Mathematical Modeling of Immunotherapy for Tumors: Computational Analysis of Adoptive Cell Therapy with Interleukin-2

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Modelagem Matemática da Imunoterapia para Tumores: Análise Computacional da Terapia Celular Adotiva com Interleucina-2

Modelización Matemática de la Inmunoterapia de Tumores: Análisis Computacional de la Terapia Celular Adoptiva con Interleucina-2

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ABSTRACT

Introduction: Cancer is one of the main causes of death in the world, but there are still unknown aspects of its dynamics. An important tool for its study is mathematical modeling, which analyzes and projects tumor behavior. A model must be validated *in silico* to be useful. **Objective:** Validate a mathematical model for immunotherapy against tumors, to evaluate how the cellular composition of the adoptive cell therapy interferes with the response and which is the most appropriate scheme for administering interleukin-2 in terms of dose and time of use. **Method:** An ordinary differential equation model was developed. The parameters were obtained from the literature, adapted or simulated. The solutions were found using Octave 8.1.0 software and compared with the literature. **Results:** The results, compared with data from clinical trials and other modeling, show that the model is valid for reproducing tumor dynamics. In addition, infusion of adoptive cell therapy with a predominance of CD8+ T lymphocytes appears slightly more advantageous than infusion with a predominance of CD4+ T lymphocytes; high but tolerable doses of interleukin-2 generate a better anti-tumor response; and longer administration of interleukin-2 maximizes the response. **Conclusion:** The model is valid for studying tumor dynamics and can help in the development of new research. In addition, immunotherapy with a predominance of CD8+ T lymphocytes over CD4+ T lymphocytes and with interleukin-2 in higher doses and for longer periods, respecting tolerance, showed better results *in silico*.

Key words: Models, Theoretical; Computer Simulation; Immunotherapy, Adoptive; Neoplasms/epidemiology.

RESUMO

Introdução: O câncer é uma das principais causas de óbito no mundo, mas ainda há aspectos desconhecidos da sua dinâmica. Uma importante ferramenta para seu estudo é a modelagem matemática, que analisa e projeta o comportamento tumoral. Um modelo deve ser validado *in silico* para ser útil. **Objetivo:** Validar um modelo matemático para imunoterapia contra tumores, avaliar como a composição celular da terapia celular adotiva interfere na resposta e qual o esquema mais adequado para administração de interleucina-2 quanto à dose e ao tempo de uso. **Método:** Foi desenvolvido um modelo de equações diferenciais ordinárias. Os parâmetros foram obtidos da literatura, adaptados ou simulados. As soluções foram encontradas usando o *software* Octave 8.1.0 e comparadas com a literatura. **Resultados:** Os resultados, comparados com dados de ensaios clínicos e outras modelagens, mostram que o modelo é válido para reproduzir a dinâmica tumoral. Ademais, a infusão da terapia celular adotiva com predomínio de linfócitos T CD8+ parece ligeiramente mais vantajosa do que a infusão com predomínio de linfócitos T CD4+; doses altas, porém toleráveis, de interleucina-2 geram melhor resposta antitumoral; e a administração de interleucina-2 por mais tempo maximiza a resposta. **Conclusão:** O modelo é válido para estudo da dinâmica tumoral e pode auxiliar no desenvolvimento de novas pesquisas. Adicionalmente, a imunoterapia com predomínio de linfócitos T CD8+ em relação a linfócitos T CD4+ e com interleucina-2 em doses mais altas e por mais tempo, respeitando a tolerância, apresentou melhores resultados *in silico*.

