BioSystems 116 (2014) 43–48

Contents lists available at ScienceDirect

BioSystems

journal homepage: www.elsevier.com/locate/biosystems

Model for tumour growth with treatment by continuous and pulsed chemotherapy

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ARTICLE INFO

Article history:
Received 1 March 2013
Received in revised form 3 October 2013
Accepted 2 December 2013

Keywords:
Tumour
Delay
Chemotherapy

ABSTRACT

In this work we investigate a mathematical model describing tumour growth under a treatment by chemotherapy that incorporates time-delay related to the conversion from resting to hunting cells. We study the model using values for the parameters according to experimental results and vary some parameters relevant to the treatment of cancer. We find that our model exhibits a dynamical behaviour associated with the suppression of cancer cells, when either continuous or pulsed chemotherapy is applied according to clinical protocols, for a large range of relevant parameters. When the chemotherapy is successful, the predation coefficient of the chemotherapic agent acting on cancer cells varies with the infusion rate of chemotherapy according to an inverse relation. Finally, our model was able to reproduce the experimental results obtained by Michor and collaborators [Nature 435 (2005) 1267] about the exponential decline of cancer cells when patients are treated with the drug glivec.

1. Introduction

Cancer is the name given to a cluster of more than 100 diseases that presents a common characteristic, the disorderly growth of cells that invade tissues and organs (Anderson et al., 2001; Brú et al., 2003). These cells may spread to other parts of the body rapidly forming tumours (Baserga, 1965).

An important mechanism of body defence against a disease caused by a virus, bacteria or tumour is the destruction of infected cells or tumours by actived cytotoxic T-lymphocytes (CTL) cells also known as hunter lymphocytes. CTL are able to kill cells or to induce a programmed cell death (apoptosis). The biological activation process occurs efficiently when the CTL receive impulses generated by T-helper cells (T_H). The stimuli occur through the release of cytokines. This phenomenon is not instantaneous; besides the time elapsed to convert resting T-lymphocytes in CTL, there is also a natural delay of the cytological process (Wodarz et al., 1998; Iarosz et al., 2011). Banerjee and Sarkar (2008) studied the dynamical behaviour of tumour and immune cells using delay differential equations. They observed the existence of oscillations in tumour cells when a time delay was considered in the growth of T-cells.

A possible way to stop the growing of cancer cells is chemotherapy. That is, the treatment with a drug or combination of drugs through some protocol. There are many experimental and theoretical studies about the effects of the chemotherapy on the cells. Moreover, mathematical models have been considered to simulate the growth of cancer cells (Liu et al., 2012), as well as, tumour-immune interactions with chemotherapy (De Pillis et al., 2007).

In this paper we investigate a mathematical model for the growth of tumours that not only take into consideration the time delay character of the lymphocytes dynamics, but also the effect of the chemotherapy. We extend the model of Banerjee and Sarkar (2008) by adding the chemotherapy, and by considering some clinically plausible protocols. Firstly, a continuous chemotherapy is analysed. Secondly, the traditional or pulsed chemotherapy protocol is analysed, in which the drug is administered periodically. According to experimental protocols, we have used both a constant amplitude (Ahn and Park, 2011) and an oscillatory amplitude (Kuebler et al., 2007) for the continuous infusion rate of chemotherapy (Pinho et al., 2002).

One of our main results is to show that there are a large range of relevant parameters that lead to a successful chemotherapy. In a successful chemotherapy, the predation coefficient of the chemotherapic agent acting on the cancer cells and the infusion rate of the chemotherapy are inversely related. For the continuous chemotherapy, we have ensured the stability of the non-cancer

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http://dx.doi.org/10.1016/j.biosystems.2013.12.001

Table 1
Parameters according to experimental evidence.

Parameter	Definition	Value	References
q_1	Growth rate of malignant tumour cells	0.18 day^{-1}	Siu et al. (1986)
K_1	Carrying capacity of tumour cells	5×10^6 cells	Siu et al. (1986)
α_1	Decay rate of tumour cells by hunting cells	1.101×10^{-7} cells $^{-1}$ day^{-1}	Kuznetsov et al. (1994)
α_2	Decay rate of hunting cells by tumour cells	3.422×10^{-10} cells $^{-1}$ day^{-1}	Kuznetsov et al. (1994)
d_1	Death rate of hunting cells	0.0412 day^{-1}	Kuznetsov et al. (1994)
q_2	Growth rate of resting cells	0.0245 day^{-1}	Banerjee and Sarkar (2008)
τ	Time delay in conversion from resting cells to hunting cells	45.6 day	Banerjee and Sarkar (2008)
K_2	Carrying capacity of resting cells	1×10^7 cells	Banerjee and Sarkar (2008)
β_1	Conversion rate from resting to hunting cells	6.2×10^{-9} cells^{-1} day^{-1}	Kuznetsov et al. (1994)

state (i.e., a successful chemotherapy) by calculating the Lyapunov exponents of the non-cancer solution. Finally, our model was able to reproduce the experimental results obtained by Michor et al. (2005) about the exponential decline of cancer cells when patients are treated with the drug glivec.

