Metastatic papillary thyroid cancer under treatment with different I-131 protocols: a mathematical model

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Reception date of the manuscript: 20/01/20220
Acceptance date of the manuscript: 23/02/2022
Publication date: 29/04/2022

Abstract—A mathematical model was used to study numerically, the metastatic papillary thyroid cancer (PTC) response to protocols of treatment with radioiodine I-131 (RAI), considering different values for the RAI efficiency ratio. Besides that, scenarios with decreasing amounts of doses, and a higher dose first, followed by smaller ones, were also proposed. In some simulations the number of tumor cells did not decrease, indicating a resistance against RAI treatment conditions. The failure may mean a poorly structured treatment protocol regarding the type of therapy, doses, application intervals, or any of their combinations. RAI treatment scenarios with alternating dosages, starting with a higher dose followed by smaller ones, presented a possible successful treatment response, i.e., tumor elimination. This variation is not common in clinical practice, but the scenario sheds light on new possible forms of treatment. Through numerical simulations with the ordinary differential equations system, it was shown that mathematical models are important tools in the study of thyroid cancer and could assist in determining the most suitable treatment protocols for metastatic PTC.

Keywords—Ordinary differential equations, Allee effect, Interleukin, Iodine, Metastasis, Thyroglobulin.

Resumen— Se utilizó un modelo matemático para estudiar numéricamente, la respuesta del cáncer papilar de tiroides metastásico (CPT) a los protocolos de tratamiento con radioyodo I-131 (RAI), considerando diferentes valores para el ratio de eficiencia del RAI. Además, también se propusieron escenarios con cantidades decrecientes de dosis, y una dosis más alta primero, seguida de otras más pequeñas. En algunas simulaciones el número de células tumorales no disminuyó, lo que indica una resistencia a las condiciones de tratamiento con RAI. El fracaso puede significar un protocolo de tratamiento mal estructurado en cuanto al tipo de terapia, las dosis, los intervalos de aplicación o cualquiera de sus combinaciones. Los escenarios de tratamiento con RAI con dosis alternas, comenzando con una dosis más alta seguida de otras más pequeñas, presentaron una posible respuesta exitosa al tratamiento, es decir, la eliminación del tumor. Esta variación no es habitual en la práctica clínica, pero el escenario arroja luz sobre nuevas formas posibles de tratamiento. Mediante simulaciones numéricas con el sistema de ecuaciones diferenciales ordinarias, se demostró que los modelos matemáticos son herramientas importantes en el estudio del cáncer de tiroides y podrían ayudar a determinar los protocolos de tratamiento más adecuados para el PTC metastásico.

Palabras clave— Ecuaciones diferenciales ordinarias, Efecto Allee, Interleucina, Yodo, Metástasis, Tiroglobulina

Introduction

Thyroid cancer, which is mainly restricted to the thyroid gland and regional lymph nodes, is one of the most common neoplasms worldwide, reaching 586,202 new cases identified only in 2020 (Kunadharaju et al., 2015; ACS, 2021). This sort of cancer is histopathologically classified, and its emergence depends on numerous factors such as age, sex, family history, and radiation exposure. Differentiated thyroid cancer (DTC) subtype - derived from follicular thyroid cells - accounts for 95 % of all thyroid cancers and includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). In this scenario PTC represents approximately 80 % of DTCs. Physicians typically diagnosed this neoplasm after discovering gland nodules in routine imaging exams (e.g., magnetic resonance and ultrasound), and most of their patients are asymptomatic at the time of initial diagnosis (Ospina et al., 2020; Ramundo et al., 2020).