Palavras-chave: Modelos Teóricos; Simulação por Computador; Imunoterapia Adotiva; Neoplasias/epidemi

RESUMEN

Introducción: El cáncer es una de las principales causas de muerte en todo el mundo, pero aún se desconocen aspectos de su dinámica. Una herramienta importante para su estudio es la modelización matemática, que analiza y proyecta el comportamiento tumoral. Para que un modelo sea útil debe ser validado *in silico*. **Objetivo:** Validar un modelo matemático de inmunoterapia contra tumores, evaluar cómo interfiere la composición celular de la terapia celular adoptiva en la respuesta y cuál es el esquema más adecuado de administración de interleuquina-2 en cuanto a dosis y tiempo de utilización. **Método:** Se desarrolló un modelo de ecuaciones diferenciales ordinarias. Los parámetros se obtuvieron de la literatura, se adaptaron o se simularon. Las soluciones se hallaron con el *software* Octave 8.1.0 y se compararon con las de la bibliografía. **Resultados:** Los resultados, comparados con datos de ensayos clínicos y otras modelizaciones, muestran que el modelo es válido para reproducir la dinámica tumoral. Además, la infusión de terapia celular adoptiva con predominio de linfocitos T CD8+ parece ligeramente más ventajosa que la infusión con predominio de linfocitos T CD4+; dosis altas pero tolerables de interleuquina-2 generan una mejor respuesta antitumoral; y la administración de interleuquina-2 durante más tiempo maximiza la respuesta. **Conclusión:** El modelo es válido para estudiar la dinámica tumoral y podría ayudar en el desarrollo de nuevas investigaciones. Además, la inmunoterapia con predominio de linfocitos T CD8+ sobre linfocitos T CD4+ y con interleuquina-2 en dosis más altas y durante más tiempo, respetando la tolerancia, mostró mejores resultados *in silico*.

Palabras clave: Modelos Teóricos; Simulación por Computador; Inmunoterapia Adoptiva; Neoplasias/epidemiología.

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INTRODUCTION

As the population ages and disease diagnostic and treatment evolves, cancer has become one of the greatest causes of death in the world. In addition to being one of the main causes of death in the United States and some Western European countries, it became the main cause of death in nearly 10% of Brazilian cities[1]. Though there have been many developments in cancer therapies, much is still unknown about how cancer cells emerge, spread, and are destroyed[2].

In this context, the scientific community has increasingly searched for mathematical models capable of helping predict tumor behavior and, consequently, develop experimental studies on treatments. Theoretical models have advantages over experimental and clinical studies for being much less expensive, less time consuming and making it easier to alter environmental influences and parameter scales[3]. Based on experience regarding the evolutionary dynamic of tumors, mathematical modeling emerges as an essential tool for creating efficient hypotheses testing[4]. Although existing models have provided useful information about the immune system action in controlling tumoral growth, improvements are still needed to incorporate new clinical developments and biological findings[2]. The choice of an appropriate growth model may lead to a better understanding of the interaction between tumoral cells and immune system cells, as well as the effect of different treatments on cancer growth or inhibition[5]. In this sense, this study suggests an adaptation of the model presented by Usman and Cunningham[6], and an improvement of the model by Kirschner and Panetta[7], mainly applicable to metastatic melanoma and renal cell carcinoma[6] (RCC) under immunotherapy with interleukin-2 (IL-2) and adoptive cell therapy (ACT).

Kirschner and Panetta[7] have developed their model after analyzing previous models and experimental data, with the aim of incorporating the most important concepts of tumoral dynamic under immunotherapy in the simplest way possible. Usman and Cunningham[6] worked on that model to make it more compatible with the reality observed in a clinical trial for IL-2 monotherapy[8]. However, ACT in the form of tumor infiltrating lymphocytes (TIL) has become increasingly interesting as an oncological treatment over the last decade[9], in addition to demonstrating more effectiveness when T lymphocytes (TL) infusion and IL-2 therapy are associated[10]. Furthermore, clinical studies suggest that the composition of TIL infusion in relation to the cell type plays an important role on the therapeutic response[10-12]. Thus, this study proposes an adaptation of that model to analyze the cellular composition of TIL infusion, and application to TIL and IL-2 therapy, assessing compatibility of results with recent clinical trials to validate it.

