Influence of Toxicity Effects on Model-Based Treatment Design for the Chemotherapeutic Docetaxel

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Introduction: Cancer is a collection of diseases resulting from a series of genetic mutations and is characterized by an imbalance between proliferation and cell apoptosis. Common modalities for treating cancer include surgical excision of the tumor mass, local exposure to radiation, or systemic administration of a chemotherapeutic agent. Whenever possible, the tumor mass will be removed, but the surgeon cannot be certain that all cancerous cells were excised, particularly if the cancerous mass has already become invasive. Also, by the time of initial tumor mass detection, undetectable metastases may have already spread to other remote body locations, motivating the use of a more systemic treatment. The scheduling of chemotherapeutic treatments, while extensively studied in an empirical fashion, has not been the subject of mathematical evaluation from an optimal scheduling standpoint in the clinical setting. The latter point is especially relevant given that chemotherapeutics also harm healthy proliferating cells, reducing patient quality of life and limiting treatment effectiveness.

Clinical studies focus on determining dose toxicity limits and drug efficacy. Throughout these trials, substantial data are obtained regarding plasma drug concentration, tumor volume progression, and toxicity. This data serves as a basis for constructing pharmacokinetic (PK) models for plasma drug distribution, typically through a compartmental approach; a more extensive data collection can motivate the development of complex, physiologically-based pharmacokinetic models. While pharmacodynamic (PD) responses are observed, clinicians are generally more concerned with the presence of a therapeutic effect rather than accurately modeling the mechanism or magnitude of action. Consequently, treatment schedules are often developed based on previous drugs with similar chemical structures or cellular targets and may not incorporate dynamics associated with drug effect. In addition, most studies collect plasma drug concentrations, but often fail to evaluate tumor drug exposure (*i.e.*, the drug concentration that drives tumor PD response). Instead, the PD effects included within tumor models are typically based on a predicted plasma drug concentration, an assumption that may lead to an over- or under-prediction of the actual drug effect.

Many authors have examined the chemotherapeutic dosing problem in a model-based control framework (examples include [1, 2]), employing constraints on inputs (*i.e.*, drug delivery) or states (*i.e.*, plasma drug concentration or body weight) to maintain drug administration within toxicity limits and having an objective function that minimizes the tumor volume at a prespecified final time point. These solutions predict a characteristic 3-phase treatment profile: maximum initial drug delivery; a non-dosing period; and the remainder of the drug delivered at the end of the treatment window. Ethically, however, a doctor cannot allow a tumor to grow untreated, thereby invalidating the controller formulation. In

addition, bulk dosing at the end of the cycle, instead of at the beginning, prohibits immediate future dosing. Dose schedule development, therefore, requires an alternative objective function to obtain clinically relevant scheduling results.

One possibility is direct inclusion of a toxicity measure within the model used for treatment design. A common toxicity, neutropenia, or a reduction in circulating neutrophil count, is a continuous and quantifiable measure available from patient plasma which is also monitored by physicians intermittently throughout therapy. Controllers that incorporate models for neutrophil proliferation, recovery, and drug effect [3, 4] can return drug dosing schedules that minimize patient neutropenia (possibly avoiding other toxicities as well) while simultaneously minimizing overall tumor volume.

The goal of the present work is to combine plasma and tumor concentration data from a docetaxel PK study with PD models for tumor regression and neutrophil response. These three models were combined and the various established docetaxel regimens were evaluated to assess overall model accuracy based on published toxicity patterns. Finally, a nonlinear model predictive controller (NMPC) was synthesized based on the PK and PD models and used to develop alternative dosing regimens capable of administering additional drug while maintaining clinically established dosing constraints.

Pharmacokinetic Model: Using pharmacokinetic data from the administration of the chemotherapeutic docetaxel, a linear physiologically-based pharmacokinetic model (PBPK) for drug distribution in mice was developed [5]. Docetaxel was administered intravenously at 10 mg/kg to female SCID mice bearing SKOV-3 human ovarian xenografts. Mice (n = 3) were euthanized at 0.083, 0.25, 0.5, 1, 2, 4, 6, 7, 18, and 24 hours after docetaxel administration. Docetaxel concentrations in plasma, tumor, liver, kidney, spleen, brain, heart, and lung were determined using an LC-MS assay. Diffusion-limited tissues (liver, brain, tumor, lung, and spleen) were characterized with tissue subcompartments, and perfusion-limited tissues (heart and kidney) were modeled using partition coefficients. Physiological parameters for organ blood flow rates were taken from the literature [6] while organ volumes were based on post-exsanguination organ masses (n = 33). Parameter estimation and structure selection was accomplished by sequentially adding tissues while minimizing the weighted sum of squares between the model predictions and collected experimental data.

