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A MATHEMATICAL MODEL OF THYROID CANCER RESPONSE TO RADIOIODINE AND INFLUENCE OF THE IMMUNE SYSTEM

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Abstract

The incidence of thyroid cancer has enhanced in the last decades and the use of mathematical models to uncover complex mechanisms and processes of this disease is increasingly common, with important results already been published. Thyroidectomy and radioiodine therapy (RAI) are means usually used to treat papillary thyroid carcinoma (PTC). Actions mediated by the immune system in cancer can influence this disease in several aspects, pro and antitumor actions caused by some interleukins, such as interleukin-6, or T-cells are often considered in PTC. This work presents a mathematical model about the PTC response to RAI and the influence of the immune system on treatment success. The results of the model captured the most important aspects for the production of scenarios in which patients respond or not to the treatment.

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Introduction

Cancer is a word that indicates a set of more than 200 diseases, for which several treatments as surgery, chemotherapy, radiotherapy and immunotherapy are used. Thyroid cancer is a malignant

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tumor with increasing incidence, and with this, mathematical models have also been used to study several of their aspects, providing a detailed understanding of mechanisms and processes including various stages of this cancer [8]. Treatment with radioiodine (^{131}I) after thyroidectomy is often used to eliminate the cancer cells in the PTC and a mathematical model to evaluate the effectiveness of RAI treatment is presented in [1]. The developed model provides classification criteria from the parameter associated with the tumor doubling-time under treatment to recognize patients responders or non-responders to RAI in the early treatment stages. The immune system is an important agent for the regulation of cancer, which can either facilitate the progression of the tumor or delay it, acting as a suppressor [2]. Although interleukin-6 (IL-6) is a representative agent for the dual role of the immune system [3], in thyroid cancer many studies have highlighted a positive influence of it on the development of tumors, such as [5, 6]. A treatment with immunotherapy via T lymphocytes in chronic lymphocytic leukemia under chemotherapy is modeled from differential equations in [7].

Thus, considering the PTC treated with RAI, the positive influence of IL-6 and immunosurveillance performed by T-lymphocytes [4], a mathematical model is presented in this work with the purpose of evaluating the efficacy of RAI in the PTC influenced by two modes of action of the immune system.

Mathematical Model

Denoting the RAI activity by A, the number of cancer cells by N, the concentration of IL-6 at the tumor site by I, the number of immune cells (T lymphocytes) by L and the concentration of thyroglobulin in the blood by T_g, in which all variables depend on time t and based on [1, 7], the proposed model is given by

$$\begin{cases} \dfrac{dA}{dt} &= -a\log(2)A, \\ \dfrac{dN}{dt} &= \left(\dfrac{\log(2)}{T_d} + \alpha(I - I_e)\right) N\left(1 - \dfrac{N}{K_N}\right) - \dfrac{\rho AN}{\beta + A} - r_1 LN, \\ \dfrac{dI}{dt} &= \sigma_1 + \dfrac{cN}{\gamma + N} + bA - mI, \\ \dfrac{dL}{dt} &= \sigma_2 + \dfrac{\lambda NL}{\tau + N} - r_2 NL - nL, \\ \dfrac{dT_g}{dt} &= pN - dT_g, \end{cases} \tag{1}$$

where a is the delayed target iodine effectiveness rate and the term $-a\log(2)A$ describes the effect of RAI on cancer cells acting continuously. The parameter T_d is the tumor doubling time under treatment, I_e is the concentration of IL-6 in the state of homeostasis and the constant α regulates how much IL-6 increases the tumor proliferation. The constant K_N is the carrying capacity of the cancer cells population; ρ is the efficiency rate of iodine on tumor cells; β is the RAI amount for which such efficiency is the half of its maximum in the cancer population; and r_1 and r_2 represent the interaction coefficients between cancer and immune cells, respectively affecting cancer and immune populations. The constants σ_1 and σ_2 represents the natural production of IL-6 and the natural influx of immune cells to the place of interaction, respectively; c is the production rate of IL-6 by cancer cells; γ is the number of cancer cells by which the immune system response is the half of its maximum; b corresponds to the increase of IL-6 due to RAI in the organism; m is the natural elimination of IL-6; λ is the production rate of immune cells stimulated by the cancer; τ is the number of cancer cells by which the immune system response is the half of its maximum; p is the concentration of T_g produced by one tumor cell; d is the elimination rate of thyroglobulin from blood and n is the natural death rate of immune cells.

