Journal of Health, Medicine and Nursing
ISSN 2422-8419 (Online)
Vol . 10, 2015

Tumor Treatments Using Certain Drug Therapies: Mathematical Modelling

Manisha Tewari[1], Yasha Sharma[2]
Panjab university, Chandigarah, Bansal Institute of Research Technology & Science Bhopal
manishatewaripu@gmail.com,angle.fun.11@gmail.com

Abstract
In this paper, we construct a mathematical model describing immune response to the growth of breast cancer cells and investigate the impact of immunotherapy, chemotherapy and biochemotherapy treatments. We present a model using coupled ordinary differential equations and are also describing the effect of tumor infiltrating lymphocytes (TIL), Interleukin-2 (IL-2) & Interferon alpha (INF-α) on dynamics of tumor cells under the influence of immunotherapy, chemotherapy & biochemotherapy. A new & promising treatment option biochemotherapy has the potential to help reduce the deaths caused by breast cancer. This model is used to evaluate the effects of pulsed application of the drugs. Numerical simulation for some cases show that efficiency of these therapies depends on both variation of tumor size & variation of parameters among two patients. The biochemotherapy more effective than other therapies.
Keywords: Immunotherapy, Chemotherapy, Biochemotherapy, Tumor Infg lymphocytes (TIL), Interleukin-2 (IL-2) Interferon-alpha (INF-α).

1. Introduction -

Cancer is one of the leading causes of death behind only heart disease. The fact that the immune system plays an important role in fighting cancer. The malignant properties of cancer differentiate malignant tumors from benign tumors which do not grow uncontrollably, directly invade locally (or) distant body sites like brain, bone, liver (or) other organs.

The Cancer Research Institute reports that in 1995, an estimated 1.252.000 cases were diagnosed, with 547.000 deaths in the United States alone. With new techniques for detection and treatment of cancer, the relative survival rate has now risen to 54 percent [5]. Cancer causes 1 in 8 deaths worldwide and is rapidly becoming a global pandemic. According to the International Agency for Research on Cancer, there were 12.7 million new cancer cases in 2008. If rates don't change, the global cancer burden is expected to nearly double to 21.4 million cases and 13.5 million deaths by 2030 [8]. It is significant to explore new treatment techniques, in order to reduce the rate of mortality due to cancer in the future.

A new treatment option, the use of monoclonal antibody drugs, has recently been explored as a possible approach to controlling kidney cancer. We have built a system of nonlinear ordinary differential equations (ODEs) that model the growth of a kidney tumor & its interaction with host's immune system. Using this model we consider three different types of treatments.

Immunotherapy (Biotherapy):- Immunotherapy is treatment uses the body's own immune system to fight diseases such as cancer. The main premise is stimulating the patient's immune system to attack the malignant tumor cells that are responsible for the disease. This can be either through immunization of the patient in which case the patient's own immune system is trained to recognize tumor cells as targets to be destroyed or through the administration of therapeutic antibodies.

Immunotherapy includes a wide variety of treatments that work different ways such as: Biologics, Monoclonal antibodies, vaccines, gardasil, BCG, etc. There are known three main categories of immunotherapy: cytokines, monoclonal antibodies & vaccines. Cytokines are chemicals made by immune system cells & play a important role in regulating the growth and activity of other immune system cells & blood cells. The most common cytokines are interleukins-2(IL-2) & interferon alpha (INF-α). Both cytokines cause these cancers to shrink to less than half their original size in about 10% to 20% of patients. Cytokines can also be used as part of some experimental immune techniques. One approach took special immune system cells called tumor-infiltrating lymphocytes (TIL_S) that can be found within kidney tumors. These cells were taken from the tumor after surgery.

