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A Stochastic Immunotherapy Model for Breast Cancer with Pulsed Chemotherapy*

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Abstract In this paper, we consider an immunotherapy model for breast cancer with stochastic perturbations and pulsed chemotherapy. By using stochastic Lyapunov analysis and the strong law of large numbers, we first prove the existence, uniqueness and the stochastic ultimate boundedness of the global positive solution for the model. Then we obtain sufficient conditions for the extinction of tumor cells and the persistence of all three kinds of cells for this model. Finally, we use numerical simulations to verify the theoretical results which are obtained in the paper.

Keywords Breast cancer, persistence, extinction, white noise, impulsive effect

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1. Introduction

Breast cancer has become one of the malignant tumors that threaten women's lives and health in today's society and its mortality rate has already been the second highest among female tumors. Further, studies have shown that age, family history, reproductive factors, estrogen and lifestyle are the five important risk factors of breast cancer [26]. With the development of medical level and treatment method, survival rates and survival time of patients have increased. However, from the prevention of breast cancer to precise treatment, many problems remain to be explored. Therefore, it is very meaningful to study the mechanism of breast cancer. It is recorded that the immune system can recognize and eliminate cancer cells before they proliferate and grow, which is called immune surveillance [12, 29]. And the immune response to tumor cells is usually mediated by natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) [1, 21, 31].

Mathematical models of tumor growth are powerful tools for understanding, predicting and improving treatment options. More and more scholars have further

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studied dynamical behaviors of tumor growth by establishing mathematical models containing NK cells and CTLs. For example, de Pillis et al. [5] set up a mathematical model to express tumor-immune interaction and they focused on the roles of NK cells and $CD8^+$ T cells in tumor monitoring. Further, Masaha et al. [20] presented a new model which involved various immune cell populations and tumor cell populations. Moreover, Wei [30] studied a four-dimensional tumor-immune model for breast cancer by comparing the results obtained from numerical simulation with those from clinical and experimental studies.

Up to now, the clinical treatment methods include surgery to remove cancerous tissue, chemotherapy, radiotherapy, immunotherapy and so on. Compared with other treatments, immunotherapy such as dendritic cell vaccine therapy [23] and HER2/neu(E75) peptide vaccine [2] has attracted more and more scholars' attention [13, 27]. Motivated by the above references, we consider the following model

$$\begin{cases} \mathrm{d}x(t) = \Big(ev - fx - p_2xz + \frac{p_3xz}{1+\alpha_3 z+\beta_3 x}\Big)\mathrm{d}t, \\ \mathrm{d}y(t) = \Big[\frac{p_5 Iy}{\alpha_4+I}\Big(1-\frac{y}{K_1}\Big)\frac{z}{\alpha_5+z} - dy + by\Big]\mathrm{d}t, \\ \mathrm{d}z(t) = \Big[z\Big(a + \frac{cE(t)z}{1+\alpha_1 E(t)+\beta_1 z^2}\Big)\Big(1-\frac{z}{K}\Big) - \frac{p_1x^2z}{1+\alpha_2 z+\beta_2 x^2} - \frac{p_6yz^2}{1+\alpha_6 z^2+\beta_6 y}\Big]\mathrm{d}t, \\ \mathrm{d}v(t) = (\alpha - \beta v)\mathrm{d}t, \\ x(0) = x_0,\ y(0) = y_0,\ z(0) = z_0,\ v(0) = v_0, \end{cases} \tag{1.1}$$

where $x(t)$, $y(t)$, $z(t)$ and $v(t)$ denote the NK cell population, the CTL population, the tumor cell population and the white blood cell (WBC) population, respectively, and $E(t)$ represents the circulating level of estradiol. Besides, $E(t)$ is a periodic function, namely, $E(t) = E(t - n\hat{\tau}), t \in [n\hat{\tau}, (n+1)\hat{\tau})$. Based on the realistic background, all parameters of system (1.1) are real and positive. Further, the significance of parameters and the schematic diagram of the interactions among four kinds of cells for system (1.1) are shown in Table 1 and Figure 1, respectively.

Table 1. The parameters and their interpretations in model (1.1).

Parameter	Description	Parameter	Description
e	Fraction of WBCs becoming NK cells	a	Tumor growth rate
f	NK cell death rate	c	Tumor growth rate induced by E_2
p_2	NK cell inactivation by tumor cells	α_1	Half saturation constant
p_3	NK cell recruitment rate	β_1	Half saturation constant
α_3	Half saturation constant	K	Tumor cell carrying capacity
β_3	Half saturation constant	p_1	NK induced tumor death
p_5	CTL growth rate induced by IL-2	α_2	Half saturation constant
I	IL-2 concentration	β_2	Half saturation constant
α_4	Half saturation constant	p_6	CTL induced tumor death
K_1	CTL carrying capacity	α_6	Half saturation constant
α_5	Half saturation constant	β_6	Half saturation constant
d	CTL death rate	α	WBC production rate
b	CTL growth rate by immunotherapy	β	WBC death rate

It is worth noting that the last equation is independent of the first three equations. Then we can derive $v(t) = \frac{\alpha}{\beta} + (v_0 - \frac{\alpha}{\beta})e^{-\beta t}$. Supposing that $v_0 > \frac{\alpha}{\beta}$, we