

---

Symposium**[S-10] S-10: Progress of TDM for hematopoietic stem cell transplantation**

Chairs: Tomohiro Terada, Japan / Erik van Maarseveen, The Netherlands

Tue. Sep 26, 2017 10:30 AM - 12:00 PM Room D (1F)

(Tue. Sep 26, 2017 10:30 AM - 12:00 PM Room D )

**[S-10-4] Improved busulfan exposure in HCT: evaluating a decade of TDM experience in children and adults**Erik van Maarseveen<sup>1</sup>, Jurgen Langenhorst<sup>2</sup>, Jurgen Kuball<sup>3</sup>, Moniek de Witte<sup>4</sup>, JaapJan Boelens<sup>5</sup>, Charlotte van Kesteren<sup>6</sup> (1.UMC Utrecht, 2.University Medical Center Utrecht, 3.University Medical Center Utrecht, 4.University Medical Center Utrecht, 5.University Medical Center Utrecht, 6.University Medical Center Utrecht)

Keywords: busulfan, monitoring, oncology, stem cell transplantation, pharmacokinetics

**Background**

Busulfan (Bu) is a chemotherapeutic agent, used in conditioning before allogeneic hematopoietic stem cell transplantation (HCT). Prior research in children elucidated a relationship between pre-HCT area under the curve (AUC) of busulfan and transplantation outcome, with an optimum and narrow AUC between 80-100 mg\*hour/L. This yields the need for accurate and precise AUC targeting to this narrow exposure optimum. Pharmacokinetic studies to date focused on either adult or pediatric patients. In this study we aimed to build an integrated model where physiological development over the entire age range is allowed to describe pharmacokinetic (PK) changes. The second aim of the study was to evaluate our Bu TDM procedure over the past decade.

**Methods**

Concentration-time data of 304 patients aged 0 to 73 years receiving Bu-based (4 consecutive days) conditioning prior to HCT were used to develop a population(P) PK model using NONMEM. Model validation was performed using bootstrap, normalized prediction distribution error and a visual predictive check. The effect of TDM on the accuracy and precision of Bu exposure was evaluated by comparison of actual AUCs obtained with routine TDM-based dose adjustments with simulated AUCs without TDM-based dose correction. Finally, AUCs were simulated for dose adjustments using the newly developed model.

**Results**

A linear two-compartment model best described the data. Clearance and central volume of distribution were allometrically scaled to body weight; no other relevant covariates were found. Clearance diminished over time and this was included in the model. Validation demonstrated the robustness and adequacy of the developed model. Figure 1 shows TDM evaluation. Omitting TDM leads to adequate average targeting, with hazardous over- and underexposure. TDM-based dosing adjustments improved target attainment to 58% and 77% of patients for TDM with current protocol and the newly developed model, respectively.

**Conclusions**

A PK model was constructed describing integrated pediatric and adult Bu data. Importantly, TDM remains necessary to prevent hazardous under- and overexposure. In future TDM based dosing may benefit from more accurate and precise predictions using population PK models.