Evolution of Proliferating Cells under Different Decaying Behaviors of the Total Tumor Cells During a Course of Treatment

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Abstract: The two compartment model of tumor growth proposed by Gyllenberg and Webb can be modified in the presence of anti mitotic agents. The evolution of proliferating cells is investigated considering this modified model and the different decaying behaviors of the total cell population.

Key–Words: Cell Kinetics, Tumor Growth

1 Introduction

Several theoretical models have been developed to describe the evolution of untreated tumor cells or under interaction with different chemotherapeutic drugs [1]-[11]. The population of tumor cells can be considered as a construction of two subpopulations comprised of the proliferating and the quiescent. Proliferating cells are those which are in the active phase of a cell cycle. Quiescent cells are found in the resting phase. Monitoring the growth evolution of the total number of tumor cells, and also considering the kinetics of each subpopulation, leads to an analytical expression of the evolution of each of the subpopulations [1]. Modeling of the dynamic of the proliferating cells improves our understanding of the inner structure of a tumor as a complex system. Furthermore, studying the evolution of proliferating cells during a course of therapy helps in constructing a better therapeutic protocol and, therefore a better understanding of the therapeutic results.

While an untreated tumor growth curve can be expressed by a logistic or a Gompertizan function, no specific mathematical function can represent the decaying behavior of the total number of tumor cells during a course of chemotherapy. In this study, three behaviors, linear decay, exponential decay and a bell shaped decay are considered for the evolution of the total tumor cell population. Considering the above assumption, and equipped with the existing model, Feizabadi et al. [2] presents the evolution of the proliferating cell subpopulation.

In the following, behavior of the proliferating cells is analyzed through a model simulation.

2 Theoretical Model

The kinetic of proliferating, $P$, cells and quiescent, $Q$, cells can be expressed by the following interaction diffusion ordinary equations [2, 3, 4]:

$$\frac{dP}{dt} = [\beta - \mu_p - r_o(N) - a_p(1 - \exp(-u))] P + r_i(N)Q$$

(1)

$$\frac{dQ}{dt} = r_o(N)P - [r_i(N) + \mu_q + a_q(1 - \exp(-u))] Q,$$

(2)

$$N = P + Q$$

(3)

In the above equations, $(r_i(N), r_o(N))$: the transition rate functions, $\mu_p$ and $\mu_q$ are natural cell decay rates for each compartment, $\beta$ represents the reproduction rate of proliferating cells, and $N$ is the total number of cell populations during the course of therapy. In these equations $a_q(1 - \exp(-u))$ and $a_p(1 - \exp(-u))$ are the $Q$ and $P$ cells response function to the drug. The diffusion of the drug is also considered to exist exponentially in the form of $u(t) = u_0 \exp(-d \cdot t)$, while $u_0$ is the initial drug concentration and $d$ is the per capita decay rate. The explicit expression for the proliferating cell subpopulation is obtained after some mathematical calculations as follows:

$$P_2(t) = \frac{dN/dt + [\mu_q + a_q(1 - \exp(-u))] N}{S + (a_q - a_p)(1 - \exp(-u))}$$

(4)
where
\[ S = -(a_q - a_p)(1 - \exp(-u_0)) \]
\[ + \frac{N_0}{P_0} [\mu_q + a_q(1 - \exp(-u_0))] + \frac{dN_0}{dt} \]

In the above expression, \( N_0 \) and \( P_0 \) are the size of \( P \) and \( Q \) cells at the beginning of the therapy and \( N \) expresses the behavior of the total number of cell populations during the course of therapy [2]. The behavior of \( P \) cells is simulated and analyzed when \( N \) follows a different decaying behavior.

### 3 Simulation and Conclusion

As indicated in equation 4, together with some parameters, the evolution of the proliferating cells is traceable upon knowing the evolution of the total number of tumor cells. In this section, the decaying behavior of the total number of tumor cells is considered to be best fitted by one of the following categories:

1. \( N = N_0 - k_1.t \)
2. \( N = N_0 \exp(-k_e.t) \)
3. \( N = N_0 \exp[k_1/k_2.(1 - \exp(k_1.t))] \)

In the above expressions, \( N_0 \) is the size of the tumor cells at the beginning of the therapy. It is considered that the growth of the tumor follows the Gompertz function and the therapy starts at \( t = 40 \) units of time. Therefore \( N_0 \) can be expressed as:
\[ N_0 = \exp[k_+/k_- (1 - \exp(-k_-(= 40)))] \]
where \( k_+ \) and \( k_- \) are the growth and retardation rate constant during the in-growth phase. Considering these linear, exponential, and bell shaped decaying behaviors as \( N \), Equation 4 is simulated to different choice of parameters. The course of therapy is considered to be started at \( t = 40 \) and ended at \( t = 45 \).

The tumor growth curve and the corresponding proliferating subpopulations are shown in figure 1-3. It is observed that the linearly decaying behavior of the total tumor cells produces a monotonically decreasing behavior of the proliferating cells. In the case of exponentially decaying, and the bell shaped decay, the decreasing size of the proliferating cells begins with a brief delay and a small growth in size can be seen in a short period even after the start of the therapeutic phase. In the next step of simulations, a sharper decay of the total tumor cells is also examined (dashed lines). In this case, for the first category, a slight change can be seen in the size of the proliferating cells at the beginning of the therapy while the reduction in size of proliferating cells becomes more

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**Figure 1**: A: decaying evolution of the total tumor cells, B: evolution of the corresponding proliferating cell subpopulations. Common parameters: \( k_+ = 2.76, k_- = 0.134, a_p = a_q = 0.9, \mu_q = 0.2, u_0 = 1, d = 1.5 \). The first row, \( k_1 = 0.4.10^3 \) (solid line), and \( k_1 = 0.4.10^8 \) (dashed line). The second row, \( k_e = 1 \) (solid line), and \( k_e = 1.1 \) (dashed line). The last row, \( k_1 = 0.3 \) and \( k_2 = 15 \) (solid line), and \( k_1 = 0.5 \) and \( k_2 = 15 \) (dashed line).
obvious at the end (t=45). In the exponentially decaying category, a very slight increase in the decaying rate causes a noticeable decrease in size of the proliferating cells at the beginning of the therapy, while no great change is detected at the end. In the last category, when a shaper decay is considered for the bell shaped evolution, the size of the proliferating cells shows a noticeable growth at the beginning of the therapy and even a slight growth at the end. In summary, the evolution of the proliferating cells is variously constructed under the different total tumor cells' decaying behavior.

In Figure 2, the evolution of the proliferating cells under a linear, exponential or a bell shaped decay of the tumor cells is compared. It can be seen that for the exponentially decaying behavior, the population of the proliferating cells is smaller in size at the end of the therapy. However, the population of proliferating cells is relatively large at the first half of the therapy as compared to other categories. This indicates that the periodic time of a therapy can be crucial in controlling the size of the proliferating cells.

In this work, the process of the decaying size of proliferating cells is investigated by combining the dynamic of inter tumor subpopulations and the evolution of the total number of tumor cells during the course of therapy. Monitoring the behavior of proliferating cells during a course of therapy is informative in order to better implement a more effective approach to treating a tumor.

References: