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Research Article

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A Mathematical Model for Glioblastoma with Human Cytokine-Induced Killer Alone or Combined with Temozolomide

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Abstract: In this paper, according to the experimental data provided by literature[12], we extracted the initial value of CIK (Cytokine-Induced Killer) cells, the initial value of GBM (Glioma Cells), and the value of hCIK (human Cytokine-Induced Killer) in three groups, respectively (once per week, 4 consecutive weeks), and each group significantly inhibited tumor growth by 44%, 54% and 72%, respectively. To control CIK cell dose, the tumor volume with CIK + TMZ(Temozolomide) combination decreased by 95% by day 28, which was better than hCIK alone. A mathematical model of glioma that includes tumor-immune interactions and immunosuppression derived from CIK cells was then developed. Before the absence of treatment, the system dynamics were first characterized by locating the equilibrium point and determining the stability. Then, the established mathematical model was used to simulate the growth of tumors under different agents and doses, and the simulation results agreed with the experimental results, showing the effectiveness of the established model.

Keywords: GBM; TMZ; hCIK; Immunotherapy; Stability

1. Introduction

Glioma is the most common intracranial malignant tumor, with nearly 466,000 new cases every year. malignant glioma is the most common and fatal primary brain tumor in adults. According to statistics, it accounts for about 40% to 50% of all intracranial tumors. The annual incidence in adults is about 8 in 100,000, which is significantly higher in men than in women. There is a trend of glioma in those over 65 years.

Traditionally, the brain has been considered as an immune-privileged organ, but recent studies have found the existence of active immunity in the brain. This offers the possibility for the immunotherapy of GBM. Immune cell-based therapies, such as CIK cell therapy, utilize the patient's own immune cells, through special culture and after activation, to have the ability to recognize and kill tumor cells. CIK cells have significant therapeutic effects on GBM in vivo, especially in the control of tumor recurrence and metastasis. However, the results of the intracranial CIK cell injection method and the GBM subcutaneous xenograft animal models are difficult to translate immediately to the clinic. Combination therapy with TMZ is the most widely used anti-GBM chemotherapy agent. TMZ is an alkylating agent used primarily for the treatment of GBM, which suppresses the growth and replication of tumor cells by introducing methylation damage into DNA molecules. Furthermore, TMZ is also used in other types of cancer therapy.

The remainder of this paper is organized as follows. In Sec. 2, we developed a mathematical model of glioma. In Sec.3, we present the position of the equilibrium point and its stability analysis. In Sec. 4, we simulated CIK cell therapy at a hCIK cell dose (once per week for 4 weeks), and simulated the effect of CIK and TMZ combination, with a brief conclusion in the last section.

2. Preliminaries

Model Description

We first developed a detailed model, the complete model, which includes GBM, CIK cells. The whole model is then reduced to a reduced model using the quasi-steady state approximation. In this paper, we focus on tissues near the tumor site and assume a homogeneous tumor cell population. Similar to references.2 and 3, the specific biological hypotheses are first proposed as follows:

1. Cancer cells can grow normally without an immune response.
2. The hCIK cells can kill the cancer cells.
3. The hCIK cells can be activated by the cancer cells.
4. hCIK cells are finally inactivated after a certain number of interactions with tumor cells

The model describes the dynamic interaction between the tumor and the immune cells, representing the cell number and the concentration of cytokines as follows:

• G(t), GBM cell population

• C(t), CIK concentration

The variables for cells have the unit of number.

Remark1. In this paper, we adopt the following basic interaction rules as in: in this paper, we adopt the following basic interaction rules: cells and the interactions between [6][7][8][9][10] cells and drugs represent the product form, where is a constant, A, B are both cell populations or one of them is a drug. The implementation of the tumor and immune system models includes a series of ordinary differential equations. Our model considered both GBM cells and CIK treatment. Each equation represents the change in the number of tumor cells, and immune cells.