Next, an equivalent PBPK docetaxel distribution model was constructed for humans. Blood flow rates and tissue volumes were adjusted based on literature values [6] and scaled for patient weights; intra-tissue exchange rates, liver clearance rate, and tissue partition coefficients were left unchanged. Resulting docetaxel plasma concentrations were then compared to clinically obtained patient docetaxel concentrations. Peak concentrations and initial drug elimination rate were underpredicted from the scale-up, though this was not unexpected as minimal alterations were made to the preexisting mouse PBPK model. Long-term decay of docetaxel plasma concentration, however, was captured using the model, and overall, the adapted mouse PBPK model is capable of representing clinical docetaxel plasma data from humans accurately. Improvements in the human PBPK model would be possible by adjusting parameters (*i.e.*, liver clearance), having mouse PK information which utilized a

longer docetaxel infusion time (> 5 seconds), or by incorporating a fat compartment within the PBPK structure as docetaxel is highly lipophilic and fat percentage is a highly varying parameter in humans.

Model reduction tools were employed on the human PBPK in order to aid subsequent controller synthesis. As the primary toxicity associated with docetaxel treatment is neutropenia and tumor regression depends on tumor drug exposure, it was necessary to maintain accurate predictions for plasma and tumor drug concentrations. Retention of five states was necessary for accurate predictions as shown in Figure 1.

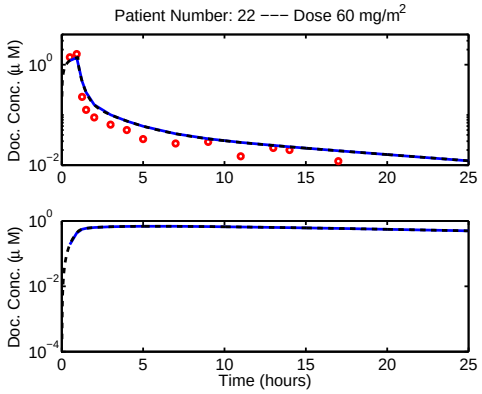

Figure 1: Top: Plasma concentration data from a patient receiving a 60 $\frac{\text{mg}}{\text{m}^2}$ infusion of docetaxel over 1-hour (circles) along with the full (solid) and reduced (dashed, overlay on solid) model plasma concentration predictions. Bottom: Full (solid) and reduced (dashed, overlay on solid) model predictions of tumor concentration.

Pharmacodynamic Models: The reduced PK model was coupled to either a Gompertz tumor growth model:

$$\frac{dN}{dt} = \frac{1}{\tau} N \ln\left(\frac{\theta}{N}\right) - k_{DG} N \left[C_{DT}\right] \tag{1}$$

or a saturating-rate cell-cycle model (SCM):

$$\frac{dX_G}{dt} = -k_{GS} X_G \ln\left(\frac{\theta}{N}\right) + 2k_{MG} X_M \ln\left(\frac{\theta}{N}\right) \tag{2}$$

$$\frac{dX_S}{dt} = -k_{SM} X_S + k_{GS} X_G \ln\left(\frac{\theta}{N}\right) \tag{3}$$

$$\frac{dX_M}{dt} = -k_{MG} X_M \ln\left(\frac{\theta}{N}\right) + k_{SM} X_S - k_{DSCM} X_M \left[C_{DT}\right] \tag{4}$$

$$N = X_G + X_S + X_M \tag{5}$$

to assess tumor regression during drug administration. The Gompertz equations contain two growth parameters, $\frac{1}{\tau}$ and θ, depicting the pseudo-doubling time of the tumor and plateau

population of the tumor, respectively; N is the volume of the tumor. For the SCM, X_i corresponds to the volume of cells in the G (growing), S (DNA synthesis), or M (mitosis) phases, k_{ij}'s denote transfer rates from cell phase i to phase j, and θ is defined as above. Drug effect is incorporated as a bilinear term, dependent on the concentration of docetaxel in the tumor, $[C_{DT}]$, the population of susceptible cells (N for the Gompertz model; X_M for the SCM), and a drug effect constant (k_{DG} for the Gompertz model; k_{DSCM} for the SCM). As docetaxel is an M-phase specific agent, drug effect for docetaxel was incorporated within the M-phase for the SCM model while docetaxel drug effect was included as a bulk effect in the Gompertz model.