Tumoral biomarkers are macromolecules present in the tu-

mor that act as indicators of the presence of cancer. For PTC, an important biomarker is thyroglobulin (Tg), responsible for predicting the evolution of the disease, as its levels are used to determine the patient's response to treatment (Barbolosi et al., 2017; Haugen et al., 2016). In addition, interleukin 6 (IL-6), a cytokine that plays a central role in the regulation of inflammatory and immune processes, is widely studied regarding its influence on cancer, including in thyroid cancer, whose overexpression can be related to a poor prognosis (Guarino et al., 2010; Lumachi et al., 2010). Among available treatments for PTC, therapy with radioiodine I-131 (RAI) is included; this therapy has been used for more than 60 years and consists of systemic administration of I-131 to irradiate remaining thyroid tissue (Schmidbauer et al., 2017). Its success depends on some factors such as the amount of iodine that is absorbed by the gland, which can be measured through the sodium/iodide symporter (NIS) (Barbolosi et al., 2017; Silva et al., 2020). Defining the dose of RAI to be used involves taking into account the size and number of lesions, metastases, lymph node involvement, degree of radioactive iodine uptaken before treatment, patient's clinical condition, among others (Haugen et al., 2016).

Considering all the patients diagnosed with DTC, up to 10% develop distant metastases, in particular affecting lung and bone. Metastases can be discovered at the initial stage of the disease or can be identified during longitudinal follow-up (Haugen et al., 2016; Schmidbauer et al., 2017). In these situations, treatment with radioiodine is indicated if the disease is responsive to it (Schmidbauer et al., 2017; Barbolosi et al., 2017) and the best responders are patients with highly avid metastases without structural correlate on high-resolution imaging studies. There is no standard protocol established for the treatment of metastasis, but what usually occurs in clinical practice are periodic administrations of 4–11GBq, not exceeding an average cumulative activity of 22.2GBq (Barbolosi et al., 2017; Schmidbauer et al., 2017). In Belerwaltes et al. (1982), data from 532 patients undergoing DTC and PTC with distant metastases treated with RAI (doses between 3.7GBq and 6.5GBq) were used to assess the survival time and remission. As a result, those considered free of metastasis after RAI therapy survived three times longer than those who could not be healed.

Another study involving 109 patients who had DTC bone metastases is presented in Bernier et al (2000), aiming to evaluate survival time and the best therapeutic approach to be used. The patients underwent total thyroidectomy followed by RAI treatment. The treatment was either with a single ablative dose of RAI or with periodic treatment (6-18 months). Thus, the therapeutic dose of RAI ranged from 3.7–7.4 GBq, and the cumulative dose received by patients ranged from 3.7–44.4GBq. As a result, through a multivariate analyses the authors established that the cumulative dose of RAI, together with other factors such as the detection of bone metastases are independent prognostic features associated with improved survival in those patients.

Two-thirds of patients may become refractory to RAI, hindering the continuation of treatment itself and making it necessary to use other therapeutic modalities, such as targeted therapy and immunotherapy (Kunadharaju et al., 2015; Schmidbauer et al., 2017; Tirro et al., 2019). There are some absolute contraindications regarding the use of RAI, such as pregnancy and breastfeeding. In addition, relative contraindications include bone marrow depression, restricted pulmonary function and central nervous system metastases (Schmidbauer et al., 2017).

In recent years, mathematical modeling has expanded cancer knowledge by describing the phenomenon as tumor growth, for example, besides predicting responses to different treatment protocols (Kebew et al., 2000; Esnaola et al., 2001; Eftimie et al., 2011; Beerenwinkel et al., 2015). In Silva et al. (2019), a systematic review of works published between 2006 and 2019 was presented, involving the mathematical modeling of thyroid cancer using differential equations or similar. From this review, two studies are highlighted. In Barbolosi et al. (2017), an ordinary differential equation (ODE) model was proposed to assess the efficacy of RAI treatment in patients who underwent thyroidectomy, but later developed metastasis. In Traino and Martino (2006), the authors used linear-quadratic models to theoretically discuss the amounts of RAI administered in cases of metastasis and ablation of cells remaining in the thyroid after surgery.

An ecology concept used in cancer research from mathematical modeling is the Allee effect (Silva et al., 2020; Delitala and Ferraro, 2020). This effect is defined as a positive association between any individual fitness component and the number or the population density in the same species (Stephens et al., 1999). The Allee effect is observed in some populations where the population is extinct below a certain threshold, that is, at an unstable equilibrium where, below it, the population decreases toward extinction. Recent progress in cancer research has shown that tumors, like other species that fight for survival, harbor an intricate population dynamics, suggesting the possibility of exploring their ecology for possible treatments (Silva et al., 2020; Kebew et al., 2000; Korolev et al., 2014).