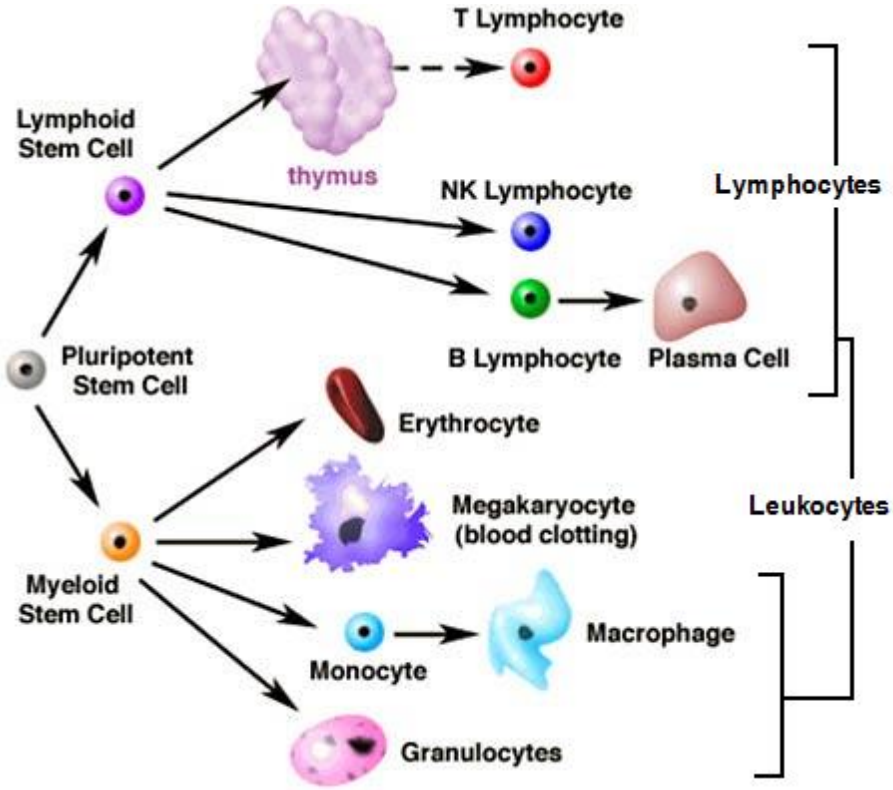
Chemotherapy: **-** Chemotherapy is a treatment of cancer with one or more cytotoxic antineoplastic drugs (chemotherapeutic agents) as part of standardized regimen. This therapy may be given with a curative

intent or it may aim to prolong life or to palliate symptoms. It is often used in conjunction with other cancer treatments such as radiation therapy or surgery.

Traditional chemotherapeutic agents act by killing cells that divide rapidly, one of the main properties of most cancer cells. This means that Chemotherapy also harms cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract & hair follicles. Different types of chemo drugs are alkylating agent's antimetabolites antitumor antibiotics, mitotic inhibitors.

Biochemotherapy: **-** Biochemotherapy, the combination of chemo and biologic response. Modifiers, was developed in the early 1990's to improve response rates and durate remissions in metastatic melanoma. This type of therapy is more effective at extending overall survival than single agent chemo, combination chemo (or) single agent immune.

CELL DIVISION: Following figure represent different types of cells, some of which we use in our model.



2. Mathematical Model –

This mathematical model is based on the de Pillis's model [6] and Isaeva and Osiopov's model [7]. For the sake of completeness, we outline the assumptions of the original model [6] here:

1. Tumor grows logistically in the absence of an immune response. NK cells always present in the body.
2. As part of the specific immune response, active tumor-specific CD8+ T cells are only present in large numbers when tumor cells are present.
3. Both NK and CD8+ T-cells are capable of killing tumor cells. Eventually become inactive after some number of encounters with tumor cells.
4. Both NK and CD8+ T-cells respond to tumor cells by expanding and increasing cytolytic activity.
5. Tumor cells inactivation due to there are present INF-α. We added assumptions are used in the development of therapeutic terms.

6. The fraction of the tumor population killed by chemotherapy depends on the amount of drug in the system. The fraction killed has a maximum less than one, since only tumor cells in certain stages of development can be killed by chemotherapy.
7. Circulating lymphocyte levels can be used as a measure of patient health. A fraction of NK cells, CD8+ T-cells, and circulating lymphocytes are also killed by chemotherapy, according to a similar fractional kill curve.
8. NK and T cells are components of the process of stimulation and elimination of activated effectors cells, a model simplification meant to reflect the self-regulatory nature of the immune system.

