Computational modeling of schedule-specific chemotherapy outcomes in mouse tumor model

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Abstract. Despite the rapid development of new innovative strategies in cancer treatment like immunotherapy, chemotherapy still remains a common choice in many cases. Standard protocols of chemotherapeutic administration rely on a maximal tolerated dose paradigm, however there is growing evidence that this approach is not always optimal. Alternative scheduling, like metronomic - low dose continuous drug administration - were recently proved their efficacy. The space of available variants of drug administration protocols is prohibitively large to be explored empirically, and there is an urgent need of predictive mathematical models for rational chemotherapeutic scheduling design. In this work we tested the ability of the minimal pharmacokinetic-pharmacodynamics model to describe schedule-specific tumor volume time evolution in different mouse tumor models.

1. Introduction

In the standard maximal tolerated dose (MTD) protocol, chemotherapeutics are administered in high doses with the aim to affect the maximal number of cancer cells. However, in some cases this does not lead to tumor eradication and the drug-resistance emerges. Alternative approaches were recently proposed, like metronomic chemotherapy (MC), which consists in low dose continuous drug administration [1]. MC is characterized with lower side effects while demonstrating promising efficacy. Tumor growth deceleration during MC therapy is attributed to anti-angiogenic, immunostimulation and cytostatic effects, which all take a minor role compared to direct toxicity in high dose MTD [1,2]. This diversity of biological mechanisms involved complicates the rational design of the optimal chemotherapeutic administration protocols in MC.

To date several predictive computational models have been developed to assist schedule optimization of MC protocol, because the huge number of possible variants makes empirical search impractical. Many of these rely on the pharmacokinetic-pharmacodynamics (PK/PD) modeling approach, which computationally links drug concentration in the body with its therapeutic action [2,3]. Such models were successfully applied in some cases [2,3,4], however they often contain a large number of adjustable parameters, and uncertainties in their estimation limits the model performance. Previously we developed the PK/PD Minimal model that is defined by a minimal set of parameters, which is sufficient to capture schedule-specific outcomes [5]. In this work we test performance and transferability of the Minimal model on the data for mice bearing different tumor types.
2. Materials and Methods

In this work two different tumor models were used, namely Ehrlich ascites carcinoma model in SHR mice (2.5 10^6 cells per mouse) and the model of colon cancer - CT26 in Balb/C mice (0.5 10^6 cells per mouse). Gemcitabine in different scheduling was used, as it is a chemotherapeutic known to be effective in MC [5]. For each tumor model, mice were divided into four groups: Control, MTD (25 mg/kg i.p.), MC (0.5 mg/kg i.p daily, 50 days) and Comb (combined protocol: 25 mg/kg+0.5 mg/kg daily). All animal experiments were approved by the local animal ethics committee in accordance with institutional guidelines for the welfare of animals ("N.N. Petrov National Research Center of Oncology", St.Petersburg, Russia).

General scheme and differential equations of the Minimal model are depicted in the bottom panel of figure 1. Unperturbed growth is defined by the linear model with three parameters (λ0, λ1 and Ψ), among which one is fixed (Ψ=20) and the remaining two together with the value of initial volume V0 were obtained by the model fit to mean tumor volume data in untreated group. Anti-tumor drug action in the Minimal model is coupled to the on-site effective drug concentration (Ceff(t)) and defined by direct cytotoxicity (k) and antiangiogenic effect (IC50). Parameter α in the second equation (figure 1) describes drug partitioning rate between plasma concentration (C(t)) and effective compartment concentration (Ceff(t)). These three parameters (k, IC50, α) together define drug action and are typically obtained by model fitting to tumor volume data in specific treatment groups.

\[
\frac{dV}{dt} = \frac{\lambda_0 \cdot V}{[1 + (\lambda_0/\lambda_1) \cdot V]^{\Psi}} \left( \frac{IC_{50}}{C_{eff}(t) + IC_{50}} \right) - k \cdot C_{eff}(t) \cdot V
\]

\[
\frac{dC_{eff}(t)}{dt} = -\alpha \cdot (C_{eff}(t) - C_{Gem}(t))
\]

**Figure 1.** Treatment protocols applied in the experiments (top) and basic description of the Minimal model (bottom).
3. Results and discussion

Previously we have shown that the Minimal model is able to efficiently and simultaneously describe tumor response of MTD and MC gemcitabine based on Ehrlich carcinoma mouse model data [5]. Here we systematically test and compare the model results on the data of two different mouse tumor models (Ehrlich carcinoma and CT26) subjected to the same treatment protocols (see figure 1 top panel). It is known that plasma gemcitabine concentration follows a one compartment pharmacokinetic model, whose parameters were obtained by fit to experimental data from ref. [7]. For each tumor model firstly parameters of unperturbed growth were obtained by the weighted (1/y) non-linear least square fit of the model to the time evolution curve of mean volume (see table 1, λ_0 , λ_1 ,V_0). With these parameters for free tumor growth the model was either simulations fitted to the data from MTD and MC groups or fitted to data from Comb group to obtain parameter estimates (see table 1. k, IC_{50}, α). With parameters from each model fit tumor volume time evolution was simulated for all treatment protocols. Resulted time curves together with experimental data points are presented in figure 2 and 3.