The aim of this work is to evaluate, through numerical simulations of a mathematical model, the metastatic PTC response to different treatment protocols regarding doses and numbers of applications of RAI. The model to be described consists of a system of ODEs, whose variables are the used doses of RAI, the number of tumor cells, and the serum concentrations of IL-6 and thyroglobulin.

MATHEMATICAL MODEL

Metastatic PTC cases under treatment with the RAI is the topic under modeling. In these cases, the therapy usually consists of periodic administrations of RAI, but it is possible to apply a treatment with periodic administrations and different doses (Barbolosi et al., 2017). The mathematical model used in the simulations was proposed by Silva et al. (2020) and takes into account the Allee effect associated with the tumor dynamics and the PTC treatment with RAI. The system of equations has four variables, all depending on the time, t, where A represents the used dose of radioiodine, N represents the number of tumor cells, I represents the serum concentration of IL-6 and T_g represents the serum concentration

of thyroglobulin. The model is given by:

$$\begin{cases} \dfrac{dA}{dt} = -a\log(2)A, \\ \dfrac{dN}{dt} = \alpha(1-k\exp(-(\beta I))N\left(\frac{N}{Q}-1\right)\left(1-\frac{N}{K}\right) - \rho AN, \\ \dfrac{dI}{dt} = \sigma + \frac{cN}{\gamma+N} + bA - mI, \\ \dfrac{dT_g}{dt} = pN - d\ T_g. \end{cases} \tag{1}$$

Table 1 presented the description of the parameters and the values used in the simulations are present in Table 2.

TABLE 1: PARAMETERS AND DESCRIPTIONS.

Parameter	Description
a	Elimination rate of RAI presenting delay in tumor cells
α	Proliferation rate of tumor cells under the influence of IL-6
k	Coefficient on the action of IL-6 on tumor proliferation
β	Rate of influence of IL-6 on tumor proliferation
Q	Population threshold of the Allee effect
K	Carrying capacity of the tumor
ρ	Efficiency rate of RAI on tumor cells
σ	Rate of normal production of IL-6
c	Rate of production of IL-6 by tumor mass
γ	Relationship between IL-6 production and tumor size
b	IL-6 production rate due to RAI treatment
m	IL-6 natural elimination rate
p	Rate of Tg production by tumor cells
d	Rate of Tg elimination from the blood flow

TABLE 2: PARAMETERS, USED VALUES, UNITS AND REFERENCES.

Parameter	Value	Unit	Reference
a	3	month^{-1}	Barbolosi et al. (2017)
α	7.5×10^{-1}	month^{-1}	Silva et al. (2020)
k	7.2×10^{-1}	-	Silva et al. (2020)
β	2×10^{3}	$({}^{\dagger}\text{pg}^{-1}\times\text{mL}^{**})$	Silva et al. (2020)
Q	5×10^{8}	cells	Wilkie and Hanhnfeldt (2013)
K	1×10^{10}	cells	Wilkie and Hanhnfeldt (2013)
ρ	-	$(\text{GBq}^{*}\times\text{month})^{-1}$	Barbolosi et al. (2017)
σ	5×10^{-2}	${}^{\dagger}\text{pg}\times(\text{mL}^{**}\times\text{month})^{-1}$	Silva et al. (2020)
c	5×10^{-1}	${}^{\dagger}\text{pg}\times(\text{mL}^{**}\times\text{month})^{-1}$	Silva et al. (2020)
γ	1×10^{9}	cells	Silva et al. (2020)
b	2×10^{-2}	${}^{\dagger}\text{pg}\times(\text{mL}^{**}\times\text{month}\times\text{GBq}^{*})^{-1}$	Silva et al. (2020)
m	2.38×10^{-2}	month^{-1}	Silva et al. (2020)
p	3.86×10^{-9}	${}^{\ddagger}\mu\text{g}\times(\text{L}\times\text{month})^{-1}$	Barbolosi et al. (2017)
d	3.19×10^{-1}	month^{-1}	Barbolosi et al. (2017)