Throughout ACT development, techniques for TIL expansion in great scale have been elaborated and many clinical trials conducted by different centers. ACT in the form of a three-part regimen including lymphocyte depletion chemotherapy, T-cell administration and high IL-2 dose has shown to be capable of mediating a durable tumoral regression in several institutions[10]. However, significant variations in protocols have left several important questions unanswered regarding therapy reproducibility and best practices, such as the number of infused TIL, IL-2 dose and duration of cultivated TIL[13]. Therefore, it is important to validate mathematical models that can be used for previous analysis *in silico,* to choose the most viable and likely to succeed therapeutic strategies for new experimental research.

The primary objective of this study is to analyze the validity of the proposed adaptation to the model discussed by Usman and Cunningham[6] for studying antitumoral immunotherapy. The secondary objective is to assess how ACT cellular composition interferes in the treatment and what is the most adequate IL-2 administration method, analyzing both dosage and treatment duration.

METHOD

The model presented by Usman and Cunningham[6] uses ordinary differential equations (ODE) to describe the growth rate of effector cells, tumoral cells and IL-2. The proposed adaptation separates effector cells in two ODE to make it possible to analyze the cellular composition of ACT regarding the presence of CD4+ and CD8+ T cells. The model proposes the following ODE to describe growth of CD4+ and CD8+ T cells, tumoral cells and IL-2, respectively:

$$\frac{dl_4}{d\tau} = ct_c - \mu_2 l_4 + \frac{p_1 l_4 i}{g_1 + i}, \tag{1.1}$$

$$\frac{dl_8}{d\tau} = ct_c - \mu_2 l_8 + \frac{p_2 l_8 i}{g_1 + i}, \tag{2.1}$$

$$\frac{dt_c}{d\tau} = r_2 t_c (1 - bt_c) - \frac{a l_8 t_c}{g_2 + t_c}, \tag{3.1}$$

$$\frac{di}{d\tau} = \frac{p_3 l_4 t_c}{g_3 + t_c} - \mu_3 i + s_3, \tag{4.1}$$

where l_4 represents the CD4+; l_8 the CD8+; t_c the tumoral cells; and i IL-2 in the tumoral space. Regarding the other parameters: τ is time; c is the tumor's

antigenicity; μ_2 is the natural death rate of lymphocytes; p_i are the formation rate of lymphocytes and IL-2; g_i are the support capacities; s_i is control, that is, the injection rate of TIL and IL-2; r_2 is the tumoral growth rate; b is the tumor reverse load capacity; a is the immune response intensity; μ_3 is the IL-2 elimination rate.

In equations 1.1 and 2.1, the first term represents the proliferation of lymphocytes against the presence of tumoral cells. The presence of these cells increases the appearance of tumoral antigens for immune cells. Moreover, the antigenicity of these molecules will define the intensity of the immune activation. Thus, tumoral antigens activate immature T-cells to turn into effector cytotoxic T lymphocytes (CTL). The second term reproduces the natural death of lymphocytes and the third models their expansion and maturing by stimulatory action of IL-2. The TIL dose is introduced in the model as an initial condition (s_1 for CD4+ and s_2 for CD8+), once it is applied in a single infusion on day 0 after the lymphocyte depletion regimen which would reduce the local quality of immune cells to an insignificant value in face of the great amount applied in therapy. The first term of equation 3.1 models the tumoral expansion in the form of logistical growth while the second reproduces the death of tumoral cells by immune action. In equation 4.1, the first term represents the production of IL-2 by helper T cells (Th) in response to the tumor's presence. The second models the natural elimination of IL-2 by the organism. The third represents IL-2 infusion. In practice, such infusion occurs every eight hours. However, to simplify and evaluate results daily, a single value of IL-2 was added per day.

