A Method for Accurate Estimation of AUC for Repeated Intravenous Infusions

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Busulfan (BU) has a narrow therapeutic window between efficacy and toxicity as well as other anticancer agents and immunosuppressants. Moreover, their pharmacokinetics exhibit wide inter-patient variability. Pharmacokinetic studies have suggested that individualization of BU doses based on the area under the curve (AUC) for plasma concentration time change is necessary to secure target BU systemic exposure.

However, standard pharmacokinetic measurements require multiple blood samples and are therefore impractical in usual clinical settings. To solve this problem, various limited sampling strategies (LSS) for the estimation of AUC have been proposed in which the number of blood samples necessary to estimate AUC was reduced to as few as possible. In this study, we propose a new LSS for repeated intravenous (IV) infusions of BU which is recently introduced.

Based on our clinical trials for BU, we estimated the distributions of the elimination rate constant, the volume of distribution and within-patient errors of log concentration by pharmacokinetic population analysis. To establish a new LSS for repeated BU IV infusions, we revised our concentration time curve database method [1], in which the best-fit curve is searched from the set of pre-calculated possible concentration time curves, so as to be applicable for various infusion parameters. Finally, the error of the AUC estimate, which is very essential to secure the actual exposure, was evaluated by Monte Carlo simulation based on the distributions of pharmacokinetic parameters.

We developed a new method which estimates AUC and its SD as a function of infusion time, infusion rate, time interval of repeated infusions and observed plasma BU concentrations at two to six sampling times. The Monte Carlo simulation showed that the estimation errors were less than 9% (in coefficient of variation (CV)).

To develop LSSs, multiple linear regression and the trapezium rule with approximation of the elimination phase by an exponential curve are frequently used. However, our Monte Carlo simulations showed that these LSSs are accurate but not precise in many cases (over 10% in CV). Contrary to these conventional methods, our new method was more precise and there was no cases in which CV was over 9 % in the first 6 hours.