As presented in Silva et al. (2020), the first equation comes from the exponencial decay law $A(t) = A_0\exp(\lambda t)$, and represents the continuous therapeutic effect of RAI on tumor cells. For the a parameter, we used the biological half-life concept, which is the closest to the elimination rate of RAI with delay in tumor cells (Schmidbauer et al., 2017). This half-life is an important factor to determine the effectiveness of radioiodine therapy because it is generally shorter in tumors than in normal thyroid tissue. For instance, biological iodine half-life in the thyroid is 80 days in patients with normal thyroid function, 5 to 40 days in patients with hyperthyroidism, and approximately 10 days in patients with DTC (Amdur and Mazzaferi, 2000). Thus, we considered $a = 3$ month^{-1}. The expression $\alpha(1-k\exp(-(\beta I))$ represents the proliferation rate of metastatic tumor cells under the influence of IL-6. The parameter Q represents the Allee threshold, with $0 < Q < K$, where K is the tumor cells' carrying capacity, i.e., the maximum of tumor cells in the microenvironment can achieve with the available nutrients (Sachs et al., 2001). The threshold Q denotes a maximum cancer resistance to antitumor immune action and treatment with RAI. If N decreases to values close enough to Q during treatment, the rate $\frac{dN}{dt}$ will always become negative, representing a therapeutic efficacy capable of tumor elimination (Silva et al., 2020; Delitala and Ferraro, 2020). The third equation represents the influence of IL-6 on tumor cells, considering its natural production (σ), the one caused by the tumor ($\frac{cN}{\gamma+N}$), the increase in its levels due to RAI treatment (b) and its natural elimination (m). The last equation deals with thyroglobulin levels, considering a production rate by tumor cells (p) and also an elimination rate (d).

The model has three equilibrium points that represent scenarios of

- tumor elimination $(N < Q)$, $P_1 = \left(0, 0, \dfrac{\sigma}{m}\right)$;
- the threshold of the Allee effect $(N = Q)$, $P_2 = \left(0, Q, \dfrac{\sigma}{m} + \dfrac{Qc}{(Q+\gamma)m}\right)$;
- the progression to metastasis $(N > Q)$, $P_3 = \left(0, K, \dfrac{\sigma}{m} + \dfrac{Kc}{(K+\gamma)m}\right)$.

In the analysis of the equilibrium points of the studied model (1), the last equation is not considered. The reason for this choice is because the variable Tg does not affect the others one, but it is a crucial tumor marker (Silva et al., 2020). The ODE system was solved numerically in MATLAB ©[1] using the fourth-order Runge-Kutta method. In all simulations the initial conditions were $N(0) = 1.12\times10^{9}$ cells, $I(0) = 7.98$ pg/mL and $Tg(0) = 10$ µg/L, with t given in months and $Q = 5\times10^{8}$cells (Silva et al., 2020).

NUMERICAL SIMULATIONS

We numerically simulated different treatment scenarios for metastatic PTC with RAI, including alternation in the value of doses (which is not always part of clinical practice), seeking to assess which therapeutic approaches regarding tumor cell elimination would be the best. According to Schmidbauer et al. (2017), for metastatic thyroid cancer, RAI doses between 4-11GBq are administered, depending on the patient's characteristics, which is the interval considered here. Different values for the RAI efficiency rate in tumor cells, ρ, were used based on the value proposed by Barbolosi et al. (2017) ($\bar{\rho} = 0.00407$ $(\text{GBq}\times\text{t})^{-1}$). The results are shown below.

