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Numerical Simulation of Interferon Alpha (INF-α) in Mathematical Model of Immunotherapy

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Abstract

In this paper, the effect of boosting interferon alpha (INF-α) in immunotherapy by using mathematical modeling was analyzed. In this model, tumor growth is described as a tumor cells population with immunotherapy. This model also describes the effect of interferon alpha (INF-α) on dynamics of tumor cells. Numerical modeling of immunotherapy with or not boosted interferon alpha (INF-α) is presented in this paper. We obtained that boosting interferon alpha (INF-α) in immunotherapy have a very significant role in killing of tumor cells. Interferon alpha (INF-α) that administered in 4 pulses from day 1 to day 34 to strength 4.8 can still kill the tumor, but when it was reduced to strength 4.7 cannot kill the tumor.

Keywords
Interferon alpha, immunotherapy, mathematical modeling, tumor

1. Introduction

Immunotherapy is also called as biologic therapy or biotherapy. Immunotherapies become an important component in the multi-pronged approach was developed to treat several types of cancer within a short time frame (de Pillis et al., 2006; Mamat et al., 2013; Kartono and Subiyanto, 2013). Immunotherapy grouped into three categories: immune response modifiers or cytokines, monoclonal antibodies and vaccines. Cytokines are chemical that mediated both natural and specific immunity. They have an 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 cancer that has been verified in the laboratory as well as with clinical experiment (Ferrar et al., 1999; O'Byrne et al., 2000). 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 into the bloodstream. Tumor infiltrating lymphocytes are white blood cells that have left the bloodstream and migrated into tumor. They are an important prognostic factor in melanoma (Galon et al., 2006; Spatz et al., 2007) higher levels being associated with a better outcome.

In this paper, it is presented a model for immunotherapy as previous work (Mamat et al., 2012; Subiyanto et al., 2014; Subiyanto et al., 2018). It is based on that originally developed by de Pillis (de Pillis et al., 2006), different in this model with de Pillis model is model of tumor growth without therapy using generalized logistic equation while in the de Pillis model using logistic equation. The equation is proposed based on Spratt work (Spratt et al., 1993), where in this work they observed in 448 patients suffering from cancer for 564 days. Then they obtained generalized logistic equation more accurate than logistic equation to describe of model tumor growth without therapy. Through numerical simulation, the effect of boosting INF-α in immunotherapy is analyzed.

2. Mathematical Model

The governing equation is a system of ordinary differential equation (ODE) whose state variables are populations of tumor cells, specific and nonspecific immune cells, and concentrations of therapeutic interventions. The mathematical model describes the kinetics of population tumor cells and three types of immune cells (NK cells, CD8+T cells, circulating lymphocytes), as well as interleukins-2 (IL-2) and interferon alpha (INF-α) in the bloodstream. The system ODE is presented as follows:

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

$$\frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - pNT \tag{2}$$

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + \left(r_1N + r_2C\right)T - uNL^2 + p_I\frac{LI}{g_I+I} + v_L(t) \tag{3}$$

$$\frac{dC}{dt} = \alpha - \beta C \tag{4}$$

$$\frac{dI}{dt} = -\mu_i I + v_I(t) \tag{5}$$

$$\frac{dI_\alpha}{dt} = -\mu_\alpha I_\alpha + v_{I_\alpha}(t) \tag{6}$$

$$D = d\frac{(L/T)^l}{s+(L/T)^l} \tag{7}$$

$$c' = c_{CTL}\left(2 - e^{-\frac{I_\alpha}{I_{\alpha 0}}}\right) \tag{8}$$

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*
- $I_\alpha(t)$, immunotherapy interferon alpha drug concentration in the bloodstream at time *t*

Where term $v_L(t)$ represent function of boosting tumor infiltrating lymphocyte in immunotherapy. While $v_I(t)$ and $v_{I_\alpha}(t)$ respectively represent drug intervention term are functions of time denoted of interleukin and interferon.

The mathematical model is solved by using parameters as described in Table 1. It necessary to obtain accurate parameters. System parameters are very sensitive to the choice of parameters. Most of parameters in this work obtained from Pillis's work (2006) and also several parameters were taken from Isaeva and Osipov's work (2009), as well as from Spratt et al. work (1993). Table 1 describes all parameters to run simulation our model.

