Should all the pediatric HSCT patients benefit from busulfan therapeutic drug monitoring? Experience on a large cohort

M. Philippe[1], S. Goutelle[2], J. Guitton[3], Y. Bertrand[4], N. Bleyzac[1]

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[1]Pharmacy Department, Pediatric Hematology and Oncology Unit, IHOP, France ; [2]Pharmacy Department, Groupement hospitalier de gériatrie, Lyon, France ; [3]Chemotherapy Targeting in Oncology Laboratory, Hospices Civils de Lyon ; [4]Transplantation Unit, Pediatric Hematology and Oncology Unit, IHOP, Lyon, France.

Introduction

Busulfan (Bu) used prior to hematopoietic stem cell transplantation (HSCT) presents a **narrow therapeutic index**: low drug exposure is associated with increased risk of graft rejection or relapse, and high drug exposure with toxicity (in particular veno-occlusive disease VOD). **Therapeutic drug monitoring** (TDM) and dose adjustment to achieve a target of area under the concentration-time curve (AUC) of **900 to 1500 µM.min** has been shown to improve the outcome.

The aim of this study was to assess the impact of Bu TDM in a large cohort of children.

Materials and methods

142 HSCT corresponding to 138 patients receiving **IV Bu 4 times a day for 4 days** were analyzed. The first dose was adjusted to the patients' **body weight** (BW) as recommended by Bu manufacturer[1].

< 9 kg	9 – 16 kg	16 – 23 kg	23 – 34 kg	> 34 kg
1.0 mg/kg	1.2 mg/kg	1.1 mg/kg	0.95 mg/kg	0.8 mg/kg

Two blood samples were drawn 2.5h and 4.5h after the first dose.

Afterwards, Bu PK parameter values (one-compartment model) and AUC were estimated by using **Bayesian estimation** implemented in the USC-PACK software[2] and were used to predict future Bu plasma levels, subsequent individual AUC and to calculate the doses needed to reach the target AUC range.

The main clinical endpoints were **engraftment** (full engraftment if donor chimerism ≥ 95%) and **occurrence of VOD**. Event-free survival (EFS) and overall survival (OS) after HSCT were evaluated for patients with a follow up of at least 6 months

Results

Bu AUC were within the AUC target range in 68% of children after the first dose and the mean predicted AUC for the 16 doses would have been in the target range in 74.8% of children if the initial dose was maintained.

Bu dose adjustment was performed in 54.9% of patients, whatever were the weight and pathology. At least one dose adjustment higher than 30% was necessary in each weight and pathology group. **Dose individualization increased the probability to achieve the AUC target to 91% after the 16 doses (*p<0.001*).** Achieving the target in thalassemia patients (75%) was less easy than other (92.3%, p=0.047).

Patients characteristics	
Follow up (months) , median (range)	54 (9 – 104)
Age, mean (range)	6.5 (0.2-21)
Weight, mean (range)	23.6 (3.2-87)
< 9 kg, no (%)	*23 (16.7)*
Allogeneic HSCT, no (%)	88
Autologous HSCT, no (%)	12
Underlying disease (%)	
Hematological malignant diseases	51
Non malignant diseases	21
Solid malignant tumors	12
Hemoglobinopathies	16

Full engraftment occurred in **80.1%** of children, while 4.3% experienced rejection.

EFS was 88.5% and OS was 92%.

VOD occurred in 26 patients (**18.3%**), none of whom showed a Bu AUC less than 1500 µM.min.

In multivariate Cox regression analysis, **BW <9kg** was found to influence the onset of VOD.

No correlation was found between Bu AUC and VOD occurrence.

% Achievement of AUC target range (% below ; % above)		
After the 1st dose		67.6 (29.5; 2.9)
Mean predicted AUC for the 16 doses	*Without TDM*	74.8† (18.0; 7.2)
	With TDM	90.8† (7.8; 1.4)

†: p<0.001 Chi-2 Pearson test

Event	Mean busulfan AUC/dose (µg/mL.h) of total course (± standard deviation)			
	No.*	Yes	No	p-value§
VOD	142	4.62 (0.55)	4.51 (0.70)	0.57
Full engraftment	115	4.58 (0.59)	4.55 (1.05)	0.87
Relapse†	110	4.40 (0.57)	4.57 (0.71)	0.40

*Number of evaluable patients; §Student's t-test; †Relapse post full or partial engraftment

Multivariate Cox regression analysis		
Risk factor of VOD	**Relative Risk**	**$IC_{95\%}$**
Hematological malignant diseases	1.43	[0.3 – 6.9]
Non malignant tumors	0.45	[0.1 – 3.2]
Hemoglobinopathies	2.94	[0.5 – 16.5]
Weight < 9 kg	**3.3**	**[1.1 – 10.6]**
AUCtot within target range	1.82	[0.7 – 4.9]

Conclusion

This study confirms the importance of **TDM** and **PK-based dose individualization** for safe and effective Bu use prior to HSCT for all children and not only a restricted population as usually done. **However, further research is necessary to identify a PK criterion linked more specifically than AUC with VOD.**

[1] Nguyen et al. Bone Marrow Transplant 2004;33(10):979–87.

[2] Laboratory of Applied Pharmacokinetics. USC* Pack P.C. University of Southern California, School of Medicine, Los Angeles, CA, 1995.