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A chemotherapy combined with an anti-angiogenic drug applied to a cancer model including angiogenesis

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ABSTRACT

Combined therapy made of a chemotherapy and antiangiogenic agents is a clinical treatment recommended for its efficiency. Since the optimization of a treatment against cancer relasp is still mostly based on oncologist's know-how, it is desirable to develop different approaches for such a task. Mathematical modelling is one of the promising ways. We here investigated the action of a combined therapy inserted to a mathematical cancer model in order to determine how the dynamics underlying tumor growth is governed by some key parameters. We here retained a chemotherapy (for instance, paclitaxel and carboplatin) combined with an antiangiogenic drug (as bevacizumab) applied to a cancer model describing the interactions between host, immune, tumor and endothelial cells. The effects of such a therapy are investigated and the relevant role played by the "normal" tissue of the tumor micro-environment is evidenced.

1. Introduction

According to a report by the National Cancer Institute, roughly 40% of humans develop a cancer during their lifetime [1]. For instance, in Australia, 254,000 potential years of life were estimated to be lost each year due to cancer-induced death before the age of 75 years [2]. Currently, cancer causes 29% male and 25% female deaths. To reduce this deleterious outcome induced by cancer, oncologists use several kinds of treatments like surgery, radiotherapy, immunotherapy, chemotherapy, anti-angiogenic drugs, etc. In spite of this, the rate of cancer-induced deaths for males only decreased annually by 1.8% between 2007 and 2011, and remained nearly constant for females between 1998 and 2011 [3].

Among different therapies, immunotherapy harnesses the immune response to recognize and to control malignant tumors [4,5], mostly because it is known that anti-tumor activity can be enhanced by stimulating immune cells [6,7]. Nevertheless, it is also known that tumor cells, when a cancer is diagnosed, may be already resistant to immune elimination and an immunotherapy is not efficient against tumor progression [8,9]. Immunotherapy is thus only able to cure a rather limited number of patients with advanced cancers whose micro-environment was not immunosuppressive. To overcome this limited success, chemotherapy is often applied but this is not always a successful strategy since, as any other therapy, it also kills a large amount of normal cells and has many side effects. Chemotherapy remains therefore a challenging topic of research to improve not only the selectivity of such treatment but also its efficacy with a reduced number of side effects [11]. Although medical studies can distinguish different mechanisms responsible for tumor growth [12], the mathematical analysis of realistic cancer models is also one of the possible ways to understand the dynamics underlying tumor growth [13–15]. Moreover, there is not yet a sufficient understanding in the interactions between a tumor and its micro-environment [10] and only very few cancer models were devoted to these interactions.

When a cancer is in an advanced stage, metastasis can occur. Metastasis result from complex processes according which malignant cells from a primary tumor can be spread at distant sites. Such a feature requires new blood vessels, created from the pre-existing ones to improve the transport of nutrients and oxygen to tumor cells [16]. This process, named angiogenesis, allows tumor cells to circulate in the whole vascular system. When it is limited, angiogenesis may be responsible for in tumor dormancy [17–21]. Contrary to this, when it is well developed, the neoangiogenesis and its related metastatic spread is clearly a deleterious process to avoid since almost 90% of patients with a cancer die when

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it is detected [22]. Although many works were performed to understand the biology of metastatic cancer, its global mechanism still remains poorly explored [23].

Since the introduction of an anti-angiogenic cancer therapy by Folkman [16], some drugs were developed for preventing tumor cells to stimulate the generation of new blood vessels but it questioned whether or not most of cancers can be efficiently treated by using antiangiogenic therapies [24–26]. Among the mediators encountered in angiogenesis, the vascular endothelial growth factor (VEGF) is the most commonly recognized for controling it. Consequently, one of the possible therapies is to inhibit VEGF as done by the first effective antiangiogenic drug, namely the bevaczumab [27,28]. Today, this antiangiogenic drug is often combined with a cytotoxic chemotherapy whose objective is to kill tumor cells [29]. As in any chemotherapy, host cells are also affected by the treatment and combining it with an antiangiogenic drug allows to significantly improves the treatment without additional side effects. Several mathematical models were constructed to investigate the treatment response to antiangiogenic drugs [30–32] but these models take into account the sole interactions between tumor and endothelial cells and not those with the tumor micro-environment. Two other models only investigate the angiogenesis without treatment [33,34]. The advantage of combined therapy was not investigated with the help of a cancer model describing the interactions with the micro-environment (host cells).

Most often, only interactions between tumor and immune cells are taken into account [35–41], sometimes with some therapies [42–45]. Although a cancer is necessarily always initiated by some "normal" cells which mutated into tumor cells [46–48], cells from the healthy tissue in the tumor micro-environment could have a major role in tumor progression [49]. This can be taken into account by considering the interactions of tumor cells with the so-called "host" cells in tumor growth [50,51]. As previously discussed, since the most deleterious cancers necessarily involve angiogenesis, we also took into account endothelial cells. We therefore used the model recently proposed by Viger et al. [52] as an extension of the model introduced by de Pillis and Radunskaya [51], and in which endothelial cells were included. The aim of the present work was thus to use this rather complete model for investigating the effect of a therapy combining paclitaxel-carboplatin with bevacizumab [29] and which is quite often used in current clinical practices.