RESULTS AND DISCUSSION

Figures 1 and 2 show treatment scenarios with doses of 4GBq of activity every five months, which is one of the protocols shown in IPEN (2015), respecting the fact that, during treatment, the average cumulative activity (defined as the sum of the round dosages) does not exceed 22.2GBq. As noted in Figure 2, RAI treatment eliminates the tumor cell population over time for larger values for ρ, which in a clinical setting represents a potential success. The ρ threshold

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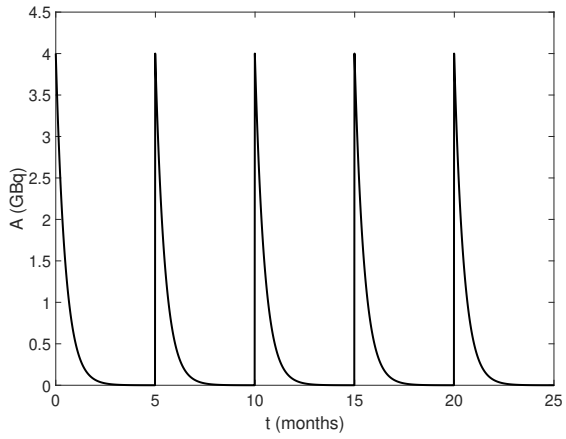

Figure 1: Representation of the treatment with periodic doses of 4GBq every five months, respecting the average cumulative activity.

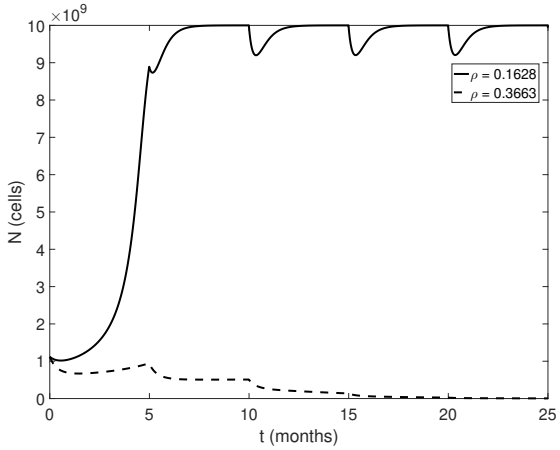

Figure 2: Number of tumor cells under treatment with doses of 4GBq of activity every five months, with $N(0) = 1.12 \times 10^9$ cells and different values for ρ $(\text{GBq}\times\text{month})^{-1}$.

that determines the success or failure of this treatment is close to $(85\bar{\rho})$, that is, $\rho = 0.3459$, as seen in Figure 3. For $\rho = 0.3418$ $(\text{GBq} \times \text{t})^{-1}$ $(\approx 84\bar{\rho})$ and values smaller than it, the cancer cells tend to carrying capacity, even with RAI treatment.

The model proposed by Barbolosi et al. (2017) aimed to identify the need to change the concentration and even the quantity of the RAI administration. Therefore, a treatment scenario with dosage change (Figures 4 and 5) was simulated. This alternation is not common in clinical practice, but it may be a possibility for future treatments. Based on the range of values presented in Schmidbauer et al. (2017), RAI treatment was administered every five months, with the first dose being 11GBq, followed by 4GBq, 2GBq and 4GBq.

Using $\rho = 0.1628$ $(\text{GBq}\times\text{month})^{-1}$ (Figure 5) and an alternating administration of RAI doses (Figure 4), it is possible to observe the number of tumor cells heading towards zero. In a clinical scenario, this result can be interpreted as a possible successful treatment. It is possible to observe that the levels of IL-6 and Tg vary over the time dependind on the number of tumor cells. This was expected and is aligned

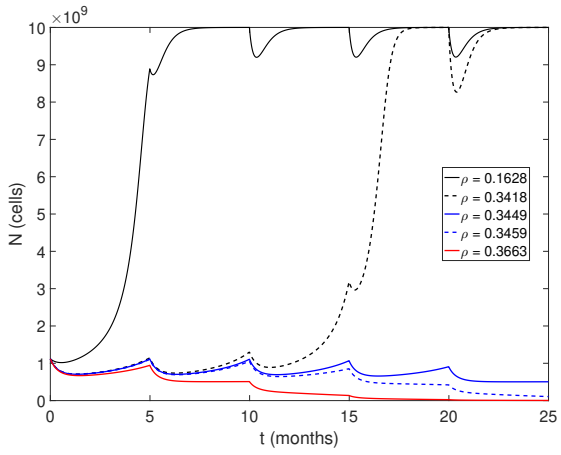

Figure 3: Number of tumor cells under RAI treatment considering different values for ρ.

