Mathematical Modeling of The Effect of Boosting Tumor Infiltrating Lymphocyte in Immunotherapy

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Abstract: This study, we analyzed the effect of boosting tumor infiltrating lymphocyte in immunotherapy using mathematical modeling. In this model, tumor growth is described as a tumor cells population with immunotherapy. This model also describes the effect of Tumor Infiltrating Lymphocytes (TIL), interleukin-2 (IL-2) and interferon alpha (INF-α) on dynamics of tumor cells. Numerical modeling of immunotherapy with or not boosted Tumor Infiltrating Lymphocyte (TIL) are presented in this study. We obtained that boosting Tumor Infiltrating Lymphocyte (TIL) in immunotherapy have a very significant role in killing of tumor cells.

Key words: Tumor infiltrating lymphocyte, immunotherapy, mathematical modeling, interleukin-2, interferon alpha, tumor cells

INTRODUCTION

Immunotherapy is also called as biologic therapy or biotherapy. Immunotherapy become an important component in the multi-pronged treatment approach, it was developed to treat several types of tumor within a short time frame (De Pillis et al., 2006). Immunotherapy grouped into three categories: immune response modifiers or cytokines, monoclonal antibodies and vaccines (Rosenbaum and Rosenbaum, 2005). Cytokines are chemical that mediated both natural and specific immunity. Cytokines have important role in responsible for lymphocyte activation, growth and differentiation (Kirschner and Panetta, 1998). Most commons of cytokines are interleukins-2 (IL-2) and interferon alpha (INF-α). Immune system have important role in fighting tumor that has been verified in the laboratory as well as with clinical experiment (Farrar et al., 1999; O’Byrne et al., 2000; Morecki et al., 1996; Muller et al., 1998; Stewart, 1996). Basic idea behind immunotherapy is boosting the immune system in vitro, so the body can eradicate cancer on its own. There are many ways in which the immune system can be boosted, including vaccine therapy, IL-2 and INF-α growth factor injections, as well as the direct injection of highly activated specific immune cells, such Tumor Infiltrating Lymphocyte (TIL) into the bloodstream. Tumor Infiltrating Lymphocytes (TIL) are white blood cells that have left the bloodstream and migrated into tumor. They are an important prognostic factor in melanoma (Spazt et al., 2007; Gallon et al., 2006) higher levels being associated with a better outcome.

In this study, the mathematical modeling of ordinary differential equations is based on that originally developed by de Pillis (De Pillis et al., 2006), but the model of tumor growth without therapy use generalized logistic equation (Spratt et al., 1993) while in the model of de Pillis using logistic equation (De Pillis et al., 2006). The generalized logistic equation is based on that originally developed by Spratt et al. (1993), where in this work, they observed in 448 patients suffering from tumor for 564 days. Therefore, they obtained a generalized logistic equation more accurate than a logistic equation to describe of model tumor growth without therapy. Moreover, we add the effect INF-α on the immunotherapy based Isaeva and Osipov’s model (Isaeva and Osipov, 2009). Through mathematical modeling we analyzed the effect of boosting tumor infiltrating lymphocyte in immunotherapy. The hypothesis explains that boosting tumor infiltrating lymphocyte play an important role on immunotherapy. Some researchers have never explained the important role this boosting tumor infiltrating lymphocyte. Therefore, this study will describe the important role of boosting tumor infiltrating lymphocyte in immunotherapy.

MATHEMATICAL MODELING

The model is a system of Ordinary Differential Equation (ODE) whose state variables are populations of tumor cells, specific and non-specific immune cells and concentrations of therapeutic interventions. In this research, the model describes the kinetics of population
tumor cells and three types of immune cells (NK cells, CD8+T cells, circulating lymphocytes), as well as two drug concentrations in the bloodstream, the equations are expressed by:

$$\frac{dT}{dt} = aT \left(1 - \left(\frac{T}{b}\right)^n\right) - cNT - DT - c'TL$$  \hspace{1cm} (1)

$$\frac{dN}{dt} = cC - fN + g \frac{T^2}{h + T} - NpNT$$  \hspace{1cm} (2)

