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Understanding the antiangiogenic effect of metronomic chemotherapy through a simple mathematical model

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HIGHLIGHTS

- A mean field model for antiangiogenic chemotherapy is proposed.
- Metronomic and maximum-tolerated schedules are compared by numerical simulations.
- Metronomic schedules are found to be more effective in eliminating tumour cells.

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ABSTRACT

Despite the current and increasingly successful fight against cancer, there are some important questions concerning the efficiency of its treatment — in particular, the design of oncology chemotherapy protocols. Seeking efficiency, schedules based on more frequent, low-doses of drugs, known as metronomic chemotherapy, have been proposed as an alternative to the classical standard protocol of chemotherapy administration. The *in silico* approach may be very useful for providing a comparative analysis of these two kinds of protocols. In so doing, we found that metronomic schedules are more effective in eliminating tumour cells mainly due to their chemotherapeutic action on endothelial cells and that more frequent, low drug doses also entail outcomes in which the survival time of patient is increased.

1. Introduction

Cancer is considered a serious public health problem worldwide. One of the most commonly applied types of cancer treatment, antineoplastic chemotherapy, consists of the administration of one or more cycle-nonspecific or cycle-specific drugs whose aim is to destroy tumour cells. In general the aim of cancer therapies, including chemotherapy, is to maximize the therapeutic effect on tumours and minimize side effects on normal cells. Despite the advances in chemotherapy in recent decades, there lacks a better quantitative understanding of its mechanism. In order to improve and clarify how chemotherapy works, one can use mathematical modelling, for example, to design oncologic chemotherapy protocols (Panetta & Fister [1]). Moreover, as we claim in this paper, mathematical modelling (as well as the *in silico* approach) may improve the comprehension of the antiangiogenic effect of metronomic chemotherapy.

Several methods have been employed to build mathematical models of tumour growth, such as ordinary and partial differential equations (Gatenby [2], Byrne & Chaplain [3] and Chaplain et al. [4]), cellular automata (Moreira & Deutsch

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et al. [5]), optimization (Panetta & Fister [1]) and multi-scale modelling (Stamatakos et al. [6], Macklin et al. [7] and Owen et al. [8]). Whatever approach is adopted, the combination of theory and data certainly provides the best results (Komarova [9]), where experiments guide theoretical models, and theoretical models lead to experiment(s) (Byrne et al. [10] and Araujo & McElwain [11]). From this viewpoint, we develop, in this study, a simple mathematical model of tumour growth under chemotherapy, which was motivated by the biological experiment reported by Browder and collaborators [12]. Our aim is to describe and simulate the antiangiogenic character of an alternative chemotherapy protocol, with more frequent low drug doses per cycle, usually referred to as metronomic chemotherapy (Hanahan et al. [13] and Kerbel & Kamem [14]).

Mathematical models (Hahnfeldt et al. [15] and Pinho et al. [16]) have been built to analyse a very relevant phenomenon for tumour growth extensively studied by Folkman's group [17]: tumour angiogenesis as well as antiangiogenic therapies for vascular tumours. The formation of new blood vessels (from a previous vascularization) due to the proliferation, migration and differentiation of endothelial cells that encase the blood vessels (Bikfalvi [18]) is essential for tumour growth after it reaches a diameter of 1–2 mm (vascular stage), and then the vascular stage is triggered by an angiogenic switch (Folkman [19]). This process induces a synthesis of several substances that stimulate the proliferation of new endothelial cells (Bussolino et al. [20]), which are not counterbalanced by small amounts of inhibitors (O'Reilly et al. [21]).

The inhibition of tumour angiogenesis may be promoted by antiangiogenic (non-chemotherapeutic) drugs or by the chemotherapeutic drug itself adopting, in comparison to standard protocols, more frequent, low-doses per cycle (metronomic chemotherapy). Using such a schedule of chemotherapy, Browder et al. [12] reported the elimination (drug-sensitive tumours) or reduction (drug-resistant tumours) of Lewis lung carcinoma in mice, which did not occurr when a standard protocol was employed. Moreover, in some preclinical studies, metronomic chemotherapy is used to increase the survival time for human life (Bello et al. [22] and Man et al. [23]); for those, the cumulative drug doses are higher than those in standard schedules (keeping, however, the dose per infusion lower).