2.1 BASIC FORMULA & EQUATION USED IN MODEL:

This mathematical model is based on the following formula used in de Pilli's model:

Rate of change of tumor cell population = {growth & death rate} – {cell-cell kill rate}

And

Rate of change of active effectors cell population = {growth & death rate} + {recruitment rate} - {Inactivation rate}

There are four populations and three drug concentration in this model. They are tumor cells population T (t), natural killer cells N (t), CD8+T cells L (t), circulating lymphocytes cell$C_1(t)$, and concentration of chemotherapy drug$C(t)$. Concentration of IL-2 I (t), and concentration of INF-α $I_\alpha(t)$. The model modified expressed in the following coupled ordinary differential equations below:

$$\frac{dT}{dt} = aT(1-bT) - \psi NT - DT - P_T(1-e^{-c})T - \psi' TL \quad (1)$$

$$\frac{dN}{dt} = jC - kN + l\frac{T^2}{g+T^2}N - eNT - P_N(1-e^{-c})N \quad (2)$$

$$\frac{dL}{dt} = -n_1 L + f\frac{D^2T^2}{h+D^2T^2}L - qLT + (m_1N + m_2C_1)T - rNL^2 - P_L(1-e^{-c})L + \frac{eiLI}{li} + v_L(t) \quad (3)$$

$$\frac{dC_1}{dt} = \alpha - \beta C_1 - PC_1(1-e^{-c})C_1 \quad (4)$$

$$\frac{dC}{dt} = -\gamma c + v_C(t) \quad (5)$$

$$\frac{dI}{dt} = -\eta iL - \phi LI - \mu TI + v_I(t) \quad (6)$$

$$\frac{dI_\alpha}{dt} = v_\alpha(t) - lI_\alpha \quad (7)$$

Where $D = d\frac{(L/T)^{l_1}}{S+(L/T)^{l_1}}$ (8)

$$\psi' = \psi_{CTL}\left(2 - j^{(-I_\alpha/I_{\alpha_0})}\right) \quad (9)$$

2.2 Description about system of equations :

The terms $\frac{dT}{dt}, \frac{dN}{dt}, \frac{dL}{dt}, \frac{dC_1}{dt}, \frac{dC}{dt}, \frac{dI}{dt}, \frac{dI_\alpha}{dt}$ from equation (1) to equation (7) represent the growth rates of the all population. We discuss more detail in following:

Equation(1) : $\frac{dT}{dt}$ {The tumor}:-

Term	Description
$aT(1-bT)$	Logistic tumor growth
ψNT	NK induced tumor death
DT	Tumor inactivation by CD8+T cells, where $D = d\frac{(L/T)^{l_1}}{S+(L/T)^{l_1}}$
$P_T(1-e^{-c})T$	Chemotherapy drug kill term, where$(1-e^{-c})$is saturation term.
$\psi' TL$	Enhancing the Tumor cell recognition.

Equation(2) : $\frac{dN}{dt}$ {The NK-cells} :-

$jC-kN$	Growth of NK-cells
$l\frac{T^2}{g+T^2}N$	The recruitment term of NK-cells
eNT	Inactivation term
$P_N(1-e^{-c})N$	Chemotherapy drug kill term.

Equation(3) : $\frac{dL}{dt}$ {The CD8+T-cells}:-

$n_1 L$	Decrease express term of CD8+T cells.
$f\frac{D^2T^2}{h+D^2T^2}L$	Interaction of CD8+T cells & tumor (recruitment term)
qLT	Inactivation term
$(m_1N+m_2C_1)T$	Recruitment term ($m_1NT+m_2C_1T$) of NK & Circulating lymphocytes.
rNL^2	NK-cell regulation of CD8+T cells (Inactivation term).
$P_L(1-e^{-c})L$	Chemotherapy drug kill term
$\frac{eiLI}{li}$	The presence of Immunotherapy drug stimulates the production of CD8+T-cells.
$v_L(t)$	Injection of TIL drug to the body.

Equation(4) : $\frac{dC_1}{dt}$ {Circulating lymphocytes}:-

$\alpha - \beta C_1$	Circulating lymphocytes are generated a constant rate.
$PC_1(1 - e^{-c})C_1$	Chemotherapy drug kill term.

Equation(5) : $\frac{dC}{dt}$ {Chemotherapy drug}:-

γc	Chemotherapy drug decays exponentially (const. rate).
$v_C(t)$	Injection of Chemotherapy drug to the body.

Equation(6) : $\frac{dI}{dt}$ {Immunotherapy drug (IL-2)}:-

$-\eta iL - \phi LI - \mu TI$	Immunotherapy drug decays exponentially.
$v_I(t)$	Injection of (IL-2) drug to the body.

Equation(7) : $\frac{dI_\alpha}{dt}$ {Interferon alpha (INF-α)}:-

$v_\alpha(t)$	Injection of (INF-α) drug to the body.
lI_α	Immunotherapy drug decays exponentially.