A bibliographical review of related articles in MEDLINE, SciELO and LILACS indexing databases was conducted, with later analysis, comparison and description of the information found. Data and parameters were obtained from literature and applied to the model's mathematical equations (Table 1). The selected parameter values were found in studies based on similar models to the ones discussed and applicable to immunotherapy[6,7,14-18]. When needed, parameters were adjusted or estimated to the model's proposition and partial results found to make them closer to reality. Studies on TIL therapy in relation to other ACT forms were prioritized, when possible, with the aim of selecting more consistent and relevant data for the analysis and future studies. In the parameters subject to variations, the more compatible values with each analyzed situation were selected. The dose scheme composed of

Table 1. Parameters used in simulations

Parameter	Meaning	Value	Unit	Reference Value
μ_2	Natural death rate of TL	0.03	$days^{-1}$	[6]
μ_3	IL-2 elimination rate	10	$days^{-1}$	[6]
p_1	CD4+ formation rate	0.1245	$days^{-1}$	[6]
p_2	CD8+ formation rate	2.241	$days^{-1}$	Estimated by the authors
p_3	IL-2 formation rate	5	$days^{-1}$	[6]
g_1	Support capacity for TL	2×10^7	mL^{-1}	[6]
g_2	Support capacity for tumoral cells	10^5	mL^{-1}	[6]
g_3	Support capacity for IL-2	10^3	mL^{-1}	[6]
a	Immune response intensity	1.3	$mL\times days^{-1}$	Estimated by the authors
b	Tumor reverse load capacity	10^{-9}	mL^{-1}	[6]
c	Tumor antigenicity	0.00005	$days^{-1}$	[6]
r_2	Tumoral growth rate	0.18	$days^{-1}$	[6]
s_1	CD4+ dose	$0.4\times2.5\times10^5$ (when not specified)	$days^{-1}$	Estimated by the authors
s_2	CD8+ dose	$0.6\times2.5\times10^5$ (when not specified)	$days^{-1}$	Estimated by the authors
s_3	IL-2 dose	$9.6\times10^7/5$ (when not specified)	$days^{-1}$	Estimated by the authors

Captions: TL = T lymphocytes; IL-2 = interleukin-2; CD4+ = CD4+ T lymphocytes; CD8+ = CD8+ T lymphocytes; mL = milliliters.

previous lymphocyte depletion, single TIL infusion on day 0, and IL-2 infusions on the following days, for up to 15 doses[19,20] was taken as reference. In addition to that, a TIL scheme composed of 40% CD4+ and 60% CD8+ was used, modified only in specific simulations towards percentage composition. Moreover, an initial population of high tumoral cells was considered, reckoning that this treatment has been suggested mainly for patients with advanced cancer[13].

The solutions were found using Octave 8.1.0 software[21] with a C++ language code developed by the authors. The result analysis followed the current literature and focused on comparing it to clinical trials and other modeling studies' results. The modeling selection considered similarities with the present study, for instance, models that simulated the same treatment, had mathematical principles in common or analyzed the same parameters. The trials used were sampled from the aforementioned databases. Studies with conventional TIL and high IL-2 dose were excluded. The exclusion criteria considered studies published before 2011 and with a sample smaller than 30 patients.

GNU Octave is an open-source software under GNU General Public License (GPL), developed by the Octave community, with significant contributions from volunteer developers. The software was chosen for being a free and open-source numerical computing and data visualization tool compatible with MATLAB. It contains tools for solving numerical linear algebra problems, finding roots of non-linear equations, integrating ordinary functions, manipulating polynomial and integrating ODE and differential algebraic equations. The tool can be tailored by the user by setting functions written in Octave's language or using modules in C++, C, Fortran, and other languages.

Following Resolution number 510/2016[22] of the National Health Council (NHC), studies that use deidentified data and public database are exempt from ethical analysis.

RESULTS

Simulations with CD8+ presented slightly better results than simulations with a predominance of CD4+, however, the difference in the graphs is barely noticeable. Specifically, simulations characterized by a predominance of 70% of CD8+ presented a slightly faster response, after 106 days, while simulation with 70% CD4+ obtained full remission after 108 days. In addition, simulation with 70% CD8+ obtained a smaller tumoral cell peak (9.62×10^8 tumoral cells) than the ones that had a predominance of 70% CD4+ (9.71×10^8 tumoral cells).