Baruchel & Stempak [24] emphasize that metronomic protocols opened a new field of research and possibilities for patient treatment, but there are some questions related to the antiangiogenic efficiency of metronomic chemotherapy, such as its clear definition, the definition of optimum biological drug doses and the design of clinical trials. To corroborate Baruchel & Stempak [24], Lien et al. [25] argue that low-dose metronomic chemotherapy can control tumour growth rate safely, but there are inconclusive phase III trial results so drug doses and intervals of drug infusion are empirical.

Motivated by both the reported experiments using metronomic chemotherapy and the open questions posed by Baruchel & Stempak [24] and Lien et al. [25] related to its antiangiogenic efficiency, we intend to ascertain which features of that schedule are relevant to promoting a significant reduction in tumours. Our simple ordinary differential equation model simulates the administration of a chemotherapeutic cycle-nonspecific drug on a tumour, which is considered a homogeneous population of normal and tumour cells. Besides the competition between normal and tumour cells and the chemotherapeutic action on both of them, the model takes into account the chemotherapeutic action on vascular endothelial cells as well as the effect of angiogenesis on the carrying capacity of tumour cells. Our main purpose here is to compare one standard protocol of chemotherapy (which we will call the conventional schedule from now on) with metronomic chemotherapy, focusing on the antiangiogenic efficiency of metronomic chemotherapy in preventing tumoural neovascularization. We shall also address the effect on survival time entailed by metronomic chemotherapy.

The current paper is organized as follows: in Section 2, we present the model and some restrictions on its parameter values. In Section 3, we discuss the response of chemotherapy action according to the model; the numerical results of administration in cycles, simulating scenarios of standard and antiangiogenic protocols, showing in the latter an increase of both survival and log-kill reduction in tumour size. The limit case of continuous drug infusion is also discussed in Section 3 and analytically studied in the Appendix. Finally, Section 4 closes the paper with concluding remarks.

2. The model

We consider a compartment model formed by four nonlinear ordinary differential equations (ODE) whose compartments are normal cells, tumour cells, vascular endothelial cells and chemotherapeutic agent. Within the modalities of chemotherapy, we address one cycle-nonspecific drug under varying protocols: the standard protocol and the metronomic schedule (smaller cycle time intervals T and lower dose-per-infusion than the conventional schedule) and the limit case of continuous drug infusion (*i.e.*, not in bolus). Some parameter values of the model are based on experimental data for human tumours.

Although the angiogenic process inherently involves a spatial structure fully and explicitly analysed by partial differential equations (PDE) models (Chaplain et al. [4]), we consider the valuable approach of Hahnfeldt et al. [15] (see also d'Onofrio & Gandolfi [26,27]). In it, a diffusion-like PDE for the factors that stimulate and inhibit tumoural angiogenesis is carefully reduced to an ODE in time that models the proliferation of vascular endothelial cells. Essentially, the modelling presented by Hahnfeldt et al. [15] and d'Onofrio & Gandolfi [26] are used here to build a simple model which extends one of our previous models [28] by explicitly considering the compartment of endothelial cells as described in the sequel.

Tumour angiogenesis is represented in the model by the increase in carrying capacity of the tumour cells due to neovascularization. Namely, as we will present later, the increasing of the carrying capacity is directly related to the number of the vascular endothelial cells. To define the equation for vascular endothelial cells, as in Hahnfeldt et al. [15], we essentially consider the net production of both proangiogenic and angiogenic inhibition factors (Maggelakis [29]). The action of macrophages stimulating the release of angiogenic factors as well as the role of pericites in inhibiting the proliferation of