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{K + D^2T^2}L - qL(T + (\tau\gammaN + \tau\gammaC)T) - uNL^2 + \frac{P_1}{g_i + I} + v_i(t)$$  \hspace{1cm} (3)

$$\frac{dC}{dt} = \alpha - \beta C$$  \hspace{1cm} (4)

$$\frac{df}{dt} = -\mu_iI + v_i(t)$$  \hspace{1cm} (5)

$$\frac{dI}{dt} = -\mu_iI + v_i(t)$$  \hspace{1cm} (6)

$$D = \frac{DL(T)^{\gamma}}{s^{(L/T)^{\gamma}}}$$  \hspace{1cm} (7)

$$c' = c_{ml} \left(2 - e^{-\frac{1}{k_0}}\right)$$  \hspace{1cm} (8)

The populations are denoted by:

\[ T(t) \] = Tumor cell population at time t
\[ N(t) \] = Total NK cell effectiveness at time t
\[ L(t) \] = Total CD8+T cell effectiveness at time t
\[ C(t) \] = Number of circulating lymphocytes (or white blood cells) at time t
\[ I(t) \] = Immunotherapy interleukin 2 drug concentration in the bloodstream at time t
\[ Ia(t) \] = Immunotherapy interferon alpha drug concentration in the bloodstream at time t

Term VL(t) represent function of boosting tumor infiltrating lymphocyte in immunotherapy. While V(t) and v(t), respectively represent drug intervention term are functions of time denoted of interleukin and interferon.

**PARAMETER DERIVATION**

To complete the simulation and analysis, it necessary to obtain accurate parameters. The model is very sensitive to the choice of parameters. Tumor size was measured as volume (in mm$^3$) while this model considers population of cells. In the following we will assume that 1 mm$^3$ corresponds to $10^6$ cells and will consider cells. Most of parameters in this model obtained from Pillis's model (De Pillis et al., 2006) and also several parameters were taken from Isaev and Osipov's model (Isaev and Osipov, 2009), as well as from Spratt's work (Spratt et al., 1993). Table 1 describes all parameters to run simulation our model.

**NUMERICAL RESULTS**

Here, we simulated the effect boosted Tumor Infiltrating Lymphocytes (TIL) in immunotherapy. In this simulation, we denoted initial tumor burden of $2 \times 10^5$ cells, since a tumor consisting of less than $10^5$ cells is considered to be undetectable. In this simulation we also denoted as an initially value with $10^3$ NK cells, 10 CD8+T cells and $6 \times 10^3$ circulating lymphocytes.

Figure 1-4 shown that immunotherapy without boosting tumor infiltrating cannot effectively kill tumor cells, where in these simulations IL-2 is administered in 6 pulses at strength $5 \times 10^3$, $5 \times 10^4$, $5 \times 10^5$ and $5 \times 10^6$ from day 8-12, respectively.

Figure 5-8 show that the effect boosting tumor infiltrating lymphocyte in immunotherapy. In these simulations, tumor infiltrating lymphocyte at strength $6.6440 \times 10^6$ boosted in the body in variation in day. Tumor infiltrating lymphocyte at strength $6.6440 \times 10^6$ boosted every weeks until four weeks, respectively, these simulations shown that at strength $6.6440 \times 10^6$ is not effective to kill tumor cells.

Figure 9-12 shown that simulation with boosting tumor infiltrating lymphocyte higher is at strength $6.6439 \times 10^6$. Figure 9 show that tumor initially decreased at day 10 then increased at day 28 leading to a dangerous level. Tumor effective kills at day 22 and never relapses again with boosting tumor infiltrating lymphocyte at strength $6.6439 \times 10^6$ in the second, third and fourth week as shown in Fig. 10-12, respectively. The last results shown the effect boosting tumor infiltrating lymphocyte higher is at strength $6.6440 \times 10^6$ boosted in every week.

Figure 13-16 show that tumor effective kills at day 28 and never relapses. Figure 14-16, respectively show that tumor effective kills at day 22 never relapses.