Equation {(8) & (9)}:

$D = d\frac{(L/T)^{l_1}}{S + (L/T)^{l_1}}$	Tumor inactivation term by CD8+T cells.
$\psi' = \psi_{CTL}\left(2 - j^{(-I_\alpha/I_{\alpha_0})}\right)$	Interaction between (INF-α), CD8+T cells & tumor cells.

3. Parameter Derivation -

To facilitate simulations of our proposed model, it is necessary to obtain accurate parameters for our equations. Unfortunately there is no plethora of tumor-immune interaction data available to choose from. Therefore we make use of human data by Rosenberg's clinical trials. We then run simulations with parameter in order to evaluate the behavior of our model.

3.1 Chemotherapy Drug Parameters :

We estimate the values of the kill parameters P_T,$P_{N,}$ P_L & P_{C_1} based on the log-kill hypothesis. We then assume the drug strength to be one log-kill, as described in [27]. $P_{N,}$ P_L & P_{C_1} Are assumed to be smaller thanP_T, but similar in magnitude, since immune cells are one of the most rapidly dividing normal cell populations in the body. We calculate the drug decay rate, γ, from the drug half-life and the relation $\gamma = \frac{log2}{t_{1/2}}$. We estimated the drug half-life $t_{1/2}$ to be more than 18 hours, based on the chemotherapeutic drug doxorubicin [9].

3.2 Immunotherapy Drug Parameters :

In addition to the original model that includes a chemotherapy differential equation, we introduce a immunotherapy drug into our system of differential equations. The cytokine Interleukin 2 (IL-2) simulates CD8+ T cell proliferation. It has been administered in clinical trials on its own, in combination with chemotherapy, as well as after a TIL (tumor infiltrating lymphocyte) injection, in which a large number of highly activated CD8+ T cells are added to the system at a certain point in time. In order to incorporate this

type of immunotherapy into our model, we create a new variable for IL-2 concentration over time, and adjust the CD8+T cell population variable accordingly.
Our three new parameters, e_i ,l_i, η_i come from Kirschner's model with minor alterations to adapt to the fact that we are only concerned with the amount of IL-2 that is not naturally produced by the immune system. Since the presence of IL-2 in the body stimulates the production of CD8+ T cells, we include a Michaelis-Menton term for the CD8+T cell growth rate induced by IL-2. The drug equation for IL-2 is identical in form to our chemotherapy term, and its half-life, η_i is taken from Kirschner's model as well [24].

3.3 Additional Regulation Parameters :

The values of m_2 and r are based on reasonable simulation outcomes of our model. The conditions we set on r are that the term rNL^2 must be smaller in magnitude, for most tumor burdens, than the negative terms that involved the tumor population in our equation for dL/dt. Our reason for this is primarily qualitative since NK cells only eliminate CD8+T cells in excess or in the absence of a tumor burden.

3.4 Human parameters :

The values shown in Table-1 and Table-2 are sets of human parameters that originate from the curve fits created by dePillis et al. [13], patients from clinical trials [20], as well as from an additional and similar tumor model [26]. We obtain the values of $b, \psi, T, l_1, k, l, g, f, n_1, e, m_1$ and s from data collected from patient 1 in a clinical trial for Biochemotherapy [13], [20]. We use the value of a from curve fits by dePillis et al. and this parameter is strictly for tumor growth and is independent of the human immune cells. We take the values of additional parameters k and g from Kuzenetsov's tumor-immune model.

$a = 0.43078$	$b = 1 \times 10^{-9}$	$c = 6.41 \times 10^{-11}$
$j = 2.08 \times 10^{-7}$	$k = 0.0412$	$l = 0.01245$
$g = 2.019 \times 10^{7}$	$f = 0.0249$	$h = 3.66 \times 107$
$m_1 = 1.1 \times 10^{-7}$	$P_T = 0.9$	$P_{N,} = 0.6$
$P_L = 0.6$	$P_{C_1} = 0.6$	$r = 3 \times 10^{-10}$
$\alpha = 7.5 \times 10^{8}$	$\beta = 0.012$	$\gamma = 0.9$
$e_i = 0.1245$	$l_i = 2 \times 10^{7}$	$\eta_i = 10$

Table 1: Model parameters shared by Patient 1 and Patient 2 [13, 20, and 24]

