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Dynamics of a tumor-immune model considering targeted chemotherapy

Peng Liu[a,b,*], Xijun Liu[a,b]

[a] Department of Mechanics, Tianjin University, Tianjin, 300354, PR China
[b] Tianjin Key Laboratory of Nonlinear Dynamics and Chaos Control, Tianjin, 300072, PR China

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ABSTRACT

Considering the targeted chemotherapy, a mathematical model of tumor-immune system was constructed on the basis of de Pillis's model. In this paper, we conducted qualitative analysis on the mathematical model, including the positivity and boundedness of solutions, local stability and global stability of equilibrium solutions. Some numerical simulations were given to illustrate the analytic results. Comparing the targeted chemotherapy model with regular chemotherapy model, we found that the targeted chemotherapy was benefit to kill tumor cells.

1. Introduction

Cancer is a disease, which can start from everywhere in human body. Normally, human cells are ordered by gene to grow and divide to form tissues and organs, i.e., the liver, the heart and the lungs. However, the order of the gene may be broken down in sometime, then the cells grow fast and disorderly to form tumors. According to the statistic data from Canadian Cancer Society, it is estimated that 41,000 Canadian men and 37,000 Canadian women will die from cancer in 2015.

Even though the high death rate, up to now, we have several types of tumor treatment such as surgery, radiation therapy, chemotherapy and immunotherapy. Each treatment has its advantages and disadvantages. Surgery is used to treat solid tumors that are contained in fixed area such as lung tumor, liver tumor. The risks of surgery include pain, infection, bleeding and damage to nearby. Radiation therapy is a treatment that uses high doses of radiation to kill tumor cells. However, radiation kill not only tumor cells, but also normal human cells to cause side effect, i.e., fatigue. Immunotherapy is a type of treatment to help human's immune system fight tumor cells, while immunotherapy can also cause side effects, such as skin reactions at the needle site, fever, pain and so on.

Chemotherapy is a treatment that uses drugs to kill tumor cells. The basic idea of chemotherapy is to stop or slow the tumor cells which grow and divide quickly, hence, chemotherapy may kill the normal cells which grow and divide quickly to induce the side effects, i.e., hair loss, mouth sores and nausea. To avoid these side effects, oncologists establish a new treatment: targeted chemotherapy. 'Targeted' means this treatment can target the changes in tumor cells that help them grow, divide and spread [1,2]. There are two types targeted chemotherapy: small-molecule drugs and monoclonal antibodies drugs. Small-molecule drugs can enter tumor cells easily [3–7], and monoclonal antibodies drugs can attach to specific targets on the outer surface of tumor cells [8–10]. Recently, more and more progress in monoclonal antibodies drugs have been made. For example, a paper published in 2015 in Nature Communications [11] gave a new targeted drug delivery method by using genetically engineered diatom biosilica, which can display specific antibodies. The drug-loaded nanoparticles can be sorbed with the diatom biosilica to kill the tumor cells. The experimental results showed that 91% of tumor cells were killed without harming the healthy ones around them.

Tumor therapy is not only a hot topic in oncology, but also focused by mathematicians. A large numbers of mathematical models have been proposed on tumor system (see in [12–17]). Among these models, the interactions between the immune system and a growing tumor are involved, since the presence of an immune component is essential for producing clinically observed phenomena such as tumor dormancy and spontaneous tumor regression [16]. Base on the tumor-immune model, some researchers established chemotherapy model to simulate the effects of the drugs (see in [18–21]). To the authors' knowledge, the modeling of targeted chemotherapy is barely to find.

In this paper, we will propose a new mathematical model to reflect the effect of the monoclonal antibodies targeted

* Corresponding author.
E-mail address: liupeng823@tju.edu.cn (P. Liu).

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Table 1
Parameter values for model (2.1).

Parameter	Definition	Value	Units	Source
a	Tumor growth rate	4.31×10^{-1}	day^{-1}	[18]
b	$1/b$ is tumor carrying capacity	1.02×10^{-14}	cells^{-1}	[18]
c_1	Fractional tumor cells killed by effector cells	3.41×10^{-10}	$\text{cells}^{-1}\,\text{day}^{-1}$	[18]
μ	Death rate of effector cells	4.12×10^{-2}	day^{-1}	[18]
g	Maximum effector cells recruitment rate by tumor cells	1.50×10^{-2}	day^{-1}	[18]
s	Steepness coefficient of the effector cells recruitment	2.02×10^{1}	cell	[18]
K_C	Fractional circulating lymphocytes killed by chemotherapy	6.00×10^{-1}	day^{-1}	[18]
K_N	Fractional effectors cells killed by chemotherapy	6.00×10^{-1}	day^{-1}	[18]
K_T	Fractional tumor cells killed by chemotherapy	8.00×10^{-1}	day^{-1}	[18]
k_T	Combination rate of chemotherapy drug with tumor cells	3.2×10^{-9}	day^{-1}	
p	Effector cells inactivation rate by tumor cells	2.00×10^{-11}	$\text{cells}^{-1}\,\text{day}^{-1}$	[18]
α_1	Constant source of effector cells	1.20×10^{4}	$\text{cells}\,\text{day}^{-1}$	[18]
α_2	Constant source of circulating lymphocytes	7.50×10^{8}	$\text{cells}\,\text{day}^{-1}$	[18]
β	Death rate of circulating lymphocytes	1.20×10^{-2}	day^{-1}	[18]
γ	Rate of chemotherapy drug decay	9.00×10^{-1}	day^{-1}	[18]
V_M	Chemotherapy treatment	$0 \le V_M \le 1$	day^{-1}	[18]
η	Efficacy of chemotherapy	$0 \le \eta \le 1$		