**DISCUSSION AND CONCLUSION**

In this study, we analyzed the effect boosting tumor infiltrating lymphocyte using our mathematical model which has never been done in previous researchers' work. From our result, we can show the effect of boosting tumor infiltrating lymphocyte in immunotherapy. Immunotherapy
Table 1: Parameter values used for numerical simulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>a = 4.31 × 10^{-3} (day^{-1})</td>
<td>Tumor growth rate</td>
<td>Diedenbach et al. (2001)</td>
</tr>
<tr>
<td>b = 1.02 × 10^{-12} (cell^{-1})</td>
<td>Tumor carrying capacity</td>
<td>Diedenbach et al. (2001)</td>
</tr>
<tr>
<td>c = 6.41 × 10^{-11} (day^{-1} cell^{-1})</td>
<td>Fractional (non) ligand transduced tumor cell kill by NK cells</td>
<td>Dudley et al. (2002) and Diedenbach et al. (2001)</td>
</tr>
<tr>
<td>d = 2.34 (day^{-1})</td>
<td>Saturation level of fractional tumor cell kill by CD8+ T Cells. Primed with ligand-transduced cells, challenged with ligand-transduced</td>
<td>Dudley et al. (2002)</td>
</tr>
<tr>
<td>e = 2.08 × 10^{-7} (day^{-1})</td>
<td>Fraction of circulating lymphocytes that became NK cells</td>
<td>Kuznetsov et al. (1994)</td>
</tr>
<tr>
<td>t = 1.65 (dimensionless)</td>
<td>Parameter which characterizes the shape of the sigmoidal growth curve</td>
<td>Spratt et al. (1993)</td>
</tr>
<tr>
<td>l = 2.09 (dimensionless)</td>
<td>Exponent of fractional tumor cell kill by CD8+ T cells. Fractional tumor cell kill by chemotherapy</td>
<td>Dudley et al. (2002)</td>
</tr>
<tr>
<td>f = 4.12 × 10^{-2} (day^{-1})</td>
<td>Rate of NK cells</td>
<td>Kuznetsov et al. (1994)</td>
</tr>
<tr>
<td>g = 1.25 × 10^{-2} (day^{-1})</td>
<td>Maximum NK cells recruitment by ligand-transduced tumor cells</td>
<td>Dudley et al. (2002)</td>
</tr>
<tr>
<td>h = 2.02 × 10^{5} (cell^{-1})</td>
<td>Steepness coefficient of the NK cell recruitment curve</td>
<td>Kuznetsov et al. (1994)</td>
</tr>
<tr>
<td>j = 2.49 × 10^{-2} (day^{-1})</td>
<td>Maximum CD8+ T cell recruitment rate. Primed with ligand-transduced cells</td>
<td>Dudley et al. (2002)</td>
</tr>
<tr>
<td>k = 5.66 × 10^{-2} (cellF.day^{-2})</td>
<td>Steepness coefficient of the CD8+ T cell recruitment curve</td>
<td>Dudley et al. (2002) and Diedenbach et al. (2001)</td>
</tr>
<tr>
<td>m = 2.04 × 10^{-1} (day^{-1})</td>
<td>Death rate of CD8+ T cells</td>
<td>Yates and Callard (2001)</td>
</tr>
<tr>
<td>q = 1.42 × 10^{-5} (day^{-1} cell^{-1})</td>
<td>CD8+ T cell inactivation rate by tumor cells</td>
<td>Kuznetsov et al. (1994)</td>
</tr>
<tr>
<td>p = 3.42 × 10^{-6} (day^{-1} cell^{-1})</td>
<td>NK cell inactivation rate by tumor cells</td>
<td>Diedenbach et al. (2001)</td>
</tr>
<tr>
<td>s = 8.39 × 10^{-3} (dimensionless)</td>
<td>Steepness coefficient of tumor-(CD8+ T cell) lysis term D. Primed with ligand-transduced cells, challenged with ligand-transduced</td>
<td>Dudley et al. (2002)</td>
</tr>
<tr>
<td>r_{1} = 1.10 × 10^{-7} (day^{-1} cell^{-1})</td>
<td>Rate of which CD8+ T cells are stimulated to be produced as a result a tumor cells killed by NK cells</td>
<td>Yates and Callard (2001)</td>
</tr>
<tr>
<td>r_{2} = 6.50 × 10^{-11} (cell^{-1} day^{-1})</td>
<td>Rate of which CD8+ T cells are stimulated to be produced as a result a tumor cells interaction with circulating lymphocytes</td>
<td>-</td>
</tr>
<tr>
<td>u = 5.00 × 10^{-10} (cell^{-1} day^{-1})</td>
<td>Regulatory function by NK cells of CD8+ T cells</td>
<td>-</td>
</tr>
<tr>
<td>α = 7.50 × 10^{-6} (cell.day^{-1})</td>
<td>Constant source of circulating lymphocytes</td>
<td>Hauser (2001)</td>
</tr>
<tr>
<td>β = 1.20 × 10^{-6} (day^{-1})</td>
<td>Natural death and differentiation of circulating lymphocytes</td>
<td>Hauser (2001)</td>
</tr>
<tr>
<td>γ = 9.00 × 10^{-6} (day^{-1})</td>
<td>Rate of chemotherapy drug decay</td>
<td>Calabrogi and Schin (1993)</td>
</tr>
<tr>
<td>p_{1} = 1.25 × 10^{-4} (day^{-1})</td>
<td>Maximum CD8+ T cell recruitment curve by IL-2</td>
<td>Kirschner and Panetta (1998)</td>
</tr>
<tr>
<td>g_{1} = 2.00 × 10^{-6} (cell^{-1})</td>
<td>Constant</td>
<td>-</td>
</tr>
<tr>
<td>μ_{1} = 1.00 × 10^{-7} (day^{-1})</td>
<td>Rate of IL-2 drug decay</td>
<td>Kirschner and Panetta (1998)</td>
</tr>
<tr>
<td>μ_{2} = 1.7 (day^{-1})</td>
<td>Decay rate of therapeutic INF-α</td>
<td>Isaev and Osipov (2009)</td>
</tr>
<tr>
<td>c_{0,1} = 4.4 × 10^{-9} (cell^{-1} day^{-1})</td>
<td>Rate of tumor cells inactivation by CD8+ T cells</td>
<td>Isaev and Osipov (2009)</td>
</tr>
<tr>
<td>T_{0} units</td>
<td>Initial Interferon</td>
<td>-</td>
</tr>
</tbody>
</table>

