

Dose Individualization for High-Dose Anti-Cancer Chemotherapy

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ABSTRACT

We discuss optimizing the dose of a preparative chemotherapeutic agent for a leukemia patient undergoing high doses of chemotherapy followed by bone marrow transplantation. The optimal dose minimizes the expected loss, where the loss is incurred when the area under the concentration-time curve (AUC) is outside the limits of a target range. We have historical pharmacokinetic (PK) data from leukemia patients who underwent similar high-dose chemotherapy. A subsequent study collected PK data on patients receiving a fixed low dose and a non-individualized high-dose of the drug. In the third study, patients will receive the same low dose as in the second study. We fit a PK model to the drug concentrations measured after administration of the test dose to infer patient-specific parameters in the PK model. We determine the optimal dose for this patient by averaging the loss function with respect to the predictive distribution for the patient's AUC with high-dose therapy as a function of dose. We use Bayesian nonparametric models and combine information across studies and patients within studies by hierarchical modeling, borrowing strength to improve the precision of the prediction.