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Cost-effectiveness analysis of optimal strategy for tumor treatment☆

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ABSTRACT

We propose and analyze an antitumor model with combined immunotherapy and chemotherapy. Firstly, we explore the treatment effects of single immunotherapy and single chemotherapy, respectively. Results indicate that neither immunotherapy nor chemotherapy alone are adequate to cure a tumor. Hence, we apply optimal theory to investigate how the combination of immunotherapy and chemotherapy should be implemented, for a certain time period, in order to reduce the number of tumor cells, while minimizing the implementation cost of the treatment strategy. Secondly, we establish the existence of the optimality system and use Pontryagin's Maximum Principle to characterize the optimal levels of the two treatment measures. Furthermore, we calculate the incremental cost-effectiveness ratios to analyze the cost-effectiveness of all possible combinations of the two treatment measures. Finally, numerical results show that the combination of immunotherapy and chemotherapy is the most cost-effective strategy for tumor treatment, and able to eliminate the entire tumor with size 4.470×10^8 in a year.

1. Introduction

Millions of people die from cancer every year. And worldwide trends indicate that millions more will die from this disease in the future [1]. Today the principal efforts are addressed to search new treatment strategies e.g., immunotherapy [2], which attempts to stimulate the immune system to reject and destroy tumors. Immunotherapy for cancer was first introduced by Rosenberg and his colleagues of National Institute of Health USA [3]. Initially immunotherapy treatments involved administration of cytokines such as Interleukin [4]. Thereafter the adverse effects of such intravenously administered cytokines [5] lead to the extraction of the lymphocytes from the blood and expanding in vitro against tumour antigen before injecting the cells with appropriate stimulatory cytokines [6]. With advance of immunotherapy, adoptive cell transfer therapy (ACT) has already demonstrated a good development prospect [7]. It uses T cell-based cytotoxic responses to attack cancer cells. T cells that have a natural or genetically engineered reactivity to a patient's cancer are generated in vitro and then transferred back into the cancer patient. Recent clinical trials have manifested that adoptive cell transfer therapy with antitumor lymphocytes can cause cancer regression in approximately 70% of patients with metastatic melanoma [8]. Therefore, in vitro manipulation of antitumor immunity may be used in the effective treatment of cancer patients [9,10].

Some models which describe the interactions between the immune system and a growing tumor have been developed (Bell [11], Stepanova [12], Michelson [13], Forys [14], Ciancio [15]). Cattani, in 2010 [16], considered a family of nonlinear models with non-monotonically time-varying coefficients to describe the asynchronous process of mutual learning of the tumour and the immune cells. d'Onofrio, in 2011 [17], proposed a epigenetic escape mechanism that adaptively depends on the interactions per time unit between cells of the two systems to describe the competition between a tumor and the immune system. Kuznstsoz, in 1994 [18], presented and analyzed a mathematical model of cytotoxic T lymphocytes (CTL) cells response to the growth of immunogenic tumor, and estimated the parameters of the target model by using the experimental data of chimeric mice. The model exhibits abundant phenomena including 'immunostimulation', 'sneaking through' and 'dormant state' of the tumor growth. The model is given by

$$\begin{cases} \dfrac{dx}{dt} = s + \dfrac{\rho xy}{\alpha + y} - c_1 xy - d_1 x, \\ \dfrac{dy}{dt} = ry(1 - by) - c_2 xy, \end{cases} \tag{1.1}$$

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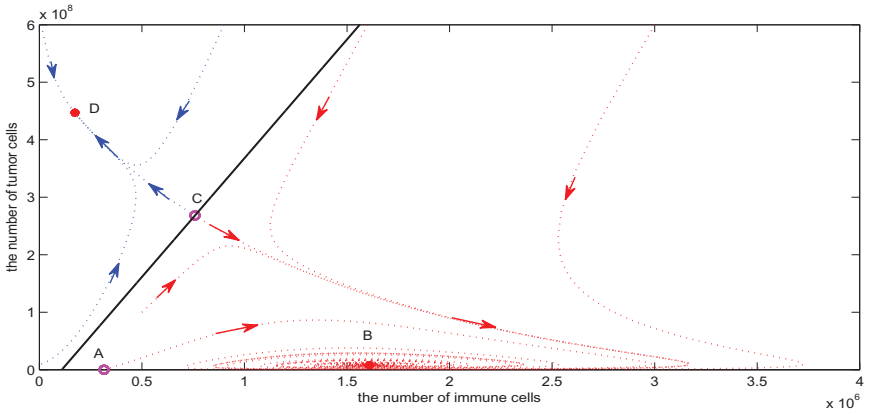

Fig. 1. Phase portrait for system (1.1). Labeling: A and C respectively denote two unstable saddle points E_0 and E_2. B represents a stable focus E_1. D is a stable node E_3.

where x denotes the number of immune cells with antitumour activity in the tumor site, y represents the number of tumor cells. The parameter values of system (1.1) come from literature [18], and are estimated by using the experimental data of the chimeric mice. Their descriptions and estimated values are listed in Table A.1 (**see** Appendix A).