Fig. 1: Simulation of immunotherapy in absence boosting tumor infiltrating lymphocyte, IL-2 is administered in 6 pulses at strength 5×10^6 from day 8-12 and INF-α is administered in 4 pulses at strength 5 from day 1-34.

without boosting tumor infiltrating cannot effectively kill tumor cells. In these simulations, IL-2 is administered in 6 pulses at strength 5×10^6, 5×10^10, 5×10^9 and 5×10^8 from day 8-12 as pictured in Figure 1-4, respectively. Figure 5-8
Fig. 2: Simulation of immunotherapy in absence boosting tumor infiltrating lymphocyte, IL-2 is administered in 6 pulses at strength $5 \times 10^{10}$ from day 8-12 and INF-α is administered in 4 pulses at strength 5 from day 1-34.

Fig. 3: Simulation of immunotherapy in absence boosting tumor infiltrating lymphocyte, IL-2 is administered in 6 pulses at strength $5 \times 10^{10}$ from day 8-12 and INF-α is administered in 4 pulses at strength 5 from day 1-34.

Fig. 4: Simulation of immunotherapy in absence boosting tumor infiltrating lymphocyte, IL-2 is administered in 6 pulses at strength $5 \times 10^{10}$ from day 8-12 and INF-α is administered in 4 pulses at strength 5 from day 1-34.
Fig. 5: Simulation of immunotherapy by present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8-12, INF-α is administered in 4 pulses at strength 5 from day 1-34 and $6.6440 \times 10^7$ of TILs boosted from day 7 through 8.

Fig. 6: Simulation of immunotherapy by present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8-12, INF-α is administered in 4 pulses at strength 5 from day 1-34 and $6.6440 \times 10^7$ of TILs boosted from day 7 through 8 and day 14 through 15.