chemotherapy. We will investigate the difference between untargeted chemotherapy and targeted chemotherapy. Our model is established on the model built by De Pillis in [18], which tracks three cell populations and one drug concentration in the tissue, as follows,

$$\begin{aligned} \dot{T} &= aT(1-bT) - c_1NT - K_TMT, \\ \dot{N} &= \alpha_1 + g\tfrac{T}{s+T}N - \mu N - pTN - K_NMN, \\ \dot{C} &= \alpha_2 - \beta C - K_CMC, \\ \dot{M} &= -\gamma M + V_M, \end{aligned} \tag{1.1}$$

the meaning of the notations in which will be given in next section.

The rest of paper is organized as follows. In Section 2, we present the modeling process of the targeted chemotherapy model, and summarize some results obtained by previous papers. Then we prove that the solutions of the model are well-posed and bounded in Section 3. In Section 4, we give the expressions of the equilibrium solutions and study their stability, further, we perform some numerical simulation to illustrate the analytic results. In Section 5, we draw a conclusion and compare the result with the result summary in Section 2 to show the advantage of targeted chemotherapy.

2. Modeling

In this section, we construct a mathematical model of tumor-immune system with targeted chemotherapy, which is based on de Pillis's model in [18]. The model is built on the base of interactions among tumor cells, effector immune cells, circulating lymphocytes and chemotherapeutics, which is presented by the following ordinary differential equations,

$$\begin{aligned} \dot{T} &= aT(1-bT) - c_1NT - K_TMT, \\ \dot{N} &= \alpha_1 + g\tfrac{T}{s+T}N - \mu N - pTN - K_N(1-\eta)MN, \\ \dot{C} &= \alpha_2 - \beta C - K_C(1-\eta)MC, \\ \dot{M} &= -\gamma M + V_M - k_TTM, \end{aligned} \tag{2.1}$$

where T, N and C is tumor cell population, effector immune cell population and circulating lymphocyte population, respectively, M is concentration of chemotherapeutic drugs in tissue, the dot denotes differentiation with respect to t, all parameter values in (2.1) are non-negative, which are shown in Table 1.

There are some considerations and assumptions in this modelling.

A1: We only consider all cells in a small volume of tissue.

A2: Tumor cells can not grow without bound, hence we select logistic growth law to describe the population growth of tumor cells, which are represented by $aT(1-bT)$ in the first equation, where a denotes the growth rate of tumor cells, b represents the inverse of carrying capacity for tumor cells.

A3: The interaction between tumor cells and effector immune cells can result in death of both cells, which are represented by $-c_1NT$ in the first equation and $-pTN$ in the second equation, where c_1 and p denote the fractional tumor cells killed by effector cells and effector cells inactivation rate by tumor cells respectively.

A4: The presence of tumor cells stimulates the immune response, which is described by the positive nonlinear growth term for the effector immune cells: $g\frac{T}{s+T}N$, where g denotes the maximum effector immune cell recruitment rate by tumor cells, s denotes the steepness coefficient of the effector cells recruitment.

A5: The source of effector immune cells and circulating lymphocyte is considered from outside of tissue and with constant input rate α_1 and α_2 respectively. In the absence of tumor cells, effector immune cells die at a per capita rate μ, circulating lymphocytes die at a per capita rate β.

A6: Chemotherapeutics kill tumor cells, effector immune cells and circulating lymphocytes, which is represented by $-K_TMT$ in the first equation of (2.1), $-K_N(1-\eta)MN$ in the second equation of (2.1) and $-K_C(1-\eta)MC$ in the third equation of (2.1), respectively, where K_T, K_N and K_C denotes the fractional tumor cells killed by chemotherapy, the fractional effectors cells killed by chemotherapy and the fractional circulating lymphocytes killed by chemotherapy, η is efficacy of chemotherapy.

A7: The targeted chemotherapeutics drugs are injected into tissue at constant rate V_M and decay at rate γ. Since monoclonal antibodies targeted drugs can attach to specific targets on the outer surface of tumor cells, the attachment between drugs and tumor cells consume drugs, which is represented in the last equation by $-k_TTM$, where k_T denotes the combination rate of chemotherapy drug with tumor cells.

Comparing the model (2.1) with the regular chemotherapy model (1.1), we introduce a parameter η to describe the effectiveness of the targeted chemotherapy, and add a term $-k_TTM$ in the four equation to represent the characteristic of monoclonal antibodies targeted drugs. For the convenience of comparison between model (2.1) and model (1.1), we summarize the results obtained by de Pillis in [18] and Valle in [22].