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Tumor cells

The evolution of breast cancer cell populations depends on the growth conditions of cancer and the clearance of cancer cells by immune cells. This equation is made up of

$$\frac{dG}{dt} = r_1 G(1 - \frac{G}{G_{\max}}) - g_1 C \frac{G}{G + k_1}. \tag{2.1}$$

Specifically, the basal growth term of the glioma cells is represented by a logical function $r_1 G(1 - \frac{G}{G_{\max}})$ and Gmax is the carrying capacity of the tumor cells. The second model is the removal of cancer cells with CIK cells, and CIK cells interact with cancer cells.

$$\frac{dC}{dt} = g_2 G - \mu_1 C - a_2 \frac{G}{G + k_2} C. \tag{2.2}$$

Among them, describes the rate at which GBM cells accumulate in the tumor cell microenvironment upon tumor cell stimulation. is the inactivation rate due to the interaction between cancer cells and CIK cells. CIK cells were inhibited by GBM, which is represented by $-a_2 \frac{G}{G + k_2} C$

Parametric Optimization

To better understand the prognostic outcome of disease progression, we will further analyze the distribution and stability properties of the equilibrium points in Eq. (2.1)– (2.2). Since the coorder model is highly nonlinear, it is difficult to obtain analytical equilibrium points. However, by setting the parameters in the model, the position of the equilibrium point and its stability can be discussed numerically.

Parametric choices

For parameter selection in this section, we will select appropriate parameters from the literature to implement subsequent qualitative analysis and numerical simulations. Because our model is extended from the reference, the initial values of GBM cells and CIK cells are consistent with them. While in cases where the parameter information is not suitable for our scenario, such as parameters from animal models or other types of tumor

models, we modify the parameter values to better fit our pancreatic cancer model. Table 1 shows the parameter values of Eq. (2.1-2.2). Since CIK suppresses the immune response to cancer, the higher the dose of injected CIK cells, the lower the number of GBM cells. Below, we will use the evolutionary computation method to determine the parameters of the system.

Since the 1g tumor volume is approximately1cm^3, which contains about 1×10^9 tumor cells [11], the maximum tumor bearing capacity of the oral cavity is $G_{max}=20\times20\%\times10^9=4\times10^9$.

In this section, we will select the appropriate parameters from the literature to implement the subsequent qualitative analysis and numerical simulations. Because our model is extended from refs. While in cases where the parameter information is not suitable for our scenario, such as parameters from animal models or other types of tumor models, we modified the parameter values to better fit our glioma model. Table 2 shows the parameter values of Eq. (2.1-2.2).

Table 1: Parameter values

Parameters	Units	Value	References
r_1	$(day)^{-1}$	0.191	Estimated from Ref.10
g_1	$(cell\ day)^{-1}$	4×10^{-9}	Estimated from Ref.10
k_1	$cell$	3.5×10^{2}	Estimated from Ref.10
g_2	$(day)^{-1}$	5×10^{-6}	Estimated
μ_1	$(day)^{-1}$	1.5×10^{-2}	Estimated from Ref.10
k_2	$cell$	3.4452×10^{4}	Estimated from Ref.10
a_2	$(cell\ day)^{-1}$	2.82×10^{-10}	Estimated from Ref.10
G_{max}	$cell$	4×10^{9}	Estimated from Ref.12

So, in Ref.11, the intrinsic growth rate of G cells is r_1 . The mathematical model developed by the authors studied tumor growth without immune intervention, but not cancer immune models. Thus, the values of g_1 and a_2 are reduced from,0.0194 to 4×10^{-9}、2.82×10^{-10} respectively (Adjusted according to the model estimates). $\mu_1$is the rate of loss of CIK due to inflammatory responses in the brain, which is significantly 0.15 compared to the loss of CD8 + T cells in Ref.10. The g_2 is the release rate of each CIK cell and to fit our model the value of g_2 is reduced to5×10^{-6} . In this paper, we refer to the semi-saturation constant of Ref.11 and adjust the values for better adaptation model of k1 and k2 to 3.5×10^{2}、3.4452×10^{4}. However, with more clinical data in the future, the hypotheses can be updated to reflect this new information.

Location and stability of equilibria

For the equation (2.1) - (2.2) in the absence of treatment. By using the Matlab software, we will analyze the equilibrium point distribution using the parameter values in Table 1.

As shown in Table 2, this system has two equilibria, namely, the tumor-free balance E1 and the high-tumor balance E2, respectively.