For Ehrlich carcinoma with parameters from simultaneous fit to MTD and MC data the model well reproduces experimental data trend of combined protocol (figure 2 B). Conversely, when fitted to Comb data the model successfully predicts trends for MTD and MC protocols (figure 2 C, D). These results demonstrate that the antitumor effect of gemcitabine is adequately described by the mathematical form of the Minimal model as we have shown in detail previously [5]. It should be noted that fit results presented here slightly differ from those published in [5] due to slight fitting protocol difference.

![Figure 2](image_url)

**Figure 2.** Ehrlich carcinoma data modeling. Lines - simulated curves. Circles - Control, triangles -MTD, squares - MC, diamonds - Comb.

Results of the analogous fitting procedure in case of CT26 tumor model are presented in figure 3. When parameters are obtained by the simultaneous model fit to MTD and MC data, the model adequately predicts trend for Comb protocol (figure 3 B), as in the previous case. Value of root mean square deviation (RMSE) for simulated Comb curve is even less than that for MTD and MC groups which were fitted in this case (see table 2). When the model is fitted to the Comb group data (figure 3 C, D), the predicted tumor volume curves go close to the experimental points of MTD and MC schedules. While it seems that the predicted curve for MTD scheduling becomes parallel to Control data too early, the curve lies within the uncertainty region and corresponding RMSE does not exceed the value for intrinsic experimental data variation (see table 2). The above observations for CT26
tumor (figure 3) are qualitatively the same as for Ehrich carcinoma (figure 2). Taken together these results indicate that the Minimal model is valid for description of outcomes of different gemcitabine scheduling in different tumor models.

**Figure 3.** CT26 tumor data modeling. Lines - simulated curves. Circles - Control, triangles - MTD, squares - MC, diamonds - Comb.

Parameter values for description of unperturbed growth are accurately estimated (with low coefficient of variance CV, table 1) and differ for Ehrlich and CT26 tumor models, as expected. Model fit to Comb data or simultaneous fit to MTD and MC data resulted in slightly different but close parameter estimates in case of Ehrlich carcinoma. In case of CT26 tumor estimate of parameter $k$ tends to zero in simultaneous fit, while converges to non-zero value with large CV when model is fitted to Comb data (table 1). It seems that the cytotoxicity term ($-k C_{eff}(t)$) may be unimportant in this case.

**Table 1.** Parameter estimates.

|                      | fit to Control | fit to MTD and MC | fit to Comb |
|----------------------|----------------|-------------------|-------------|
|                      | Param.         | Values (CV(%))     | Values (CV(%)) | Values (CV(%)) |
| Ehrlich carcinoma    | $V_0 [cm^3]$   | 0.036 (27)         | 0.28 (18)    | 0.43 (11)   |
|                      | $\lambda_0 [1/day]$ | 0.40 (11)    | 0.48 (4)     | 0.58 (30)   |
|                      | $\lambda_1 [cm^3/day]$ | 0.24 (4)    | $IC_{50} [\mu M]$ | 0.0059 (5) | 0.0048 (7) |
| CT26 tumor model     | $V_0 [cm^3]$   | 0.048 (12)         | 0.00 (N/A)   | 0.041 (326) |
|                      | $\lambda_0 [1/day]$ | 0.23 (6)     | $IC_{50} [\mu M]$ | 0.0231 (16) | 0.0234 (26) |

The Minimal model is able to describe tumor response to a different scheduling for both tumor models. Because the model prediction looks qualitatively similar for such a different experimental setting like Ehrlich carcinoma and CT26 tumor, we may conclude that the mathematical components of the model capture universal gemcitabine biological effect. Surprisingly, for both Ehrlich and CT26
tumors when the model is fitted to Comb data, predictions for other schedules are characterized by relatively low RMSE comparable with intrinsic data variance (table 2). Parameter estimates with which the model best describes the data differs in case of Ehrlich or CT26 tumor. This is not surprising because the tumor growth in Control groups differs in these two cases (cf. figures 2 and 3 and table 1). We expect that there may be a relationship between parameters for unperturbed tumor growth and parameters for anticancer drug action. The ability to estimate the treatment response based on the native tumor growth data with such a relationship will substantially increase transferability of the Minimal model results in preclinical settings and may be a promising tool for future personalized medicine. Further work with various tumor mouse models is needed to establish such interrelations.

| Table 2. Goodness of fit estimation. |
|-------------------------------------|
| RMSE [cm$^3$] | Control | MTD | MC | Comb |
| fit to MTD and MC (Ehrlich carcinoma) | 143.4 | 117.7 | 74.2 | 240.0 |
| fit to Comb (Ehrlich carcinoma) | 143.4 | 186.6 | 209.5 | 86.5 |
| Exp.$^a$ (Ehrlich carcinoma) | 233.3 | 226.5 | 246.7 | 211.1 |
| fit to MTD and MC (CT26 tumor model) | 122.6 | 132.6 | 100.4 | 76.0 |
| fit to Comb (CT26 tumor model) | 122.6 | 276.3 | 101.0 | 58.0 |
| Exp.$^a$ (CT26 tumor model) | 272.6 | 285.0 | 174.6 | 246.7 |

$^a$ Experimental RMSE are estimated as a root of mean square standard deviations of mean tumour volumes

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