Population Pharmacokinetics of Busulfan in Children—Letter

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Appropriate busulfan dosing in children is a highly sensitive issue in the context of high-dose-conditioning regimens for bone marrow transplantation (BMT). Indeed, a therapeutic window of plasma exposure to busulfan [area under the curve (AUC) from 900–1,500 μmol/L min] has been defined both avoiding severe toxicities and ensuring efficient engraftment. The article by Trame and colleagues (1) in the November 1, 2011, issue of Clinical Cancer Research proposed a new individualized i.v. busulfan dosing in children, either based on body weight or body surface area, which was derived from the results of a population pharmacokinetics (PK) analysis.

The major concern is that this newly reported dosing by Trame and colleagues is much lower than that recommended in the approved European Medicines Agency (EMA) dosing and may consequently result in underexposure and thus in a dramatic increase of graft failure and decreased disease control.

To evaluate the magnitude of the discrepancy between the dosing reported in the study by Trame and colleagues and the EMA dosing, each dosing strategy was retrospectively applied to a large cohort of pediatric patients who had been treated with i.v. busulfan in earlier studies (2, 3) and from which the PK at dose 1 was fully determined. This test cohort comprised 205 children adequately distributed with respect to body weight (3.5–62.5 kg, median 9 kg) as well as biologic and disease (both malignant and nonmalignant) characteristics, who were thus representative of the high heterogeneity of children undergoing BMT after busulfan-containing regimens.

For each individual of the test cohort, the busulfan AUCs were calculated on the basis of each dosing strategy and the results were summarized by body weight groups. To gain more objectivity, another dosing strategy developed by an independent research group (4) was added into the comparison. This last dosing nomogram is currently recommended in ongoing European Group for Blood and Marrow Transplantation (EBMT) clinical protocols for primary immunodeficiencies in children (5). To enable reliable comparisons, the EBMT doses were adjusted to achieve the same target AUC value (1,200 μmol/L min) as that used with the 2 other dosing strategies. The results on the test cohort, as shown in Fig. 1, clearly indicate that both EMA and EBMT dosing strategies yield similar exposure within the therapeutic window in all body weight groups, whereas the strategy of Trame and colleagues exhibits a large amount of underexposure in children weighing 9 kg or above.

Forty-five percent to 75% of patients weighing 9 kg or above had an AUC less than 900 μmol/L min with the use of Trame’s dosing, whereas the targeting performance was adequate with the 2 other dosing nomograms, with 75% to 100% of patients reaching the AUC target. In Trame’s article, the authors stated that the clearances estimated by their model were significantly lower than those previously published and no explanation on such a difference was provided. Nevertheless, we feel that several limitations deserve further attention.

First, Trame’s model was developed on a mix of oral and i.v. busulfan series (total of 94 patients, 4.2–80 kg; median, 27.2 kg). The minority of data were collected in the i.v. series (40 patients) whereas the majority of data come from the oral series (54 patients) which is well known to be difficult to use as a model due to the large variability in drug absorption and bioavailability. Second, data were unbalanced with respect to the body weight groups, with only 5 children weighing less than 9 kg (2 of whom were treated by oral route). The limited sample size in this extreme body

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weight group may have markedly influenced the model shape. Third, the authors did not report any cross-validation process of the busulfan concentration measurement techniques between the different series. All these factors either combined or taken separately may have contributed to unreliable estimates of clearance by the model. In line with this aspect, the model estimated a bioavailability of almost 100%, an unexpectedly high value considering the well-established value of 80% in adults (6) and the known glutathione S-transferase (GST) metabolism upregulation in children which would rather limit their bioavailability.

To conclude, 3 dosing strategies, each one developed from independent research groups and data sets, were compared on a large and representative cohort of more than 200 patients.

The dosing suggested by Trame and colleagues was shown to significantly underexpose the children weighing 9 kg or more, whereas the EMA and EBMT dosing gave consistent and comparable targeted exposures. We feel that it is important to provide such comparisons for the prescribers involved in BMT to have a full scenario of the different dosing strategies and to make their own opinion.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interests were disclosed.
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