The Jacoby determinant for (2.1) – (2.2) is as follows

$$J=\begin{pmatrix} 0.156-(39\times G)/5\times10^{11} & -1.404\times10^{-6} \\ 5\times10^{-6} & -0.015 \end{pmatrix}. \qquad (3.1)$$

Table 2: Position of the equilibria

Equilibrium	*G*	*C*
E1	*0*	*0*
E2	*3999999988*	*1332495*

Table 3: Eigenvalues of equilibria and stability

Equilibrium	*stability*	λ_1	λ_2
E1	*unstable*	*0.156*	*-0.015*
E2	*stable*	*-0.156*	*-0.015*

The eigenvalues of the Jacobian (see Appendix) and the stability of E1 and E2 are shown in Table 3 respectively. The instability of E1 is determined by the positive eigenvalue. In contrast, E2 is a stable equilibrium. E1 instability and E2 stability mean that cancer cells continue to grow to high-tumor balance E2. Even if the treatment was performed. As long as treatment is stopped, the cancer cells will inevitably return to high-tumor status, that is, the tumor will escape immune surveillance.

Main result

When the hCIK cells were injected into the tail vein of immunodeficient mice carrying U-87MG tumors in the brain, a large number of CIK cells were infiltrated into the brain tumor, and the initial value of GBM (glioma cells) was 2.3×10^7 .The process of CIK cell therapy is to extract immune cells and then exposure to specific cytokines to activate them into the body. The normal range of immune cells is 60g / L-80g / L, while the range of glioma is less than 60g / L, and we assume it to be 40g / L. In addition, for human glioma small generally only a few ml, relatively large will be greater than 30ml, we assume that it is 15ml.Thus, the number of human glioma cell nuclei $\frac{40g}{1000ml} \times 15ml = 6 \times 10^6 ng = 6 \times 10^6 cell$.(pour: Number of cells $= \frac{\text{total mass}}{\text{Mean cell mass}} = \frac{1000\text{ng}}{1\text{textng/cell}} = 1 \times 10^3$cells)Generally speaking, the ratio of human to mouse tumors is $3 \times 10^2 : 1$, and the number of immune cells in rat glioma is 2×10^7cells, namely, the initial value of CIK cells is 2×10^7.

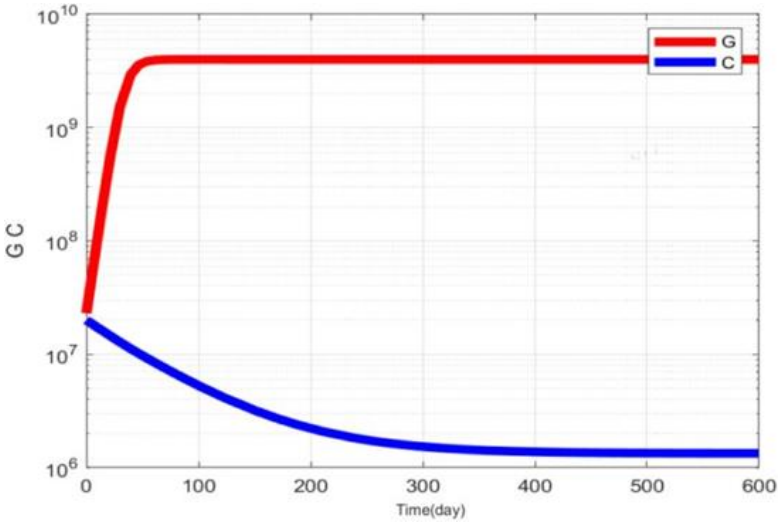

Figure 1: Simulation result without immunotherapy.The initial states at median immunity level are $G_0 = 2.3 \times 10^7$、 $C_0 = 2 \times 10^7$.

High levels, namely, the "median" level of the median number of lymphocytes, and "high" levels, where the number of immune cells is high. In the following sections, we only consider the initial states of the "median".

Tumor-immune response without treatment

By simulating median initial conditions, we show that without treatment, cancer cells continue to grow to high tumor balance E2 and exceed the body's carrying capacity. For the median immune level, as shown in Figure 1, the cancer cells will exceed the capacity of the body after 38 days.

