Busulfan administration and blood sampling for TDM

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INTRODUCTION

Busulfan is a chemotherapeutic drug that is used in conditioning regimens for hematopoietic stem cell transplantation (HSCT). The drug is administered once daily in a three hour infusion according to the following scheme[1]:

Table 1: Model-based individualized dosing table of busulfan related to the body weight of the patient, aiming for a myeloablative conditioning regimen (AUCday0-4 of 90 mg*h/L in combination with fludarabine), a non-myeloablative conditioning regimen (AUCday0-3 of 60 mg*h/L) or treatment of juvenile myelomonocytic leukemia (JMML) (AUCday0-4 of 75 mg*h/L)

Body weight	**Myeloablative** target AUCday0-4 90mg*h/L		**Non-myeloablative** target AUCday0-3 60mg*h/L		**JMML** target AUCday0-4 75 mg*h/L		**NICORD study and others** target AUCday0-3 75 mg*h/L	
	4 days, 1dd, mg/kg		3 days, 1dd, mg/kg		4 days, 1dd, mg/kg		3 days, 1dd, mg/kg	
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

A cumulative exposure of 90 mg*h/L relates to 21.6 mM*min total, or 5400 µM*min/day.

Optimal exposure to busulfan in combination with fludarabine (90-100 mg*h/L in 4 days for myeloablative and 60 mg*h/L for non-myeloablative) with or without ATG leads to higher chances of (event free) survival. When busulfan is combined with another alkylating agent (cyclophosphamide, thiotepa, melphalan) an exposure of 75 mg*h/L administered over 4 days is generally advised. This exposure can be achieved by drawing blood samples on the first day of busulfan treatment and adjust the dose of busulfan on the second day of treatment based on the results of therapeutic

drug monitoring (TDM). During intravenous administration of busulfan it is important to draw blood samples exactly according to protocol. In these samples concentrations of busulfan in plasma will be measured and the 3-or-4-day-cumulative area under the curve (cAUC) will be calculated using pharmacokinetic (PK) software and a PK-model.

AIM

Correct and uniform administration and blood sampling of busulfan to estimate exposure (cAUC) based on TDM.

PREPARATION

Inform the patient and parents about the procedure.

1. Administration of busulfan
   - Busulfan is administered on 3 or 4 consecutive days. Blood samples must be drawn on day 1 and are measured by the laboratory on day 2. Administration of busulfan on day 2 will take place only after TDM is performed and the advised dose is calculated and communicated to the treating phycisian. Of note: When the first administration of busulfan takes place on a Saturday, blood samples are drawn on Saturday and Sunday, and the TDM procedure is performed on Monday with a dosing correction before the third administration.
   - The pharmacy department compounds the busulfan solution by diluting busulfan (Busulfex®) 6 mg/ml with NaCl 0,9% to a fixed concentration of 0,6 mg/ml. This solution is stable for 8 hours at room temperature (including infusion time). A cytostatic connector (Connect Z, Codan) filled with NaCl 0,9% is connected to the infusion bag to prevent contact with the busulfan solution when connecting to the infusion system.
   - Use NaCl 0,9% for flushing the infusion system before and after administration of busulfan.
   - For administration use an infusion system with cytostatics adapter and follow the general rules for the administration of cytostatics.
     The complete infusion system is described in appendix 1.

Tools:

- Syringe 10 ml filled with NaCl 0,9%
- Infusion bag (or syringe) with busulfan solution
- Cytostatic drug infusion system (see appendix 1)
- Infusion pump
- Non sterile gauze, with dsinfectant (alcohol 70%)
- Non sterile nitril gloves
- If needed: plaster, non sterile gauze

2. Blood sampling management
   - The patient must have a double-lumen central venous catheter (CVC) (usually a Hickman catheter), because administration and drawing blood samples necessitates 2 separate intravenous lines. To the blood sampling lumen a Microclave® is connected.
   - The physician or HSCT coordinator provides pre-printed laboratory forms showing date, time of collection and blood sample number. The laboratory forms are available on our website, see below for URL).

