 years	OR 2.78	NR	NR	<0.001

	(3.4%) {100}			Age < 5 years	OR 2.17	NR	NR	0.005
				Weight < 9 kg	OR 2.7	NR	NR	0.002
Schechter, 2018 (50)	Q6H 4 days, Q24H 4 days {100}	Pediatric	Dose 1	Young age (< 6.7 years)	OR 1.7 per year of decreasing age below 6.7 years	1.16	2.56	0.012
				Early engraftment day	OR 1.4 per day of earlier engraftment	1.08	2.14	0.041
Bognàr, 2022 (4)	Q24H 4 days, Q6H 4 days, {100}	Pediatric, young adults	Dose 1, Dose 4[b]	≤ 78 mg*h/L (subset of patients receiving 1 alkylator)	1	1	1	-
				> 78 mg*h/L (subset of patients receiving 1 alkylator)	OR 2.95	1.13	7.76	NR
Bartelink, 2014 (33)	Q24H 4 days {100}	Pediatric	Dose 1[a], Dose 4[b]	Median AUC_{cum} (Bu/Cy): 78 mg*h/L	1	1	1	-
				Median AUC_{cum} (Bu/Flu): 91 mg*h/L	0.05	0	0.4	0.005
Perkins, 2012 (51)	Q24H 4 days {100}	Adults	Dose 1	$AUCc_{um}$ target: 98.4 mg*h/L	VOD/SOS incidence = 0% (n=0/40)			
				$AUCc_{um}$ target: 123.2 mg*h/L	VOD/SOS incidence = 7% (n=2/29)			
				$AUCc_{um}$ target: 98.4 mg*h/L	VOD/SOS incidence = 100% (n=3/3)			

Table 4 (5). Determinants for the development of VOD/SOS. AUCcum = cumulative exposure measured by area under the concentration versus time curve, Q12H = twice daily, Bu = busulfan, CI = confidence interval, C_{max} = maximum concentration, CTH = cystathionine gammalyase, Flu = fludarabine, HR = hazard ratio, IV = intravenous, NR = not recorded, Q24H = once daily, OR = odds ratio, PO = oral, Q6H = four times daily, RR = relative risk, VOD/SOS = veno-occlusive disease/sinusoidal obstructive syndrome. [a]All patients, [b]Some patients.