Fig. 7: Simulation of immunotherapy by present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8-12 and INF-α is administered in 4 pulses at strength 5 from day 1-34 and $6.6440 \times 10^7$ of TILs boosted from day 7 through 8, day 14 through 15 and day 20 through 21.
Fig. 8: Simulation of immunotherapy in present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength 5×10^6 from day 8-12 and INF-α is administered in 4 pulses at strength 5 from day 1-34 and 6.64×10^7 of TILs boosted from day 7 through 8, day 14 through 15, day 20 through 21 and day 27 through 28.

Fig. 9: Simulation of immunotherapy in present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength 5×10^6 from day 8-12, INF-α is administered in 4 pulses at strength 5 from day 1-34 and 6.64×10^7 of TILs boosted from day 7 through 8.

Fig. 10: Simulation of immunotherapy in present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength 5×10^6 from day 8-12, INF-α is administered in 4 pulses at strength 5 from day 1-34 and 6.64×10^7 of TILs boosted from day 7 through 8 and day 14 through 15.
Fig. 11: Simulation of immunotherapy in present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8-12, INF-α is administered in 4 pulses at strength 5 from day 1-34 and $6.6439 \times 10^3$ of TILs boosted from day 7 through 8, day 14 through 15 and day 20 through 21

Fig. 12: Simulation of immunotherapy in present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8-12, INF-α is administered in 4 pulses at strength 5 from day 1-34 and $6.6439 \times 10^3$ of TILs boosted from day 7 through 8, day 14 through 15, day 20 through 21 and day 27 through 28

Fig. 13: Simulation of immunotherapy in present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8-12, INF-α is administered in 4 pulses at strength 5 from day 1-34 and $6.6410 \times 10^3$ of TILs boosted from day 7 through 8
**Fig. 14:** Simulation of immunotherapy in present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8-12, INF-γ is administered in 4 pulses at strength 5 from day 1-34 and $6.640 \times 10^6$ of TILs boosted from day 7 through 8 and day 14 through 15.

**Fig. 15:** Simulation of immunotherapy in present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8-12 and INF-γ is administered in 4 pulses at strength 5 from day 1-34 and $6.440 \times 10^6$ of TILs boosted from day 7 through 8, day 14 through 15 and day 20 through 21.

**Fig. 16:** Simulation of immunotherapy in present boosting tumor infiltrating lymphocyte with IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8-12, INF-γ is administered in 4 pulses at strength 5 from day 1-34 and $6.640 \times 10^6$ of TILs boosted from day 7 through 8, day 14 through 15, day 20 through 21 and day 27 through 28.
shown that the effect of boosting tumor infiltrating lymphocyte be analyzed in immunotherapy; these simulations tumor infiltrating lymphocyte at strength \(6.644 \times 10^6\) boosted in the body in variation in day. Tumor infiltrating lymphocyte at strength \(6.644 \times 10^6\) boosted every weeks until four weeks as pictured in Fig. 5-8, respectively, these simulations shown that at strength cannot effective to kill tumor cells. In Fig. 9-12, simulation with boosting tumor infiltrating lymphocyte higher is at strength \(6.6439 \times 10^6\). In Fig. 9, tumor cells decreased at day 10 then increased at day 28 leading to a dangerous level. Tumor effective kills at day 22 and never relapses again with boosting tumor infiltrating lymphocyte at strength \(6.6439 \times 10^6\) in the second, third, and fourth week as shown in Fig. 10-12, respectively. The last results shown the effect boosting tumor infiltrating lymphocyte higher is at strength \(6.6440 \times 10^6\) in every week. Figure 13 show that tumor effective kills at day 28 and never relapses. Figure 14-16 show that tumor effective kills at day 22 and never relapses.

Based on our simulation results, we can conclude that the boosting of tumor infiltrating lymphocyte on immunotherapy has a very significant role in killing tumor cells. Boosting tumor infiltrating lymphocyte in immunotherapy is more effective in two week at strength \(6.6439 \times 10^6\).

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REFERENCES