Tools:

- Adapter with a Microclave® on the blood sampling lumen of the CVC
- Laboratory form; use 1 form for each blood sample
- EDTA laboratory sampling tube (2 ml)
- Sterile syringes of 2 ml and 5 ml
- Needle
- Syringe 10 ml filled with NaCl 0,9%

PROCEDURE

Check whether the information provided is understood by the patient and parents.
Before and after the procedure hand hygiene is applied.
Gather all the required supplies before starting the procedure.

1. Administration of busulfan in infusion bag
   - Disinfect the connections with alcohol 70%.
   - Prepare the infusion bag with busulfan and set the infusion pump to "wait".
   - Connect the bag with busulfan solution with the Connect Z to the cytostatics adapter, close the clamp between the adapter and the flushing fluid and open the clamp of the tubing of the infusion bag with cytostatics.
   - Fill the infusion system at maximum speed with 20 ml busulfan solution.
   - Calculate the infusion rate:
     [total content infusion bag busulfan (X ml) + total volume infusion system (at UMC Utrecht: 35 ml) – volume filling infusion system (20 ml)] / 3 hours = infusion rate in ml/hour
   - Have a colleague check the calculated infusion rate.
   - After filling the system set the pump to the calculated infusion rate. This is the time of starting infusion busulfan.
   - Have a colleague check the set infusion rate.
   - At the end of the busulfan infusion set the infusion pump to "wait".
   - Close the clamp of the tubing of the infusion bag with busulfan and open the clamp between the adapter and the rinsing solution.
   - Flush with 35 ml NaCl 0,9% at the same infusion rate that was used for infusion of the busulfan solution.
   - When the flushing phase is completed, set the pump back to the infusion rate prior to infusion of busulfan. This is the time point of the end of the infusion busulfan (as the full dose is now in the patient).

2. Collecting and processing of blood samples
   - On day 1 blood samples are drawn for TDM, in case of dose adjustment of > 25% blood samples are also drawn on day 2 (or 3).
   - Blood collection takes place via the Microclave® which is connected to the second lumen i.e. not the one via which busulfan was administered.
   - Stop all ongoing infusions of all lumens.
   - Draw the blood sample according to the general rules for blood collection from a central venous line at the times indicated on the laboratory forms.
     ☐ 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

* Write down the exact time the sample was drawn on the pre-printed laboratory form

- Please note on the first form:
  - dosage
  - time of starting and ending the busulfan infusion
- Restart the pump for both lumens.
- After every collection please send the blood sample and laboratory form immediately to the laboratory where the samples are placed directly in the refrigerator. Alternatively, samples can be stored in a refrigerator at the ward directly after sampling and then shipped to the laboratory as a batch.
- After the complete procedure please fill out patient, dosing and sampling information and contact details of the treating physician at our website via the following link: https://www.umcutrecht.nl/nl/Ziekenhuis/Professionals/Diagnostiek-aanvragen/Farmalab/Busulfan_English/Form

REFERENCES

[1] Bartelink IH, Boelens JJ, Bredius RG, Egberts AC, Wang C, Bierings MB, Shaw PJ, Nath CE, Hempel G, Zwaveling J, Danhof M, Knibbe CA. Body weight-dependent pharmacokinetics of busulfan in paediatric haematopoietic stem cell transplantation patients: towards individualized dosing. Clin Pharmacokinet. 2012 May 1;51(5):331-45.

