

OPTIMIZING CANCER CHEMOTHERAPY ADMINISTRATION: EFFECT OF MODEL STRUCTURE ON TREATMENT COST AND EFFECT

**Mary Regina Boland¹ and Robert S Parker, PhD²*

1. Summer Intern, Pittsburgh Tissue Engineering Initiative;

*2. Department of Chemical and Petroleum Engineering, University of Pittsburgh; *Presenter*

A crucial component for effective chemotherapy treatment lies in the appropriate dosing of medications, otherwise known as drug dose scheduling, to provide the patient with maximum effect (i.e., tumor shrinkage) and minimum toxicity simultaneously. In the clinical setting, physicians are required to alter their treatment strategies based upon changes in patients' health that result from either the continued progression of the disease or adverse effects associated with the medication. 9-Nitrocamptothecin (9NC) is a preclinically active chemotherapy agent that bolsters the treatment of ovarian, breast, colon, and prostate cancers. A model that properly characterizes the drug's pharmacokinetics and pharmacodynamics (the effect of the body on the drug, and drug on the body as both efficacy and toxicity, respectively) would aid in the design and implementation of more effective dose administration. Consequently, our goal focused on the development and parameter estimation of a mathematical model that could both accurately describe the pharmacokinetic and pharmacodynamic profile of the drug as well as predict the response to varying administration schedules.

In order to construct this model, data from a prior mouse study was used. The maximum tolerated dose (MTD) of 9NC is 1.0 $\mu\text{g}/\text{kg}$; hence, data from the 1.0 $\mu\text{g}/\text{kg}$ dose level was used in identifying the model. A set of three linear ordinary differential equations, having 5 parameters, was used to describe the distribution of 9-Nitrocamptothecin throughout the three compartments that mathematically represent the body. Models were fit using ADAPT 5 (bmsr.usc.edu), a computer code specifically designed for pharmacokinetic / pharmacodynamic modeling, and MATLAB (The Mathworks). Model quality was evaluated using Akaike's

Information Criterion (AIC), which incorporates terms for model quality, based on sum of squared error in fitting the data, and model complexity as measured by the number of model parameters. The model's predicted parameter values were evaluated to determine whether or not they could be estimated with confidence from the data. Overall, the three-compartment model provided a good fit to the PK.

9-Nitrocamptothecin is the parent compound for the equally effective 9-Aminocamptothecin (9AC) that also inhibits topoisomerase I and slows or reverses cancer growth. The pharmacokinetic effects of 9AC were added to the 9NC model to provide a more complete model of the antitumor activity of 9NC **in vivo**. A pharmacokinetically-driven pharmacodynamics model of tumor growth and drug-induced cell kill was the final model constructed. Overall the model describes the pharmacokinetic and pharmacodynamic temporal response of 9-Nitrocamptothecin and its metabolite, 9-Aminocamptothecin. Model-based treatment design uses mathematical models to design drug administration profiles using optimization and systems engineering tools. The final step was to assess the impact of model quality and structure on the administration profile generated by the dosage advisor. A key tenet of model-based control states that model quality limits achievable controller performance [4]. However, the degree to which this is true in the cancer domain has not been studied. Our results show that, while model quality impacts the optimal solution, the clinical implementation may be less decisive.

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