Tumor-immune response with CIK therapy

n this subsection, using CIK immunotherapy, and then we observe median changes and disease progression when assuming the initial status of cancer and immune cells as median levels. The cancer response to immunotherapy will be simulated in three conditions over a 7-day dosing period.

In this model, immunotherapy was performed by upregulating the dose of CIK cells, 1×10^5, 1×10^6, 1×10^7(once a week for 4 consecutive weeks). As shown in the figure. At 40 days of CIK, the tumor growth rate was inhibited, and at the fourth cycle, when a dose of 1×10^5,the GBM number is 1.12×10^9.

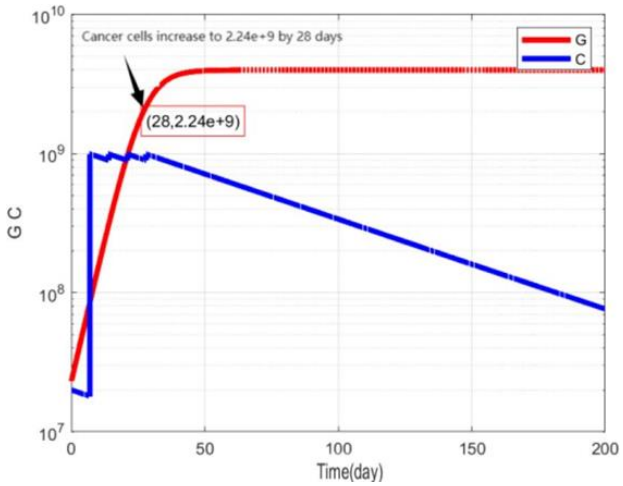

Figure 2: One administration mode with intensity of 1×10^5 *in a 7-day cycle. The initial states at median immunity level are* $G_0 = 2.3 \times 10^7$、$C_0 = 2 \times 10^7$.

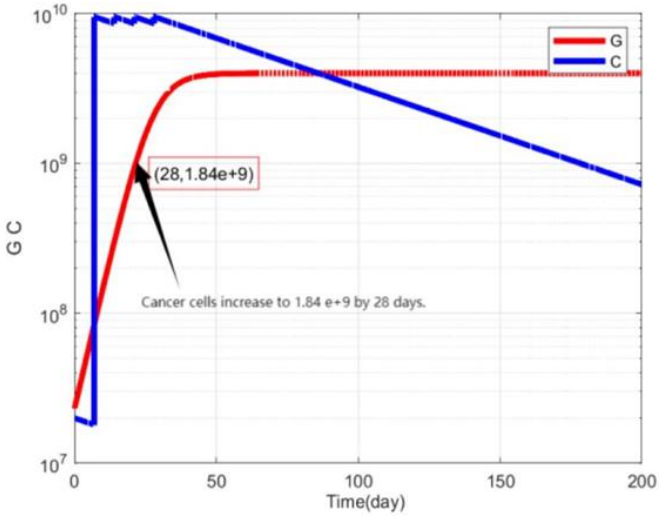

Figure 3: One administration mode with intensity of 1×10^6 *in a 7-day cycle. The initial states at median immunity level are* $G_0 = 2.3 \times 10^7$、$C_0 = 2 \times 10^7$.

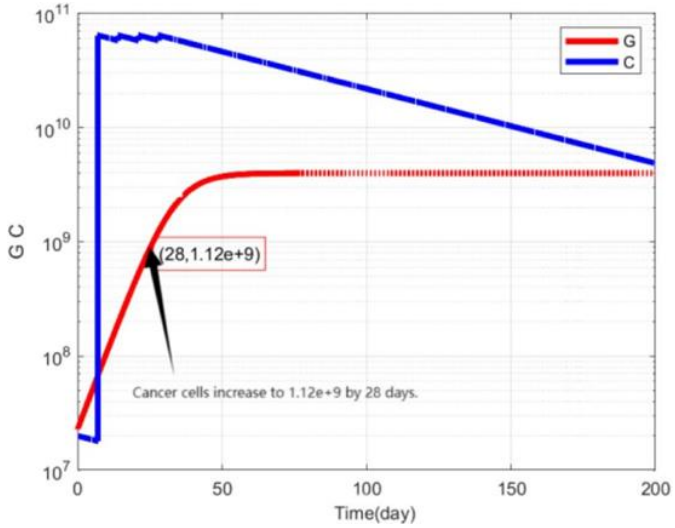

Figure 4: One administration mode with intensity of 1×10^7 *in a 7-day cycle. The initial states at median immunity level are* $G_0 = 2.3 \times 10^7$、$C_0 = 2 \times 10^7$.

