Application of the Optimal Design Approach to improve Therapeutic Drug Monitoring of Busulfan in Children receiving Hematopoietic stem cell transplantation (HSCT).

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[Objetivo]

Busulfan is the most commonly used agent in Hematopoietic stem cell transplantation (HSCT) conditioning regimes, given alone or in combination. Considerable inter-patient variability exists in the effectiveness and toxicity of busulfan-containing conditioning regimens. Therefore, personalizing Busulfan doses improves the clinical outcomes, and it is clinically accepted due to a narrow therapeutic window. The **objective** of this study was to find a design that minimizes the uncertainty of population parameters used for busulfan dose prediction.

[Metodos]

Data on 72 patients receiving Busulfan prior an HSCT (7 months-18 years, 5.1–47.0 Kg), suffering from immunodeficiencies or malignant diseases, was used to build a 2 compartment pharmacokinetic (PK) model of the drug. Busulfan (1-2 mg/Kg) was administered intravenously in a 2 or 3-hour infusion for four days prior HSCT, either every day, twice daily or every 6 hours. Blood samples to determine busulfan concentration in plasma were obtained prior the first administration, and 5, 10 and 30 minutes, 1, 2 and 4 hours after the end of the infusion. Once the PK model was built, a distribution of the population parameters was used in the optimization as prior information. The software PopED was used to perform optimal design of the sampling schedule. The covariates included in the PK model were taken into account in the optimization exercise (weight affecting the dose and the all the PK model parameters and age, affecting clearance).

[Resultados y Discusión]

The optimized design considered the three different administration schedules of busulfan, so there is only one protocol of sampling extraction independently from busulfan administration schedule. The optimized sample times that rendered best performance than the protocol times were: 15 minutes after the administration of the drug, and 5 minutes, 35 minutes, 1 hour and 45 minutes after the end of the infusion, and the last sample right after the next administration. Therefore, the new design represents a 16.6 % reduction (n=1) in sampling demanding with respect the

current protocol. The efficiency of the optimized design with respect to the protocol was calculated to be 2.84, indicating significantly better performance of optimized design.
The expected Residual Standard Errors (RSE%) of the parameters under the optimal designs were compared to the RSE% of the protocol, showing a reduction from 1 to 27% RSE in the parameters. In addition, prediction performance of the optimized design was evaluated, obtaining similar parameter precision compared to the protocol (maximum bias <10 %).

[Conclusiones]

An optimized sample times design for monitoring busulfan in pediatric patients under HSCT was developed. The evaluation of the reduced design suggests better performance than the original protocol, even reducing the samples per patient. We firmly believe that this work is of potential implementation in the clinical setting, improving patient care.