Optimisation of chemotherapy dosage under antiangiogenic treatment: preventing chemotherapy resistance

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Abstract. A mathematical model of heterogeneous tumor growth under angiogenic signaling is considered in this study. Cancer chemotherapy is formulated under the Norton-Simon hypothesis as an optimal control problem with non-standard objective functional. Extending patient's survival time by means of preventing drug resistance is the main therapeutic goal. Using mathematical modeling and optimal control techniques we investigate the hypothesis that lower doses of chemotherapy may be beneficial for patients. It supports clinicians in choosing the right chemotherapy protocols.

Introduction

Based on Hahnfeldt et al. model [1], we formulate a mathematical model of tumor growth under angiogenic signaling adapted to heterogeneous tumors treated by combined antiangiogenic agent and chemotherapy. We assume that the tumour cell population is heterogeneous and can be divided into two compartments that differ in their sensitivity to chemotherapy: sensitive (N_1) and resistant (N_2). The effect of the chemotherapeutic drug on the sensitive cells in response to treatment is assumed to be directly proportional to the tumour growth rate at the time of treatment. The above assumptions lead to the following system of differential equations:

$$\begin{aligned} \dot{N}_1 &= -\left(\lambda_1 - \beta_1 u(t)\right) N_1 \ln\frac{N_1+N_2}{K} - \tau_1 N_1 + \tau_2 N_2, \quad \dot{N}_2 = -\lambda_2 N_2 \ln\frac{N_1+N_2}{K} + \tau_1 N_1 - \tau_2 N_2, \\ \dot{K} &= -\mu K + b(N_1+N_2) - d(N_1+N_2)^{2/3} K - \beta K u(t) - \gamma K v(t), \end{aligned} \tag{1}$$

where $u(t)$ and $v(t)$ are chemotherapy and anti-angiogenic treatment doses at time t, respectively; τ_1 and τ_2 are mutation rates; λ_1 and λ_2 are proliferation rates; β_1 is a parameter describing the sensitivity of the tumour to the chemotherapeutic agent; β and γ are sensitivity rates of the vasculature to the chemotherapeutic and anti-angiogenic agents, respectively; μ is a natural death rate of endothelial cells; b is a vascular growth rate stimulated by cancer cells and d is a vascular inhibition rate by cancer cells. Derivation of the equation for K and detailed descriptions of parameters can be found in the original article [1].

Results and discussion

The optimal control problem is as follows: find a measurable function $u : [0,T] \to [0,1]$ for a given fixed terminal time T, which minimizes the functional

$$J(u) = \omega_1 N_1(T) + \omega_2 N_2(T) + \int_0^T \left(\eta_1 N_1(t) + \eta_2 N_2(t) + \frac{\xi}{2}\left(1 + \tanh\left(\frac{N_2 - N_1}{\epsilon}\right)\right) + \theta u(t)\right) dt,$$

under the dynamics of System (1). Here, parameters ω_1, ω_2, η_1, η_2, ξ and θ are nonnegative weights, while ϵ is a positive weight. The non-standard term is included to penalize time period during which the tumor is resistant, i.e. it consists of more resistant than sensitive cells (see [2, 3]).

Changing the therapeutic target from tumor eradication to maintenance treatment, we show that in the short term optimal chemotherapy scheduling consists mainly of administering a low dose of the drug (Fig. 1). It supports the hypothesis that metronomic therapy is an attractive alternative to maximum tolerated dose therapies.

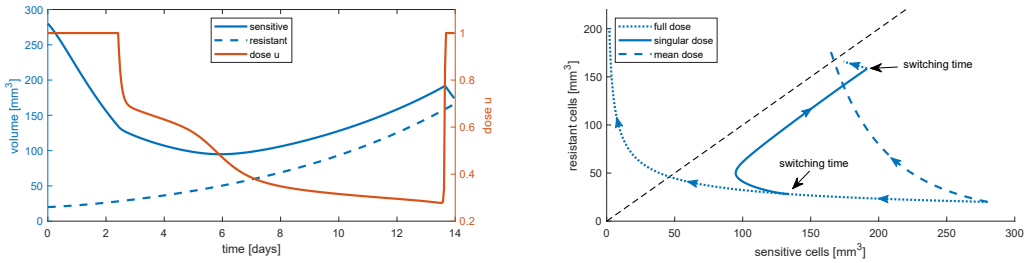

Figure 1: Optimal solution with corresponding optimal control (left) and trajectories: comparison between optimal, full-dose and mean-dose protocols (right). Full-dose and mean-dose protocols lead to acquired drug resistance.

References

[1] Hahnfeldt P., Panigrahy D., Folkman J., Hlatky L. (1999) Tumor development under angiogenic signaling: A dynamical theory of tumor growth, treatment response, and postvascular dormancy. *J. Cancer Research* **59**:4770–477.

[2] Bajger P., Bodzioch M., Foryś U. (2019) Singularity of controls in a simple model of acquired chemotherapy resistance. *Discrete and Continuous Dynamical Systems Series B* **24**:2039–2052.

[3] Bodzioch M., Bajger P., Foryś U. (2021) Angiogenesis and chemotherapy resistance: optimizing chemotherapy scheduling using mathematical modeling *Journal of Cancer Research and Clinical Oncology* **147**:2281–2299.