The subsequent part of this paper is organized as follows. Section 2 introduces the four-dimensional model for describing the interactions between host, immune, tumor and endothelial cells in which the action of a chemotherapy combined with antiangiogenic drugs is introduced. Section 3 is devoted to a stability analysis of the singular points of the model and Section 4 presents some numerical simulations of different scenarii, that is, of few different "patient conditions" and few different strategies for treatment. Section 5 provides a discussion and some conclusions. Appendix A provides an observability analysis of the model.

2. Model

De Pillis and Radunskaya proposed a model which presents the advantage to consider normal tissue micro-environment, the so-called "host cells", interacting with immune and tumor cells [45,51]. In order to take into account the angiogenesis, this model was extended by considering the interactions between these three types of cells with the endothelial cells [52]. Our aim was here to investigated the action of a therapy combining a cytotoxic chemotherapy with an antiangiogenic drug [29].

Let $H(t)$ be the density of host cells, $I(t)$ the density of immune cells, $T(t)$ the density of tumor cells and $E(t)$ corresponds to the density of endothelial cells at time t. These four populations of cells interact according to [52]

$$\begin{cases} \dot{H} = \rho_h H(1-H) - \alpha_{ht} HT \\ \dot{I} = \dfrac{\rho_i IT}{1+T} - \alpha_{it} IT - \delta_i I + \alpha_{ie} IE \\ \dot{T} = \rho_t T(1-T) - \alpha_{th} HT - \alpha_{ti} IT + \dfrac{\alpha_{te} TE}{1+E} \\ \dot{E} = \dfrac{\rho_e ET}{1+T} - \delta_e E\,. \end{cases} \tag{2.1}$$

In order to investigate the effects of a chemotherapy (paclitaxel and carboplatin) combined with an antiagniogenic drug (bevacizumab), we considered that the cytotoxic chemotherapy was killing tumor cells according to a term $-\epsilon_t T$ to introduce in the third equation of model (2.1). The side effects of the chemotherapy on the host and immune cells were taken into account with the terms $-\epsilon_h H$ and $-\epsilon_i I$ to add in the first and second equations, respectively. The antiangiogenic drug reduces the neo-vascularization, a phenomenon which was described by a coefficient ξ_e inserted in the growth rate of endothelial cells occurring in the fourth equation. The antiangiogenic drugs induce a destruction of tumor cells due to a lack of nutrients and oxygen: this is described by a term $-\epsilon_t \xi_t T$ to add in the third equation. Our resulting model with the combined therapy is thus

$$\begin{cases} \dot{H} = \rho_h H(1-H) - \alpha_{ht} HT - \epsilon_h H \\ \dot{I} = \dfrac{\rho_i IT}{1+T} - \alpha_{it} IT - \delta_i I + \alpha_{ie} IE - \epsilon_i I \\ \dot{T} = \rho_t T(1-T) - \alpha_{th} HT - \alpha_{ti} IT + \dfrac{\alpha_{te} TE}{1+E} - \epsilon_t(1+\xi_t)T \\ \dot{E} = \xi_e \dfrac{\rho_e ET}{1+T} - \delta_e E\,. \end{cases} \tag{2.2}$$

There is no immunotherapy here considered and, consequently, there is no constant term corresponding to a constant increase of immune cells as discussed in [53,54]. Since antiangiogenic drugs do not act significantly on host and immune cells, we have neglected these side-effects. Parameter ϵ_t corresponds to the death rate of tumor cells due to the chemotherapy agent and ξ_t is the rate at which the antiangiogenic drug enhances the efficacy of the chemotherapy agent against tumor cells by improving the quality of blood vessels in the tumor and, consequently, the diffusion of chemotherapy drugs in the tumor. The total loss of tumor cells due to the combined therapy is thus given by the term $-\epsilon_t(1+\xi_t)T$. We designed the action of the antiangiogenic drug on endothelial cells in such a way that, when $\xi_e = 0$, this drug fully stops the growth rate of endothelial cells. All the variables and parameters used in model (2.2) are reported in Table 1. The chemotherapy is commonly killing more tumor cells than host and immune cells, we therefore choose $\epsilon_h = \epsilon_i = \frac{\epsilon_t}{2}$. It is not possible to have realistic parameter values, mainly because i) most of them are not measured in humans and ii) they can be significantly different in line cells, mice models and in humans [55]. We therefore performed a qualitative analysis. The default parameter values correspond to a chaotic solution as investigated in [52] without any treatment. As recently showed, chaotic parameter values could correspond to a slowly progressive tumor [56]. The default parameter values for the treatment are close to the median values of what the model can receive without ejecting the trajectory to infinity: this can be considered as a moderated treatment. The flow diagram of our four-dimensional cancer model with its combined therapy is shown in Fig. 1. An observability analysis of this system is provided in Appendix A.

3. Stability analysis of the singular points

Model (2.2) has ten singular points whose coordinates are all positive and there are two others which have always at