Simulation results with higher doses of IL-2 presented a more robust antitumoral response. In the simulations, lower doses did not reach satisfactory answers, according to what is demonstrated in Figure 1, while elevated doses promoted a faster and more effective tumor decrease (Figure 2). It is noteworthy that results did not detect signs of uncontrolled IL-2 amounts, which is potentially related to cytokine release syndrome.

Results show different responses depending on the IL-2 application interval following TIL infusion in modulating the antitumoral response. Simulations indicate a more pronounced antitumoral response when maximizing duration of IL-2 administration, keeping a constant dose. IL-2 infusion for 15 days (Figure 2) generated a more robust and faster response than infusion for seven days only (Figure 3). Notably, a more effective response is observed when extending the use of IL-2, following a stipulated limit of 15 days (Figure 2).

DISCUSSION

The use of mathematical modeling to simulate the behavior of solid tumors under treatment is an established approach that has been observed in a vast number of studies[2,6,7,14-16], which justifies its choice. However, this study amplifies the works by Kirschner and Panetta[7] and Usman and Cunningham[6] on the behavior of metastatic melanoma and RCC. A specific analysis of ACT with IL-2 in these two cancer types was performed, which expanded the possibilities of studying the influence of cellular composition of TIL infusion in the therapeutic response. The authors that inspired this research[6,7] have developed a simplified model of tumoral dynamic under

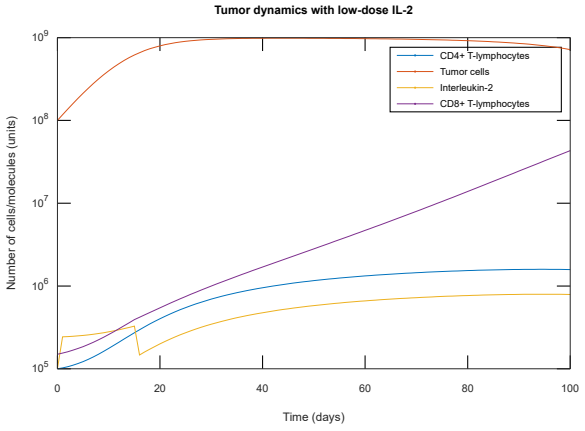

Figure 1. Simulation with low IL-2 dose for 15 days: A lower IL-2 dose did not generate a satisfactory response in the evaluated period ($s_3 = 9{,}6\times10^6/5$)

Captions: IL-2 = Interleukin-2; CD4+ = CD4+ T lymphocytes; CD8+ = CD8+ T lymphocytes.

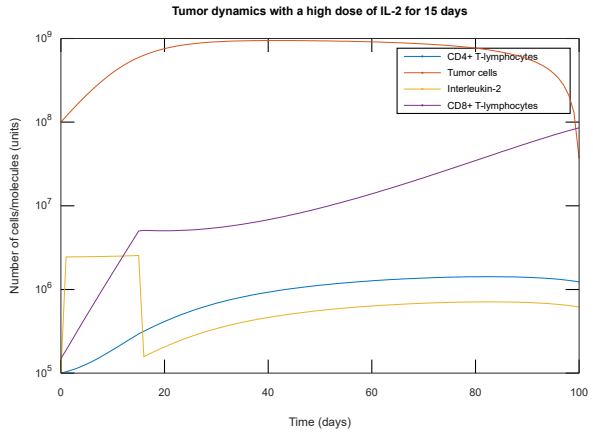

Figure 2. Simulation with high IL-2 dose for 15 days: A higher dose of IL-2 generated an earlier and more intense response (s3 = $9.6\times10^7/4$). Tumoral and immune behavior was also observed with the application of IL-2 for 15 days. The simulation generated an antitumoral response without losing control of IL-2 amounts.

Captions: IL-2 = Interleukin-2; CD4+ = CD4+ T lymphocytes; CD8+ = CD8+ T lymphocytes.