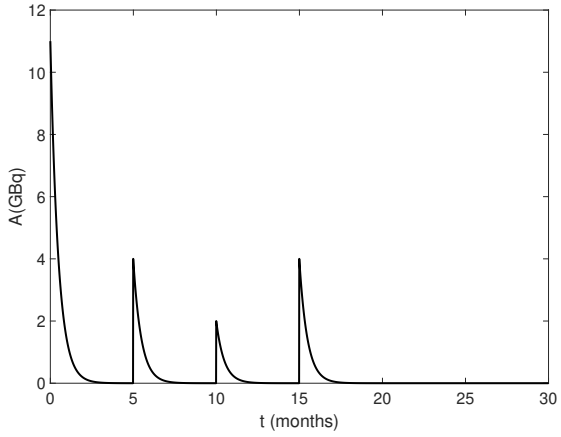

Figure 4: Representation of dose change over time, starting with 11GBq, followed by doses of 4GBq, 2GBq and 4GBq every five months.

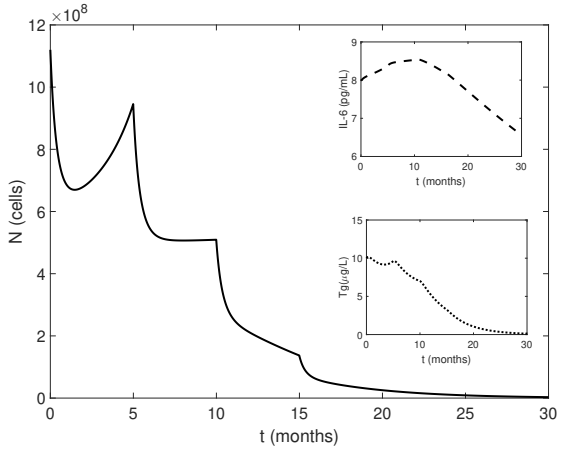

Figure 5: The effect of the treatment on the cell population with RAI with different doses, where $\rho = 0{,}1628$ $(\text{GBq}\times\text{month})^{-1}$, $N(0) = 1.12 \times 10^9$ cells, $I(0) = 7.98$pg/mL and $Tg(0) = 10\mu$g/L.

with their use in clinical practice as biomarkers. Without the alternating doses, as presented in Figure 2, the tumor cells tend towards carrying capacity.

Still using the same efficiency rate $\rho = 0.1628$

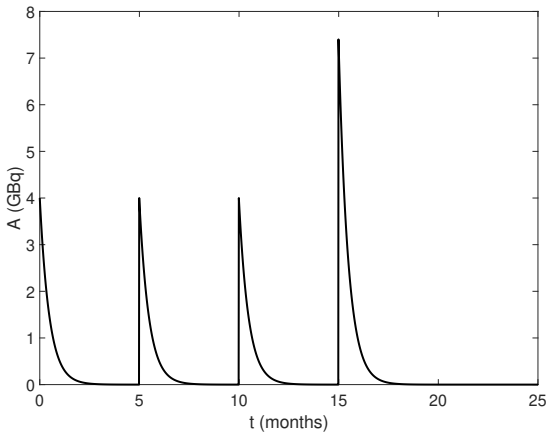

Figure 6: Representation of the treatment with three doses of 4GBq every five months and a 4th dose of 7.4GBq.

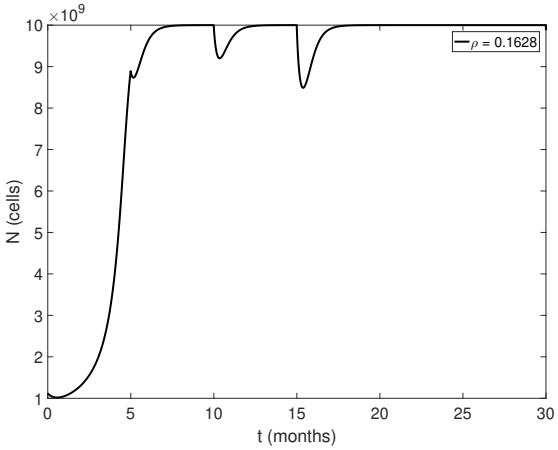

Figure 7: Number of tumor cells under treatment with alternating doses, where $\rho = 0.1628$ (GBq×month)$^{-1}$ and $N(0) = 1.12 \times 10^9$ cells.

