Pharmacokinetically-guided dosing of melphalan in children undergoing hematopoietic stem cell transplantation: a test dose approach using sparse optimal sampling

Kana Mizuno, Sharat Chandra, Tsuyoshi Fukuda, Junfang Zhao, Ashley Teusink-Cross, Stella M. Davies, Rebecca A. Marsh, M. Christa Krupski, Kenneth Setchell, ParindaA Mehta, Alexander A. Vinks

1.Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, 2.Cincinnati Children's Hospital Medical Center, 3.Cincinnati Children's Hospital Medical Center, 4.Cincinnati Children's Hospital Medical Center, 5.Cincinnati Children's Hospital Medical Center, 6.Cincinnati Children's Hospital Medical Center, 7.Cincinnati Children's Hospital Medical Center, 8.Cincinnati Children's Hospital Medical Center, 9.Cincinnati Children's Hospital Medical Center, 10.Cincinnati Children's Hospital Medical Center, 11.Cincinnati Children's Hospital Medical Center

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Background
High dose melphalan is widely used as part of standard curative therapy in children undergoing hematopoietic stem cell transplantation (HSCT), but is associated with severe toxicity especially in younger children. A pharmacokinetically (PK)-guided precision dosing strategy using a test dose with sparse sampling is an attractive approach to optimize the dose. Previously, we identified the 4 most informative sampling times (4OSS) in a melphalan PK study in adult patients. The objectives of this study were to explore the feasibility of a test dose strategy and validate our previously developed 4OSS in pediatric patients.

Methods
Patients were administered a test dose of 10% of the standard 140 mg/m² full dose or 4.7 mg/kg for children less than 10kg body weight, followed by the full dose. PK sampling included 4-10 timed samples per patient. PK data were collected in 24 patients (0.3-16.7 years). Individual PK parameters were estimated by non-compartmental analysis (WinNonlin 6.4) and Bayesian estimation (MW/Pharm ver. 3.82). The PK parameters estimated with the test and full dose were compared using regression analysis. The developed 4OSS was validated by comparing the area under the curve (AUC) estimates with the full and 4OSS data sets.

Results
A significant correlation between melphalan clearance estimates for test dose and full dose was observed ($R^2=0.78$; $p<0.001$). In addition, an excellent correlation was observed between the AUC obtained with the full and the 4OSS ($R^2=0.99$; $p<0.001$), suggesting that this sampling strategy is also applicable to children. In two patients with poor renal function and additional complications, the full dose was adjusted based on the test dose results. In both patients the predicted exposure very well matched the observed AUC.

Conclusions
This is the first study to show the feasibility of a melphalan test dose strategy using sparse optimal sampling as part of PK model-based precision dosing in HSCT children. This approach has a great potential to minimize toxicity and provide better clinical outcomes in children undergoing HSCT.