The value of q that we use in our model is similar in magnitude to that of dePillis etal. However we adjust it accordingly after the addition of the new m_1, m_2 and r terms in the dL/dt equation.
In order to calculate α and β for the human population, we estimate the amount of blood in the average human to be 5 liters [12]. Based on a typical white blood cell count for humans of 4.2×10^{10}, and the percentage made up of circulating lymphocytes of about 25% to 70% of white blood cells [23]. Therefore we obtain an equilibrium number of circulating lymphocytes of 6.25×10^{10}. Once we find the lifespan of circulating lymphocytes [10], we take the reciprocal to findβ. We then use the equilibrium solution of the differential equation for c_1 in the *absence of treatment*, $6.5 \times 10^{10} = c_{1_{equilibrium}} = \alpha / \beta$, to calculate$\alpha$. We then use the equilibrium number of circulating lymphocytes to convert the parameter j from [13] to our new model, according to $j_{old} / c_{1_{equilibrium}} = j$.

3.5 Parameter Investigation :

We use these sets of parameters to produce simulations for our model and determine its qualitative behavior. Choosing a variety of parameter sets allows us to test our model with several sets of experimental data and take a closer look at patient specific behavior.

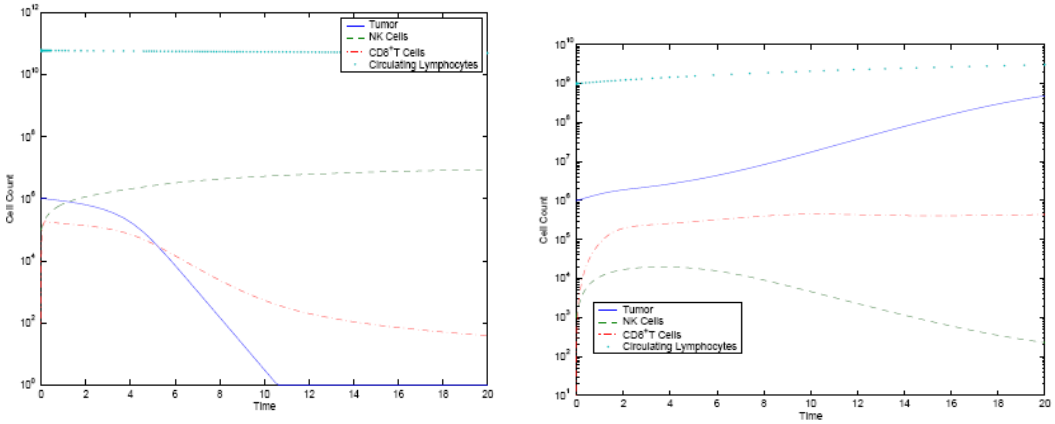
Patient -1		Patient-2	
T = 2.3389	l_1 = 2.0922	T = 1.8792	l_1 = 1.8144
$h = 3.66 \times 10^7$	n_1= 0.2044	h = 5.66×10^7	n_1 = 9.1238
$e = 3.422 \times 10^{-6}$	$q = 1.422 \times 10^{-6}$	$e = 3.593 \times 10^{-6}$	$q = 1.593 \times 10^{-6}$
$m_2 = 2 \times 10^{-11}$	s = 0.0839	m_2 = 6.81×10^{-10}	s = 0.512

Table 2: Model parameters that differ between Patient -1 and Patient -2 [13, 20, 24].

4. Model Behavior & Accuracy -

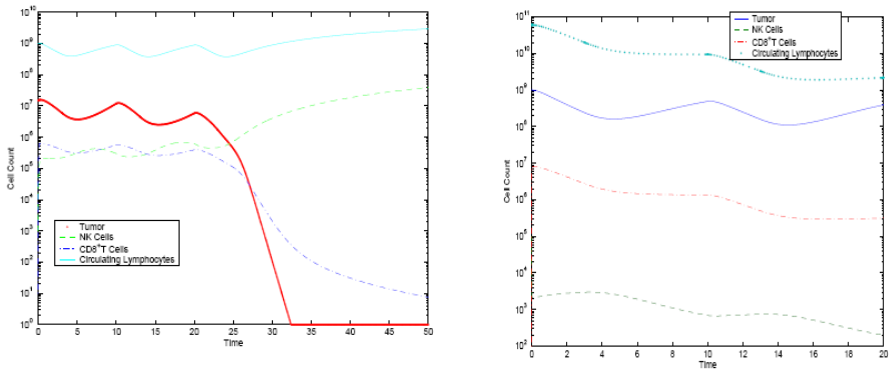
We test the behavior and accuracy of our model with experimental results of two patients in Rosenberg's study on metastatic melanoma [20]. We modified our additional parameters, m_2 and r, to fit these results. First we examine the model with the set of parameters provided in Table 2, which is taken from results of Rosenberg's clinical trials. We discover a case where a healthy immune system can control a tumor that a weak immune system cannot, a case where chemotherapy or immunotherapy can kill a tumor burden, and a case where combination therapy is essential to the survival of the patient. We then compare these results for patient 1 to the behavior of our model with patient 2 and described by following graphs.