(GBq×month)$^{-1}$, a third treatment scenario with doses of 4GBq every five months was simulated. In this case, the first three doses were 4GBq and, before the fourth dose, the effectiveness of the treatment in eliminating the tumor population was verified. If the number of tumor cells did not decrease to the limit associated with the Allee effect, the fourth dose of RAI would be 7.4GBq (see Figure 7). Otherwise, the fourth dose would remain at 4GBq. As treatment with doses of 4GBq of activity every five months was not sufficient for tumor elimination, the fourth dose of 7.4GBq was necessary. However, even applying the four doses, as shown in Figure 7, tumor cells tend to carrying capacity over time.

Through the presented results, it is noted that the tumor will only possibly be eliminated if the population of tumor cells is reduced to a value close to the parameter $Q = 5 \times 10^8$ cells (Figures 2 and 5). This is easier when there is a combination of a high dose of RAI at the beginning of treatment, when there are fewer tumor cells. Otherwise, as the population already tends to carrying capacity, the Allee effect threshold is more difficult to be reached, and therefore, the treatment tends to have no effect on elimination (Figures 1 and 7).

Figure 8 shows the relationship between the initial dose

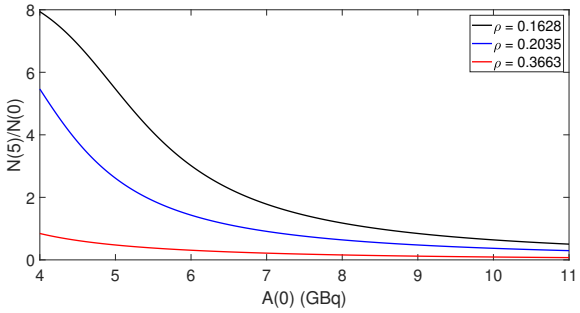

Figure 8: The effect of the initial dose of radioiodine $A(0)$ on the behaviour of the number of tumor cells at $t = 5$ months, $N(5)$ divide by its initial number, $N(0)$.

$A(0)$ and the ratio $N(5 \text{ months})/N(0)$. For $\rho = 0.1628$, an initial dose approximately 10GBq would be necessary for the number of tumor cells at the end of five months to be lower than $N(0)$. Considering $\rho = 0.2035(50\bar{\rho})$, the same result would be possible for an initial dose starting at 8GBq. Finally, for $\rho = 0.3663$, a initial dose starting at 4GBq already promote $N(5) < N(0)$.

Thus, the scenarios obtained with simulations of different doses show that the largest applications must be administered in the first doses for a possible successful treatment. In a personalized treatment, the ideal would be for this alternation of doses to be accompanied by the measurement of Tg indices, given that the objective in this case is precisely to reduce the size or number of doses throughout the treatment.

CONCLUSIONS

Using the model proposed by Silva et al. (2020), we simulated different treatment scenarios for metastatic PTC using RAI. The low values attributed to the parameter ρ, based in Barbolosi et al. (2017), may be associated with the lack of response to treatment, or correlated with the tumor undergoing a series of molecular changes (Smith et al., 2009; Ringel et al., 2001). Usually, in such cases, patients are refractory to RAI treatment due to a reduction in NIS, requiring other therapeutic modalities not based on iodine incorporation. A strategy that proved to be efficient in a potentially successful treatment was the alternation of doses of RAI, where the treatment started with a higher dose and was followed by smaller doses, even in cases where low values were attributed to ρ. For this alternation to be used in clinical practice, more studies and clinical trials are needed. Also, we observed that mathematical modelling is an important tool in cancer clinical studies as they might assist in determining the most effective treatment protocols for metastatic PTC and, thereby, avoid harmful side effects or ineffective treatments.

ACKNOWLEDGEMENTS

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. No potential conflicts of interest were disclosed.

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