Results

The equilibrium points of model (1) are given by

- $P_1 = (A, N, I, L, T_g) = (0, 0, \sigma_1/m, \sigma_2/n, 0)$, in which I and L represent levels equal to those found in healthy individuals. Then P_1 illustrates the situation in which RAI with the immune system eliminated the disease.
- $P_2 = (A, N, I, L, T_g) = (0, N^*, I^*, L^*, T_g^*)$, where

$$\begin{aligned} N^* &= \frac{K_N(s + \alpha(I - I_e) - r_1 L)}{s + \alpha(I - I_e)}, \\ I^* &= \frac{\sigma_1(\gamma + N) + cN}{m(\gamma + N)}, \\ L^* &= \frac{\sigma_2(\tau + N)}{(r_2 N + n)(\tau + N) - \lambda N}, \\ T_g^* &= \frac{pN}{d}. \end{aligned}$$

The equilibrium point P_2 indicates situations where the disease presents resistance over time, overcoming the activity of radiotherapy and the antitumor action of the immune system. The numerical simulations model were performed by Runge–Kutta 4th order method.

Figure 1 presents the solutions obtained with the two values estimated to parameter T_d in [1]: $T_d = 66.8$ and 9.8 months, with these values the two possible convergence scenarios, represented by P_1 and P_2, are obtained. Considering $T_d = 66.6$, the cancer cells are eliminated before 30 months, in this scenario the level of thyroglobulin always decay over time, indicating absence of recidive of the disease. When the value of $T_d = 9.8$ is considered, the treatment is ineffective in eliminating tumor cells and the thyroglobulin levels decays only at the beginning of treatment. In both situations, $T_d = 66.8$ and 9.8, a small growth in IL-6 levels is observed, with the increase from $I_0 = 2.17$ to 2.4 pg/mL. The behavior of the immune cells is similar in both situations, where a continuous growth of this population is noted over time, with an increase of approximately 1.5×10^7 cells in the period considered.

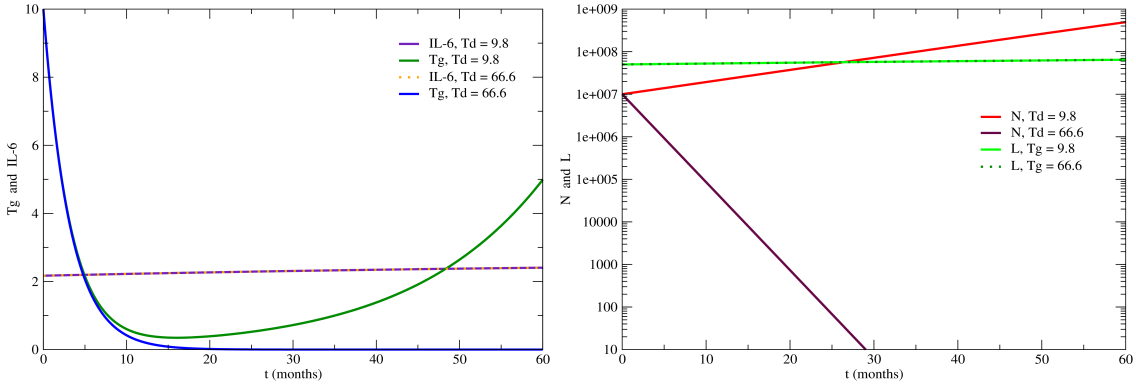

Figure 1: Evolution of levels of Tg, IL-6 and number of cancer cells in patients with PTC. Initial conditions: $A_0 = 5.5$ GBq, $N_0 = 10^7$ cells, $I_0 = 2.17$ pg/mL, $L_0 = 10^7$ cells and $T_{g,0} = 10$ µg/L. Parameters: $a = 0.0169$, $K_N = 10^{10}$, $\sigma_1 = 5 \times 10^{-4}$, $b = 10^{-3}$, $m = 2.3 \times 10^{-4}$, $p = 3.86 \times 10^{-9}$, $d = 0.319$, $\alpha = 10^{-4}, I_e = 2.17$, $\beta = 4$, $\gamma = 10^5$, $\sigma_2 = 3 \times 10^5$, $\lambda = 10^{-10}$, $\tau = 10^2$, $r_2 = 1 \times 10^{-13}$ and $n = 10^{-3}$. The parameter $T_d = 9.8$ was used with $\rho = 0.00407$ and $r_1 = 5 \times 10^{-11}$, while $T_d = 66.6$ was combined with $\rho = 0.407$ and $r_1 = 5 \times 10^{-9}$.

Conclusions

From the numerical simulations it was verified that the model produced scenarios with elimination of the disease or the progression of the cancer to a metastasis. The situation with the spread of cancer was understood from an advance of tumor cells in terms of mutations to a state of poorly differentiated cells. The most important parameters for both scenarios were the effectiveness of iodine on tumor cells, ρ; the doubling time of the tumor under treatment, T_d; the interaction between cancer and immune cells, r_1 and r_2; and the natural influx of immune cells to the interaction site, σ_2. Then, the model (1) was able to capture the most important processes associated with RAI treatment in PTC combined with the immunosurveillance via T lymphocytes.

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