In addition, a neutrophil model was incorporated as a measure of docetaxel dosing schedule toxicity. The model was developed by Friberg *et al.* [4] for representing neutrophil response following administration of various chemotherapeutics, one of which was docetaxel. The model consists of five differential equations with cell proliferation occurring in compartment 1, maturation occurring in compartments 2-4, and circulating neutrophil count represented by compartment 5. Drug effect was limited to compartment 1 and recovery was influenced by the ratio of circulating neutrophils to a normal baseline neutrophil value. Parameters were adjusted from literature values based on the neutrophil data provided for 25 patients. Model predictions along with actual neutrophil count data for one patient are shown in Figure 2.

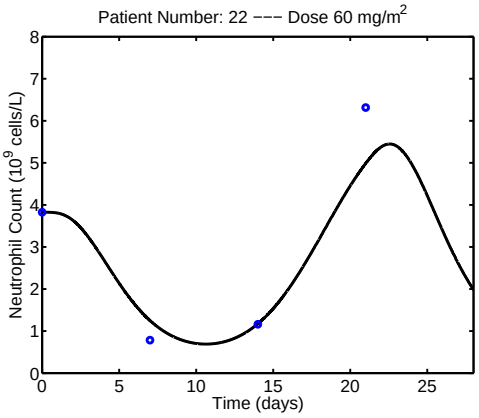

Figure 2: Neutrophil count data from a patient receiving a 60 $\frac{\text{mg}}{\text{m}^2}$ infusion of docetaxel over 1-hour (circles) every three weeks along with model predictions for neutrophil count (solid).

Dose Schedule Development: During each cycle (12-week period), the objective function was set to maximize total drug delivered subject to maintaining patient neutrophil counts within accepted toxicity limits. If a patient has a measured neutrophil count $< 0.5 \times 10^9$ cells/L, treatment will be discontinued (NIH Grade 4 neutropenia toxicity). Similarly, if the patient has consecutive weekly measured neutrophil counts $< 1.0 \times 10^9$ cells/L, drug doses would be reduced or treatment would be discontinued (Grade 3 neutropenia). NMPC algorithm results using the above dosing constrains and $m = 1$, $p = 2$, are shown in Figure 3

(dashed line). In addition, algorithm results based on Grade 2 and Grade 3 neutropenia toxicity constraints are shown, along with neutrophil profiles predicted by two typical docetaxel administration schedules (1-hour infusions once every three weeks or 1-hour infusions for three weeks followed by one week off).

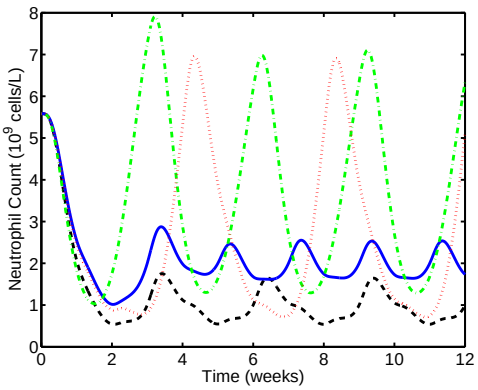

Figure 3: Neutrophil predictions under four separate dosing regimens: 60 $\frac{\text{mg}}{\text{m}^2}$ every three weeks starting on week 0 (dash-dot); 35 $\frac{\text{mg}}{\text{m}^2}$ for three weeks, then one week off starting on week 0 (dotted); dosing constrained to maximize delivered drug subject to medical Grade 3 and 4 toxicity constraints (dashed); and dosing constrained to maximize delivered drug subject to medical Grade 2 and 3 toxicity constraints (solid). (circles) every three weeks along with model predictions for neutrophil count (solid)

Overall, the model-based algorithm incorporates clinically relevant dosing constraints and returns clinically viable treatment schedules.

References

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