Table 1. Parameter values used for numerical simulation

Parameter	Units	Description	Source
$a = 4.31 \times 10^{-1}$	day^{-1}	Tumor growth rate	Diefenbach *et al*. (2001)
$b = 1/1.02 \times 10^{-9}$	$cell^{-1}$	Tumor carrying capacity	Diefenbach *et al*. (2001)
$c = 6.41 \times 10^{-11}$	$day^{-1} \cdot cell^{-1}$	Fractional (non) ligand transduced tumor cell kill by NK cells	Dudley *et al*. (2002); Diefenbach *et al*. (2001)
$d = 2.34$	day^{-1}	Saturation level of fractional tumor cell kills by CD8+ T Cells. Primed with ligand-transduced cells, challenged with ligand-transduced	Dudley *et al*. (2002)
$e = 2.08 \times 10^{-7}$	day^{-1}	Fraction of circulating lymphocytes that became NK cells	Kuznetsov et al. (1994)
$\varepsilon = 1.65$	dimensionless	parameter which characterizes the shape of the sigmoidal growth curve	Spratt *et al*. (1993)
$l = 2.09$	dimensionless	Exponent of fractional tumor cell kill by CD8+ T cells. Fractional tumor cell kill by chemotherapy	Dudley *et al*. (2002)
$f = 4.12 \times 10^{-2}$	day^{-1}	Date rate of NK cells	Kuznetsov *et al*. (1994)
$g = 1.25 \times 10^{-2}$	day^{-1}	Maximum NK cells recruitment by ligand-transduced tumor cells	Dudley *et al*. (2002); Diefenbach *et al*. (2001)
$h = 2.02 \times 10^{7}$	$cell^{2}$	Steepness coefficient of the NK cell recruitment curve	Kuznetsov *et al*. (1994)
$j = 2.49 \times 10^{-2}$	day^{-1}	Maximum CD8+ T cell recruitment rate. Primed with ligand-transduced cells	Dudley *et a*l. (2002); Diefenbach *et al*. (2001)
$k = 3.66 \times 10^{7}$	$cell^{2} \cdot day^{-2}$	Steepness coefficient of the CD8+ T cell recruitment curve	Dudley *et al*. (2002); Diefenbach *et al*. (2001)
$m = 2.04 \times 10^{-1}$	day^{-1}	Death rate of CD8+ T cells	Yates and Callard (2002)
$q = 1.42 \times 10^{-6}$	$day^{-1} \cdot cell^{-1}$	CD8+ T cell inactivation rate by tumor cells	Kuznetsov *et al*. (1994)
$p = 3.42 \times 10^{-6}$	$day^{-1} \cdot cell^{-1}$	NK cell inactivation rate by tumor cells	Diefenbach *et al*. (2001)
$s = 8.39 \times 10^{-2}$	dimensionless	Steepness coefficient of tumor – (CD8+ T	Dudley *et al*. (2002)

		cell) lysis term D. Primed with ligand-transduced cells, challenged with ligand-transduced.	
$r_1 = 1.10 \times 10^{-7}$	$day^{-1} \cdot cell^{-1}$	Rate of which CD8+ T cells are stimulated to be produced as a result a tumor cells killed by NK cells	Yates and Callard (2002)
$r_2 = 6.50 \times 10^{-11}$	$cell^{-1} \cdot day^{-1}$	Rate of which CD8+ T cells are stimulated to be produced as a result a tumor cells interaction with circulating lymphocytes	-
$u = 3.00 \times 10^{-10}$	$cell^{-2} \cdot day^{-1}$	Regulatory function by NK cells of CD8+ T cells	-
$\alpha = 7.50 \times 10^{8}$	cell · day−1	Constant source of circulating lymphocytes	Hauser (2001)
$\beta = 1.20 \times 10^{-2}$	day^{-1}	Natural death and differentiation of circulating lymphocytes	Hauser (2001)
$\gamma = 9.00 \times 10^{-1}$	day^{-1}	Rate of chemotherapy drug decay	Calabresi and Schein (1993)
$p_I = 1.25 \times 10^{-1}$	day^{-1}	Maximum CD8+ T cell recruitment curve by IL-2	Kirschner and Panetta (1998)
$g_I = 2.00 \times 10^{2}$	$cells^2$	Constant	-
$\mu_i = 1.00 \times 10^{1}$	day^{-1}	Rate of IL-2 drug decay	Kirschner and Panetta (1998)
$\mu_\alpha = 1.7$	day^{-1}	Decay rate of therapeutic INF-α	Isaeva and Osiopov (2009)
$c_{CTL} = 4.4 \times 10^{-9}$	$cell^{-1}day^{-1}$	Rate of tumor cells inactivation by CD8+ T cells	Isaeva and Osiopov (2009)
I_{α_0}	Units	Initial Interferon	Isaeva and Osiopov (2009)