2. The model

We extend a mathematical model proposed by Sarkar and Banerjee (2005) including the chemotherapic agent. The model is based on the predator-prey system. The T-lymphocyte is the predator, while the tumour cell is the prey that is being attacked. The predators can be in a hunting or a resting state. The resting cells do not kill tumour cells, but they can become hunters. The activation occurs not only due to cytokines released by macrophages that absorb tumour cells, but also by direct contact between resting and tumour cells. As a result, the resting cells suffer a degradation while the hunting cells are actived. The activated cells do not return to the resting state. This way, the predator-prey model is a three dimensional deterministic system, consisting of tumour cells, hunting cells, and resting cells. We added the chemotherapic agent in the equations as a predator on both cancerous and lymphocytes cells. The time delay of about 60 days considered in our model was observed by Balduzzi et al. (2005) and Villasana and Radunskaya (2003), when they were realising experiments about lymphoblastic leukaemia. It incorporates many different phenomena in the system. It is one order of magnitude larger than the one observed in Becker et al. (2010). In our model, the time delay represents the total time interval for cancer cells to be identified by T-cell receptors and transfer this information to the killer cells, and the time related to the process of cytolytic information in the resting cells (Becker et al., 2010; Matta et al., 2013). The model is then given by

$$\begin{aligned}
\frac{dC(t)}{dt} &= q_1 C(t)\left(1-\frac{C(t)}{K_1}\right) - \alpha_1 C(t)H(t) - \frac{p_1 C(t)}{a_1 + C(t)}Z(t),\\
\frac{dH(t)}{dt} &= \beta_1 H(t)R(t-\tau) - d_1 H(t) - \alpha_2 C(t)H(t) - \frac{p_2 H(t)}{a_2 + H(t)}Z(t),\\
\frac{dR(t)}{dt} &= q_2 R(t)\left(1-\frac{R(t)}{K_2}\right) - \beta_1 H(t)R(t-\tau) - \frac{p_3 R(t)}{a_3 + R(t)}Z(t),\\
\frac{dZ(t)}{dt} &= \Delta - \left(\xi + \frac{g_1 C(t)}{a_1 + C(t)} + \frac{g_2 H(t)}{a_2 + H(t)} + \frac{g_3 R(t)}{a_3 + R(t)}\right)Z(t),
\end{aligned} \tag{1}$$

where C, H and R are the number of cancerous, hunting and resting cells, respectively, t is the time and Z is the concentration of the chemotherapic agent. The cancerous and resting cells have a logistic growth. The term $-d_1 H(t)$ represents the natural death of the hunting cells. The terms $-\alpha_1 C(t)H(t)$ and $\alpha_2 C(t)H(t)$ are the losses due to encounters between the cancerous and hunting cells. The term $\beta_1 H(t)R(t-\tau)$ is associated with the conversion of resting to hunting state, where τ is the delay in the conversion. The terms with Z correspond to interaction of the chemotherapic agent with the cells.

Table 2
Parameters according to the literature.

Parameter	Definition	References
p_i	Predation coefficients of chemotherapic agent on cells (C, H, R)	Pinho et al. (2002)
a_i	Determine the rate at which C, H, R, in the absence of competition and predation, reach carrying capacities	Pinho et al. (2002)
g_i	Represent the combination rates of the chemotherapic agent with the cells	Pinho et al. (2002)
Δ	Represents the infusion rate of chemotherapy	Pinho et al. (2002)
ξ	Washout rate of chemotherapy	Pinho et al. (2002)

Table 1 shows the parameters obtained from the literature, according to experimental evidence, and Table 2 shows the definition of some of the parameters. Table 3 presents the values that we consider in our simulations for the sake of numerical integration.

Introducing the following dimensionless variables

$$\begin{aligned}
\bar{t} &= \frac{t}{\text{day}}, \quad \bar{C} = \frac{C}{K_T}, \quad \bar{H} = \frac{H}{K_T},\\
\bar{R} &= \frac{R}{K_T}, \quad \bar{Z} = \frac{Z}{\Delta_M \xi^{-1}},
\end{aligned} \tag{2}$$

where $K_T = K_1 + K_2$ is the total carrying capacity and Δ_M is equal $1\,\text{mg}\,\text{m}^{-2}\,\text{day}^{-1}$. Combining (2) with (1), and relabelling the variables $\{\bar{t}, \bar{C}, \bar{H}, \bar{R}, \bar{Z}\}$ as t, C, H, R, Z, respectively, and the parameters $\{\bar{q}_1, \bar{K}_1, \bar{\alpha}_1, \bar{p}_1, \bar{g}_1, \bar{a}_1, \bar{\beta}_1, \bar{d}_1, \bar{\alpha}_2, \bar{p}_2, \bar{g}_2, \bar{a}_2, \bar{q}_2, \bar{K}_2, \bar{p}_3, \bar{g}_3, \bar{a}_3, \bar{\Delta}, \bar{\xi}\}$ as $\{q_1, K_1, \alpha_1, p_1, g_1, a_1, \beta_1, d_1, \alpha_2, p_2, g_2, a_2, q_2, K_2, p_3, g_3, a_3, \Delta, \xi\}$, respectively, we obtain the same equations for C, H and R. However, the equation for Z presents a small alteration,

$$\frac{dZ(t)}{dt} = \Delta\xi - \left(\xi + \frac{g_1 C(t)}{a_1 + C(t)} + \frac{g_2 H(t)}{a_2 + H(t)} + \frac{g_3 R(t)}{a_3 + R(t)}\right)Z(t), \tag{3}$$

Table 3
Dimensionless parameters.

Parameter	Value	Parameter	Value
q_1	0.18	K_1	1/3
α_1	1.6515	α_2	5.133×10^{-3}
d_1	0.0412	q_2	0.0245
τ	45.6	K_2	2/3
β_1	9.3×10^{-2}	p_1	1×10^{-3}
p_2	1×10^{-3}	p_3	1×10^{-3}
a_1	1×10^{-4}	a_2	1×10^{-4}
a_3	1×10^{-4}	g_1	0.1
g_2	0.1	g_3	0.1
Δ	$0 - 10^4$	ξ	0.2