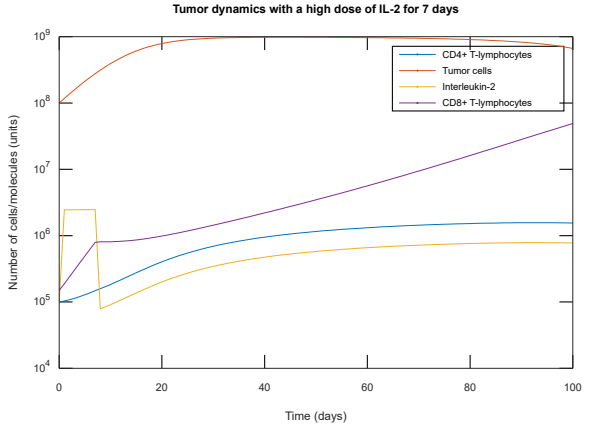

Figure 3. Simulation with high IL-2 dose during seven days: Tumoral and immune behavior with application of IL-2 (s3 = $9.6\times10^7/4$) during seven days. A desirable response was not observed in the tested period

Captions: IL-2 = Interleukin-2; CD4+ = CD4+ T lymphocytes; CD8+ = CD8+ T lymphocytes.

immunotherapy[7] and adapted it for IL-2 monotherapy[6]. This study broadens the scope by simulating ACT and IL-2 combined treatment, considering different proportions of CD4+ and CD8+ in TIL infusion. Although clinical works value the cellular composition of ACT[10-12], previous models[6,7] were not appropriate for studying it as they used single equation to represent immune cells. Moreover, the study investigated the effect of dose and duration of IL-2 administration, without failing to investigate the role of cytokine in the therapeutic response. The simulations provide information about the efficacy of therapy in different situations, suggesting adequate IL-2 dosages and the most efficient composition of TIL infusion to maximize antitumoral response.

The validation of mathematical models contributes to understanding a model's quality regarding the established objectives, aligning it to the observed data[23]. The proposed model's simulation presents a similar behavior to the ones reported in the literature regarding its key factors, such as response time frame of two to four months[24], possibility of treatment success or failure, therapy application period and possibility of success with no toxicity. Though models are powerful tools for capturing reality's complexities, their limitations should not be overlooked. Instead of searching for absolute validation, one must try to understand and quantify uncertainties associated with a model for a responsible interpretation of its results[25]. Thus, the results of theoretical experiments are useful, but must not be taken as predictions[25].

The composition of TIL infusion, particularly the proportion between CD4+ and CD8+ seems to play some role in modulating the response to ACT with IL-2. Though CD8+ are frequently the main effectors in eliminating tumoral cells[26], the presence and proportion of CD4+ may be key to empower antitumoral efficacy[27]. In fact, another study[28] suggests that a balanced proportion of CD4+ and CD8+ may be crucial for homeostasis and optimal function during ACT. Moreover, the use of IL-2 in conjunction with therapy favors expansion and survival of T lymphocytes[29]. However, the ideal percentage of CD4+ and CD8+, which maximizes therapeutic efficacy, should be continuously investigated, and may vary according to the clinical context.

The simulations performed suggest that a CD8+ predominance in relation to CD4+ may be capable of inducing a slightly better antitumoral response, in less time and smaller peak. Other studies showed that a predominance of CD8+ may lead to greater antitumoral activity[10-12]. In fact, a great number of CD8+ may be needed to destroy large numbers of affected cells, while a relatively small number of cytokines producing CD4+ may be enough[30]. In contrast, while CD4+ T lymphocytes are key to coordinating the immune response, an excessive proportion in relation to CD8+ may not have the same direct cytotoxic effect against tumoral cells[11]. However, a consensus regarding the exact impact of the percentage composition on the results has not been reached. The variation in the infusion composition was not able to conclusively and definitively distinguish patients who had positive responses from those who had not, though a tendency for better response when CD8+ is predominant was observed[10].

