Mathematical Modeling of Immunotherapy for Tumors: Computational Analysis of Adoptive Cell Therapy with Interleukin-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.
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. Though there have been many developments in cancer therapies, much is still unknown about how cancer cells emerge, spread, and are destroyed.

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. Based on experience regarding the evolutionary dynamic of tumors, mathematical modeling emerges as an essential tool for creating efficient hypotheses testing. 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. 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. In this sense, this study suggests an adaptation of the model presented by Usman and Cunningham for studying antitumoral immunotherapy. 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:

\[
\frac{dL_4}{dt} = c t_e - \mu_4 L_4 + \frac{p_i j l_i}{s_4 r_4},
\]

\[
\frac{dL_8}{dt} = c t_e - \mu_8 L_8 + \frac{p_i j l_i}{s_8 r_8},
\]

\[
\frac{dt}{dt} = r t \left(1 - b t_e \right) - \frac{a s_4 r_4}{s_4 r_4},
\]

\[
\frac{di_2}{dt} = \frac{p_i j l_i}{s_4 r_4} - \mu_2 i_2 + s_3.
\]

where \( L_4 \) represents the CD4+; \( L_8 \) the CD8+; \( t_e \) the tumoral cells; and \( i \) IL-2 in the tumoral space. Regarding the other parameters: \( \tau \) is time; \( c \) is the tumor's
antigenicity; $\mu_2$ 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; $\mu_3$ 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. 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning</th>
<th>Value</th>
<th>Unit</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_2$</td>
<td>Natural death rate of TL</td>
<td>0.03</td>
<td>days$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$\mu_3$</td>
<td>IL-2 elimination rate</td>
<td>10</td>
<td>days$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$p_1$</td>
<td>CD4+ formation rate</td>
<td>0.1245</td>
<td>days$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$p_2$</td>
<td>CD8+ formation rate</td>
<td>2.241</td>
<td>days$^{-1}$</td>
<td>Estimated by the authors</td>
</tr>
<tr>
<td>$p_3$</td>
<td>IL-2 formation rate</td>
<td>5</td>
<td>days$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$g_1$</td>
<td>Support capacity for TL</td>
<td>$2 \times 10^7$</td>
<td>mL$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$g_2$</td>
<td>Support capacity for tumoral cells</td>
<td>$10^5$</td>
<td>mL$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$g_3$</td>
<td>Support capacity for IL-2</td>
<td>$10^3$</td>
<td>mL$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$a$</td>
<td>Immune response intensity</td>
<td>1.3</td>
<td>mL$\times$days$^{-1}$</td>
<td>Estimated by the authors</td>
</tr>
<tr>
<td>$b$</td>
<td>Tumor reverse load capacity</td>
<td>$10^{-9}$</td>
<td>mL$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$c$</td>
<td>Tumor antigenicity</td>
<td>0.00005</td>
<td>days$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$r_2$</td>
<td>Tumoral growth rate</td>
<td>0.18</td>
<td>days$^{-1}$</td>
<td>6</td>
</tr>
<tr>
<td>$s_1$</td>
<td>CD4+ dose</td>
<td>$0.4 \times 2.5 \times 10^6$ (when not specified)</td>
<td>days$^{-1}$</td>
<td>Estimated by the authors</td>
</tr>
<tr>
<td>$s_2$</td>
<td>CD8+ dose</td>
<td>$0.6 \times 2.5 \times 10^6$ (when not specified)</td>
<td>days$^{-1}$</td>
<td>Estimated by the authors</td>
</tr>
<tr>
<td>$s_3$</td>
<td>IL-2 dose</td>
<td>$9.6 \times 10^{7/5}$ (when not specified)</td>
<td>days$^{-1}$</td>
<td>Estimated by the authors</td>
</tr>
</tbody>
</table>

Captions: TL = T lymphocytes; IL-2 = interleukin-2; CD4+ = CD4+ T lymphocytes; CD8+ = CD8+ T lymphocytes; mL = milliliters.
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 ($9.62 \times 10^8$ tumoral cells) than the ones that had a predominance of 70% CD4+ ($9.71 \times 10^8$ 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, which justifies its choice. However, this study amplifies the works by Kirschner and Panetta and Usman and Cunningham 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 have developed a simplified model of tumoral dynamic under
immunotherapy\textsuperscript{7} and adapted it for IL-2 monotherapy\textsuperscript{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\textsuperscript{10-12}, previous models\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{25}. Thus, the results of theoretical experiments are useful, but must not be taken as predictions\textsuperscript{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\textsuperscript{26}, the presence and proportion of CD4\(^+\) may be key to empower antitumoral efficacy\textsuperscript{27}. In fact, another study\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 \textit{in vivo}\(^{10,11,13}\) and \textit{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\(^{15}\). 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, 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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REFERENCES


22. Conselho Nacional de Saúde (BR). Resolução nº 510, de 7 de abril de 2016. Dispõe sobre as normas aplicáveis a pesquisas em Ciências Humanas e Sociais cujos
procedimentos metodológicos envolvam a utilização de dados diretamente obtidos com os participantes ou de informações identificáveis ou que possam acarretar riscos maiores do que os existentes na vida cotidiana, na forma definida nesta Resolução [Internet]. Diário Oficial da União, Brasília, DF. 2016 maio 24 [acesso 2023 set 14]; Seção I:44. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/cns/2016/res0510_07_04_2016.html


