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Original articles

Modelling pulsed immunotherapy of tumour–immune interaction

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Highlights

- We develop a novel mathematical model that describes the tumour–immune interaction with pulsed immunotherapy.
- The existence and stability of the tumour free periodic solution are addressed.
- The effects of ACI associated or not with IL-2 on immunotherapy are investigated numerically in detail.
- The results showed that the tumour can be eradicated or controlled with combined therapies.

Abstract

We develop a mathematical model that describes the tumour–immune interaction and the effect on it of pulsed immunotherapy, based on the administration of adoptive cellular immunotherapy (ACI) combined with interleukin-2 (IL-2). The stability conditions for the tumour-free periodic solution are provided with different frequencies of ACI applications and IL-2 infusions. Furthermore, the effects of period, dosage and times of drug deliveries on the amplitudes of the tumour-free periodic solution were investigated. The most feasible immunotherapy strategy was determined by comparing immunotherapy with ACI treatment with or without IL-2. However, to investigate how to enhance the efficacy of chemotherapy (radiotherapy) and reduce its side-effects, we developed a model involving periodic applications of immunotherapy with chemotherapy (radiotherapy) applied only when the density of the tumour reached a given threshold. The results revealed that the initial densities, the effector cell: tumour cell ratios, the periods T and a given critical number of tumour cells C_T are crucial for cancer treatment, which confirms that it is important to customize treatment strategies for individual patients.
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Keywords: Cancer; Immunotherapy; Periodic solution; Combined therapy; Threshold

1. Introduction

Cancer is an aggressive disease with high mortality rates. Without treatment, malignant tumour cells can grow uncontrollably and often metastasize from their initial site to other parts of the body with fatal consequences. Common therapies include surgery, radiotherapy, chemotherapy, immunotherapy or combinations thereof [37]. Immunotherapy,

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used to stimulate a strong immune response to target tumours, has become one of the most common approaches in cancer therapy [4,29,30].

Various mathematical models have been developed to describe tumour–immune dynamics. Mathematical models of tumour–immune dynamics not only help understanding of the involvement of immune cells and cancer cells and how they interact, but can also provide a useful tool to predict the results of immunotherapy and indicate improved treatment strategies. Many researchers have used ordinary differential equations (ODEs) to model populations of immune cells and tumour cells [28,14,7,20,19,8,21,36,38]. In these studies, the effects of the immune response and immunotherapy treatment on tumour growth and eradication have been studied in detail.

The preferred treatment for cancer depends on its stage and grade at diagnosis and the dosage, frequency and duration of immunotherapy are important for its success or failure. Optimal schedules for drug administration in immunotherapy have been widely investigated [9,15,16,23,24]. In 1994, Kuznetsov developed a tumour–immune model that was described by two ordinary differential equations, where the immune cells play the role of the predator, while the tumour cells are the prey: many complex dynamics were examined including immunostimulation of tumour growth, sneaking through of the tumour, and formation of a tumour dormant state [22]. Later, Kirschner and Panetta extended this work by incorporating tumour–immune dynamics together with interleukin-2 (IL-2) dynamics. The continuous administration of immunotherapy treatment was considered and short-term oscillations in tumour size as well as long-term tumour relapse were discussed [20].

Recently, the mathematical model of tumour–immune interaction developed by Kirschner and Panetta has been re-considered with pulsed immunotherapy described by impulsive differential equations [37] and a bifurcation analysis related to key parameters and its biological implications were discussed briefly. Note that Adoptive Cellular Immunotherapy (ACI) refers to the injection of cultured effector cells that have anti-tumour activity into the tumour site [20], so that ACI acts directly on the tumour cells. However, sufficient lead time is needed for inputs of IL-2 to stimulate a strong immune response to fight against tumour cells. Therefore, what we need to show is how the time interval between injection of ACI and input of IL-2 affects the efficacy of immunotherapy. So we consider a more general case in this paper: ACI is applied only at each impulsive point τ_n, and at each impulsive point λ_m there is an impulsive injection of IL-2. These modifications result in the following model based on the two impulsive point series:

$$\begin{cases} \left.\begin{aligned} \frac{dE(t)}{dt} &= cT - \mu_2 E + \frac{p_1 E I_L}{g_1 + I_L}, \\ \frac{dT(t)}{dt} &= r_2 T(1 - bT) - \frac{aET}{g_2 + T}, \\ \frac{dI_L(t)}{dt} &= \frac{p_2 ET}{g_3 + T} - \mu_3 I_L, \end{aligned}\right\} & t \neq \tau_n,\ t \neq \lambda_m, \\ \left.\begin{aligned} E(\tau_n^+) &= E(\tau_n) + s_1, \\ T(\tau_n^+) &= T(\tau_n), \\ I_L(\tau_n^+) &= I_L(\tau_n), \end{aligned}\right\} & t = \tau_n, \\ \left.\begin{aligned} E(\lambda_m^+) &= E(\lambda_m), \\ T(\lambda_m^+) &= T(\lambda_m), \\ I_L(\lambda_m^+) &= I_L(\lambda_m) + s_2, \end{aligned}\right\} & t = \lambda_m, \end{cases} \tag{1}$$

with initial conditions: $E(0) = E_0, T(0) = T_0, I_L(0) = I_{L_0}$, where $E(t)$, $T(t)$ and $I_L(t)$ represent the number of effector cells, tumour cells, and the concentration of IL-2, respectively. The parameter c models the antigenicity of the tumour, $1/\mu_2$ is the average lifespan of the effector cells, r_2 denotes the growth rate of the tumour, $1/b$ is the tumour carrying capacity, μ_3 represents loss/degradation rate of IL-2. s_1 is an ACI treatment term that represents an external source of effector cells such as lymphokine-activated killer (LAK) or tumour infiltrating lymphocyte (TIL) cells, s_2 is a treatment term that represents an external input of IL-2 into the system. Moreover, the interactions between the tumour and the immune system are modelled by Michaelis–Menten kinetics, g_1 is the semi-saturation point, and p_1 is the maximal production rate of an effector cell, while the meanings of g_2, g_3, a, and p_2 are similar to g_1 and p_1. Finally, τ_n $(n = 1, 2, \ldots)$ and λ_m $(m = 1, 2, \ldots)$ are impulsive point series at which ACI (such as LAK or TIL cells) and inputs of IL-2 are applied, respectively. Based on system (1), de Pillis and his co-workers modelled tumour growth with respect to a total cell count by including the influence of several immune cell effector subpopulations,

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