3. Results and Discussion

In this section, the numerical results of model tumor growth with therapy by using parameter set in Table B1 are presented. For cases in which the tumor would grow to dangerous level if left untreated such as shown in Figure 1.

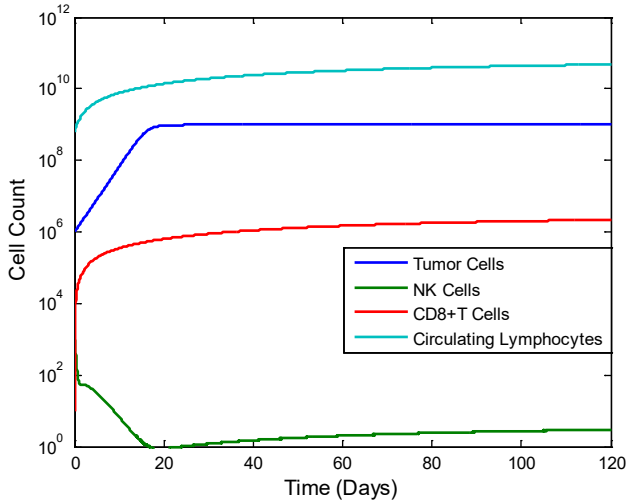

Figure 1. Simulations the immune system response to tumor that treatment fails to kill tumor cells when left untreated.

In this simulation using TIL injection followed by short doses of IL-2. This reflects the treatment that was given in Rosenberg's experiment (Dudley et al., 2002), the difference is addition short doses of INF-α. As previous work (de Pillis et al., 2006), TILs was administered from day 7 through 8 followed IL-2 in 6 pulses from day 8 to day 12 and

INF-α is administered in 4 pulses from day 1 to day 34. For this case the initial size of the tumor can kill up to size cells as shown in Figure 2.

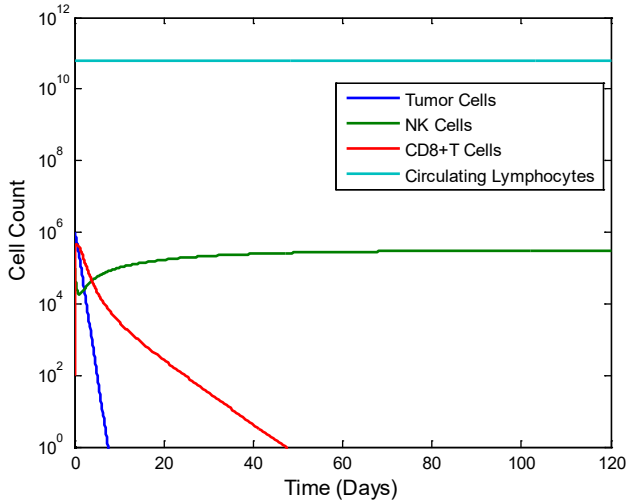

Figure 2. Simulations the immune system response to tumor that treatment effectively kills tumor cells.

These results reflected a condition in which these initial values allowed us to design the best strategy treatment. According to these results we obtained initial value for used in the next simulation is 10^3 NK cells, 10 CD8+ T cells, and 6 x 10^8 circulating lymphocytes. Analytically, these results are consistent with previous work (de Pillis et al., 2006). In order to minimize the effects of INF-α used for the patient, we analyzed the effect of INF-α. In Figure 3 shown that the tumor size of cells can still be killed when INF-α was administered in 4 pulses at strength 5 Million Units (MU) from day 1 to day 34.