The IL-2 dose is a determinant factor for ACT efficacy. Simulations suggest that low IL-2 doses generate an insufficient response against the tumor, while higher doses of IL-2 were observed to generate better responses

(Figure 2). This result is compatible with a clinical study[8] that concluded that high doses of IL-2 may induce a fast expansion of T lymphocytes, potentially improving antitumoral activity. Other studies *in vivo*[10,11,13] and *in silico*[15] have also pointed out that higher IL-2 doses tend to generate better antitumoral responses. However, extremely high doses may generate significant side effects, like cytokine release syndrome, which may limit its application in some patients[14]. Despite that, tolerable doses are often observed to be sufficient for causing tumor remission in computational simulations. In clinical studies that used TIL+IL-2, 41% of the patients presented an objective response to tolerable treatment protocols[13]. Therefore, the present study did not simulate extremely high doses and did not find signs that could suggest cytokine release syndrome as the suggested IL-2 dose did not surpass the toxicity threshold. This confirms another study[31], that claims that adverse effects are noteworthy, but sequential exposition is safe and may be worth the risk. In this regard, results suggest the ideal IL-2 dose would be the maximum dose in which the adverse effects are tolerable. This value varies among each patient, which highlights the importance of following up on side effects.

The duration of IL-2 administration seems to play a significant role in modulating ACT response. The study observed that using IL-2 in a tight time frame may impair an effective antitumoral response (Figure 3). At the same time, cytokine infusion for up to 15 days generated a more satisfactory result (Figure 2), with a more effective response, with no hint of adverse effects. It has been highlighted for some time that the prolonged persistence of IL-2 may result in a greater expansion of transferred T lymphocytes, potentially improving antitumoral activity[8]. However, a limit must be imposed to the period of IL-2 use due to its double role as immunomodulator, once the continuous exposure may favor the expansion and function of regulator T lymphocytes, which may suppress the antitumoral immune response[32]. Thus, 15 days was considered the maximum time for IL-2 infusion. Moreover, the duration of IL-2 administration may impact the incidence of side effects, and prolonged treatments with high doses may exacerbate adverse reactions such as capillary leak[32]. Therefore, optimizing IL-2 treatment duration is crucial for balancing therapeutic strength and patient safety.

Though it presents important information on the tumoral response dynamic and deepens the knowledge on the studied tumors, there are some approach limitations in this study that may be reconsidered in future works. For instance, variations in T lymphocytes proliferation rate throughout time were not considered in this model, neither the formation of memory T cell population, as the objective was to simplify the analysis without having to estimate a great number of new parameters, which could generate relevant imprecisions in the dynamic. By maintaining a steady rate of lymphocytes proliferation, tumoral control will eventually occur, even in the long run, which is why this research simulates a shorter period to evaluate if there is a response in a clinically significant time frame. In general, mathematical modeling aims to simplify tumoral dynamic, but future research may improve the model to further investigate immune behavior.

CONCLUSION

Mathematical modeling was observed to be an important tool for studying and understanding tumoral dynamic. An adapted model to simulate solid tumors under immunotherapy was proposed. Results indicate that the discussed model is valid for predicting tumoral behavior in face of immunotherapy. Moreover, ACT infusion with a predominance of CD8+ is suggested to be slightly more advantageous than a predominance of CD4+. Regarding IL-2 administration scheme, results show that high IL-2 doses during a longer time frame, respecting the patient's tolerance, should be preferred. Thus, this study concludes that high, but tolerable, IL-2 doses have generated a good antitumoral response, so there is no need to pursue much higher doses that could cause important adverse effects. Furthermore, the use of IL-2 for the maximum period of 15 days after TIL administration, respecting the patient's tolerance, is desirable. Thus, some key points to guide future researches in the field were observed, with modeling being a useful tool to support them. Further studies may assess the best therapeutic schemes for different tumor and organism conditions to assist in the assertiveness of immunotherapy treatment.

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CONTRIBUTIONS

Both authors have substantially contributed to the study design, acquisition, analysis and interpretation of the data, wording, and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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