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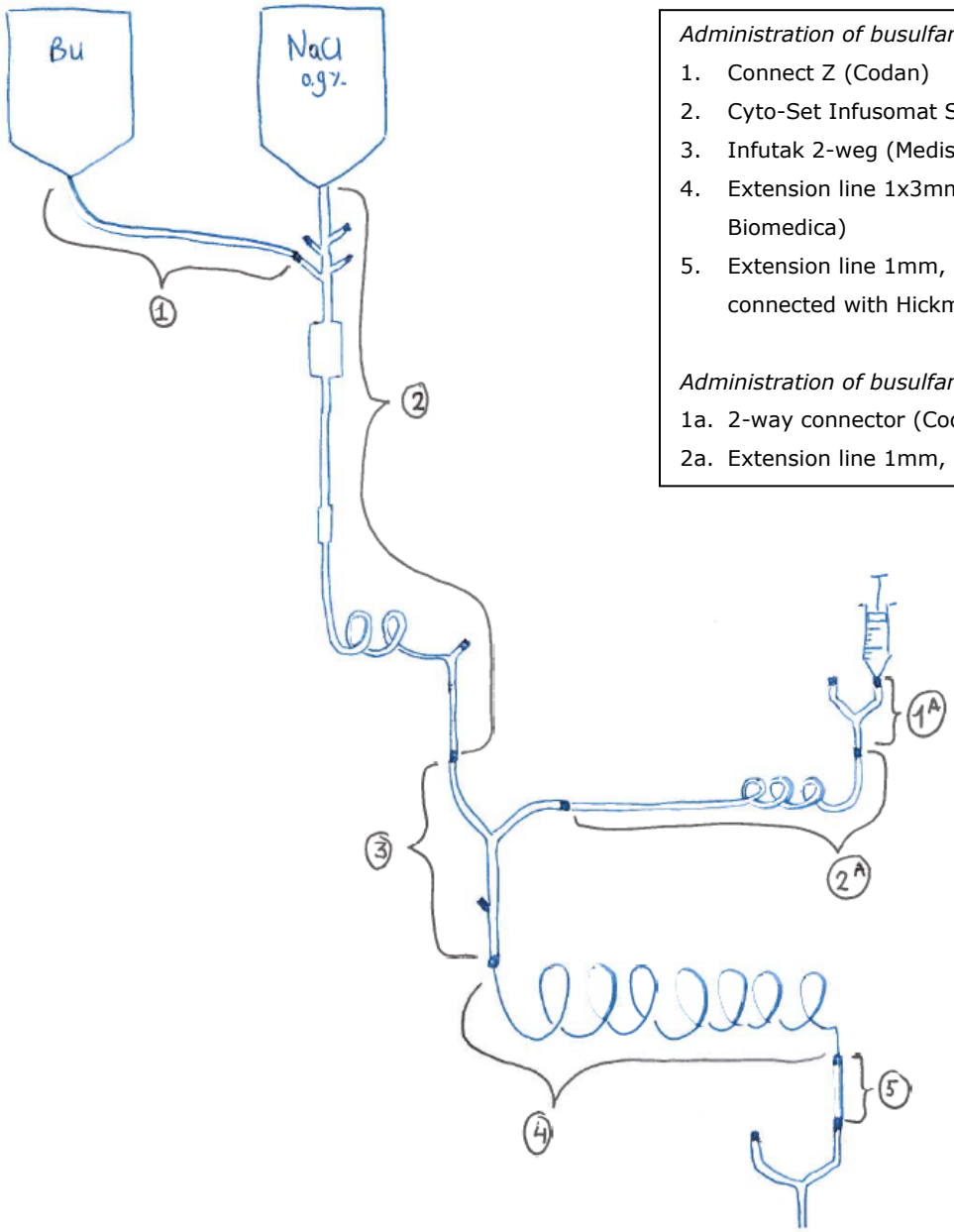
APPENDIX I: infusion system busulfan



Administration of busulfan in infusion bag:

1. Connect Z (Codan)
2. Cyto-Set Infusomat Space (B. Braun)
3. Infutak 2-weg (Medisize)
4. Extension line 1x3mm, 700cm (Dialex Biomedica)
5. Extension line 1mm, 25cm (Cair), connected with Hickman catheter

Administration of busulfan in syringe:

1a. 2-way connector (Codan)

2a. Extension line 1mm, 200cm (Cair)

APPENDIX II: schedule of busulfan administration and blood sampling