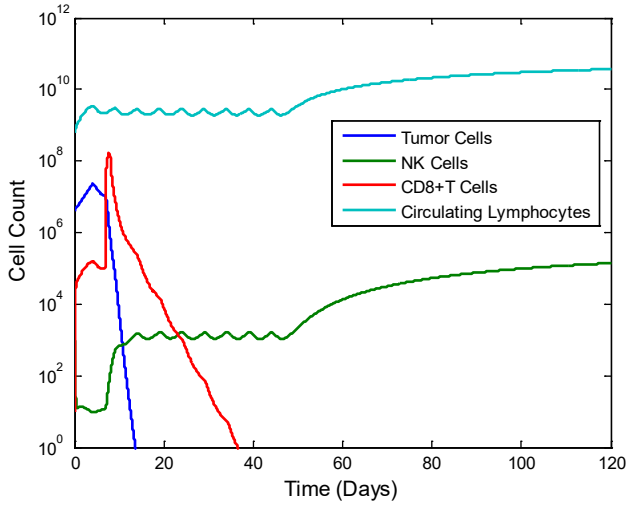

Figure 3. Simulations of the interaction between tumor and immune system with INF-α was administered in 4 pulses at strength 5 MU from day 1 to day 34.

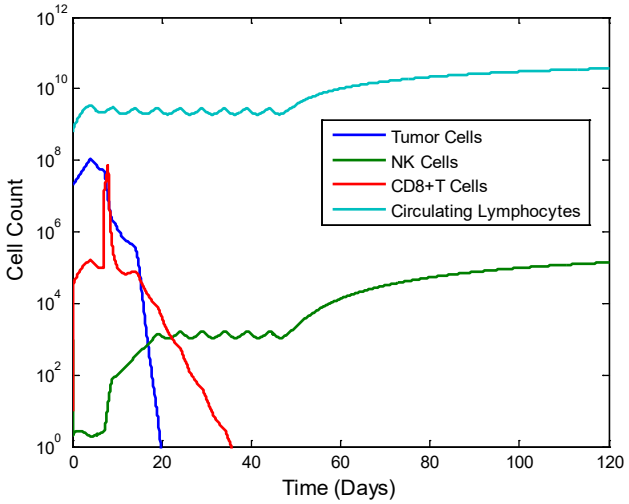

Figure 4. Simulations of the interaction between tumor and immune system with INF-α was administered in 4 pulses at strength 4.8 MU from day 1 to day 34.

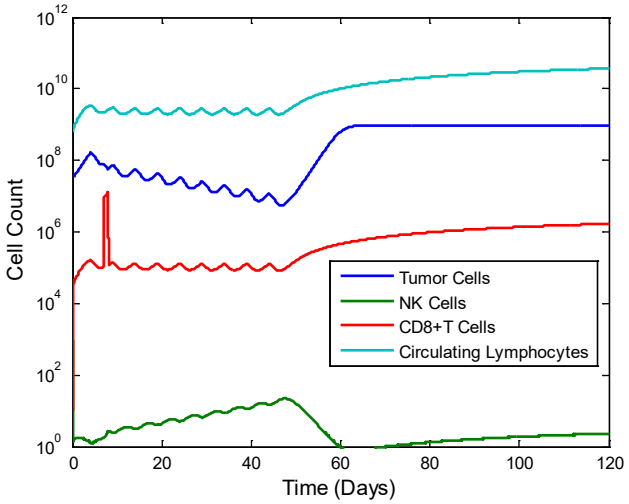

Figure 5. Simulations of the interaction between tumor and immune system with INF-α was administered in 4 pulses at strength 4.7 MU from day 1 to day 34.

Figure 4 and Figure 5 shows that reduction INF-α that administered in 4 pulses from day 1 to day 34 to strength 4.8 MU can still kill the tumor, but when it was reduced to strength 4.7 MU cannot kill the tumor. These results imply that to obtain optimal treatment is limited to using interferon alpha of 4.8. When using above that limit will increase the possibility of the side effects from the drug. Whereas, it is below the limit it will not be able to treat the tumor.

4. Conclusion

Based on numerical results, we can conclude that the boosting of interferon alpha (INF-α) on immunotherapy has a very significant role in killing tumor cells. Boosting interferon alpha (INF-α) in immunotherapy is more effective if done in one month with administered in 4 pulses at strength 4.8 MU. The result of this simulation will be the optimal limit for the administration of interferon alpha in immunotherapy. So that, the side effects of INF-α drugs can be minimized

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