GBM cells decreased their tumor volume by 44%, 54%, and 72% at the fourth week, respectively, matching the clinical data in the literature.

Combination therapy with CIK and TMZ

Two previous studies have shown that CIK cells have significant therapeutic effects on GBM [Error! Reference source not found.Error! Reference source not found.]. However, the results of the intracranial CIK cell injection method [Error! Reference source not found.] and GBM subcutaneous xenograft animal models [Error! Reference source not found.] are difficult to translate immediately to the clinic. The clinical efficacy of temozolomide (TMZ) combination therapy is the most widely used anti-GBM chemotherapeutic agent. Therefore, we evaluated the antitumor effects of intravenous CIK cells using a U-87MG GBM orthotopic xenograft animal model. CIK cells had a significant therapeutic effect on GBM and enhanced in combination with TMZ. Figure 5 shows that tumors grew to 28 days with CIK and TMZ, which is more than single-agent CIK.

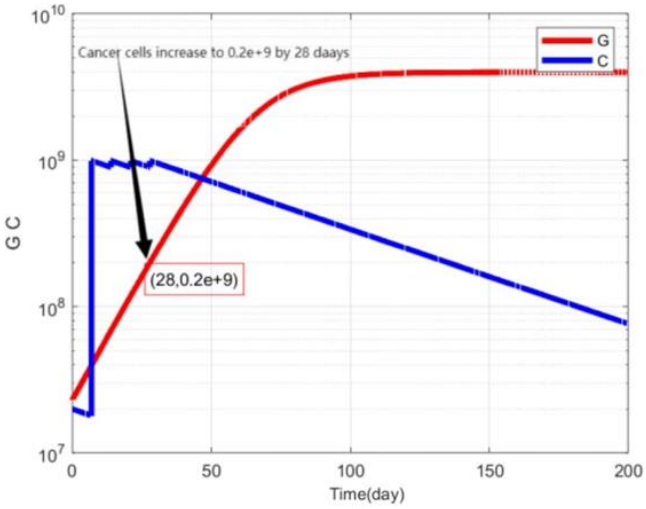

Figure 5: Combination with CIK and TMZ. One administration mode with intensity of in a 7-day cycle. The initial states at median immunity level are $G_0 = 2.3 \times 10^7$、$C_0 = 2 \times 10^7$,*the CIK intensity was* 1×10^7.

Table 4: Eigenvalues of equilibria and stability

Equilibrium	***Therapy***			
	CIK (1×10^5)	***CIK*** (1×10^6)	***CIK*** (1×10^7)	***CIK*** (1×10^7)***and TMZ***
Tumor reduction （%）	44%	54%	72%	95%

In this part, we hypothesized that low-dose TMZ combined with CIK immunotherapy is feasible. According to the above experiments, tumor growth was significantly inhibited at hCIK cell doses 1×10^5、1×10^6、1×10^7 (once per week for 4 weeks), with tumor reduction of 44%, 54% and 72%, and controlled CIK cell dose 1×10^7, as shown in Figure 5, CIK + TMZ by day 28, which was better than 72% in hCIK treatment alone.

4. Conclusion

In this work, we developed a mathematical model to study the dynamic behavior of gliomas, with a focus on the role of CIK cells and related therapies. The model was organized as a system of ordinary differential equations describing the dynamic interactions between tumor and immune cells, and the correlation between CIK cells and GBM cells. To better understand the disease progression, without treatment, we analyzed the location of the equilibrium points and their stability properties as well. The presence of two equilibria, one unstable and one stable high tumor volume, means that cancer cells will continuously grow to high tumor balance without treatment, and even with therapeutic management, the tumor will inevitably evade immune surveillance as long as treatment ceases. By observing the GBM cells data of 4 cycles of CIK immunotherapy after different doses of cell surgery, we found that GBM (glioma cells) was dose-dependent on CIK treatment, and the larger the dose, the better the treatment effect.

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