Chemotherapy, as a conventional treatment, has become a part of therapy regimen of most tumor patients, and aims at shrinking primary tumors, slowing their growth, and killing tumor cells that may have metastasized to other parts of the body from the original, primary tumor. However, one of the defects of chemotherapy is that it also kills the normal fast dividing cells, which causes fearful side effects in patients. Recent clinical data have shown that combined immunotherapy with traditional chemotherapy has a more prominent effect in inhibiting tumor growth and lengthening patient survival times than either single chemotherapy or single immunotherapy [19]. Hence, Pillis adopted the numerical simulations to investigate the treatment effects of combined immunotherapy and chemotherapy [20–22]. Afterward, optimal control was applied to design the cancer therapeutic regimen with immunotherapy or chemotherapy [23]. Castiglione considered dendritic cell transfection immunotherapy to describe the immune-cancer interaction, and characterized the optimal infusion dose of dendritic cells [24]. Bratus applied optimal control method to obtain an optimal chemotherapy regimen which makes tumor cells wipe out eventually [25].

The aim of this paper is to investigate how immunotherapy and chemotherapy should be implemented, for a certain time period, in order to reduce the number of tumor cells, while minimizing the total cost of the implementation of the two therapeutic strategies. Hence, we will introduce combined immunotherapy and chemotherapy to develop the model (1.1), and consider the infusion dose of immune cells and the increment of drug concentration caused by chemotherapy as control variables. Further, we attempt to explore the existence of optimal combined immunotherapy and chemotherapy strategy, and apply numerical simulations to characterize an optimal combined treatment regimen. Finally, we will find out which strategy is the most cost-effective.

2. Preliminaries

In order to obtain our results, we first give the basic properties of system (1.1). Obviously, system (1.1) has a tumor-free equilibrium $E_0(\frac{s}{d_1}, 0)$. At the tumor-free equilibrium E_0, the Jacobian matrix becomes

$$J(E_0) = \begin{bmatrix} -d_1 & \frac{\rho x_0}{\alpha} - c_1 x_0 \\ 0 & r - c_2 x_0 \end{bmatrix}.$$

The eigenvalues of system (1.1) linearized at E_0 are $\lambda_1 = -d_1$ and $\lambda_2 = r - c_2 x_0 = \frac{r d_1 - c_2 s}{d_1}$. Since $d_1 > 0$, λ_1 is always negative, then the tumor-free equilibrium E_0 is stable if and only if

$$R = \frac{r d_1}{c_2 s} \langle 1 \Leftrightarrow s \rangle s_c \triangleq \frac{r d_1}{c_2}. \tag{2.1}$$

According to the parameter values in Table A.1, by calculating, we can obtain $R = 5.1860 > 1$ and $s_c = 6.7418 \times 10^4$. Since s is much less than s_c, the tumor-free equilibrium E_0 is unstable, we have the following proposition.

Proposition 2.1. *The tumor-free equilibrium E_0 is a saddle.*

Further, we can obtain the three positive equilibria of system (1.1). They are given by $E_1(1.6096 \times 10^6, 8.1930 \times 10^6)$, $E_2(7.5873 \times 10^5, 2.6817 \times 10^8)$ and $E_3(1.7343 \times 10^5, 4.4701 \times 10^8)$, where E_1 and E_3 are called as the small tumor-present equilibrium and the lager tumor-present equilibrium, respectively. Applying numerical calculations, we get the eigenvalues of the Jacobian matrix at the tumor-present equilibrium E_i $(i = 1, 2, 3)$ as follows:

$$\begin{cases} \lambda_{11} = -0.0055 + 0.0634i, \\ \lambda_{12} = -0.0055 - 0.0634i, , \end{cases} \quad \begin{cases} \lambda_{21} = 0.0356, \\ \lambda_{22} = -0.1493, \end{cases}$$

$$\text{and} \begin{cases} \lambda_{31} = -0.0496, \\ \lambda_{32} = -0.1862, . \end{cases}$$

Hence, the following proposition is obvious.

Proposition 2.2. *The positive equilibrium E_1 is a stable focus, E_2 is an unstable saddle and E_3 is a stable node.*

The phase diagram is exhibited in Fig. 1, which indicates that if the ratio between the numbers of immune cells and that of tumor cells is not enough big, then system (1.1) tends to a big tumor equilibrium E_3, otherwise, system (1.1) approaches a relatively small tumor equilibrium E_1.

Lemma 2.1. *$\Omega = \{(x, y) \in R_+^2 : x + y \le \frac{k}{d_1}\}$ $(k = s + \frac{(r+d_1)^2}{4rb})$ is a positively invariant set of system (1.1).*