.



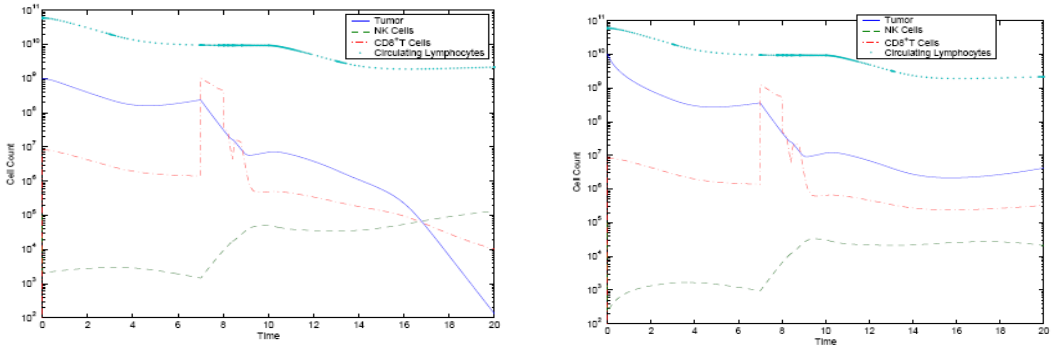
(A) (B)

Fig.1 (A):- A healthy immune system effectively kills a small tumor. Initial Conditions: 10^6 Tumor cells, 10^5 NK cells, 10^2 CD8+ T cells, 6×10^{10} circulating lymphocytes.
Parameters for this simulation are documented in Table 2.
(B):- A depleted immune system fails to kill a small tumor when left untreated. Initial Conditions: 10^6 Tumor cells, 10^3 NK cells, 10 CD8+ T cells, 6×10^9 circulating lymphocytes. Parameters for this simulation are documented in Table 2



(A) (B)

Fig.2 (A):- A case where three doses of chemotherapy is enough to kill off a tumor. Initial Conditions: 2×10^7 tumor cells, 1×10^3NK cells, 10 CD8+ T cells, 6×10^9 circulating lymphocytes.
(B):- A 10^9 cell tumor is not killed by the body with only the aid of chemotherapy.
Parameters for this simulation are documented in Table 2.



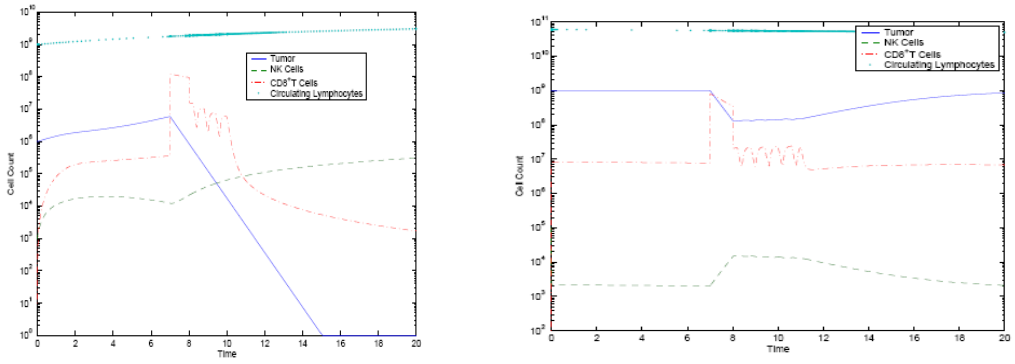
(A) (B)

Fig.3 (A):-Combination therapy is effective in eliminating a tumor burden of 10^9 cells.
(B):-Combination therapy is ineffective for a tumor burden of size 10^9 . Parameters for this simulation are documented in Table 2.

4.1 Comparison with Patient -2 :

In order to look at how much these treatment simulations vary from patient to patient, we change patient specific parameters from Rosenberg's study, and run similar experimental simulations with the parameters for patient-2. These parameters are presented in Table2.
First we repeat the experiment simulated in Fig.1 (A) for a tumor burden of size that the immune system in a healthy state can kill on its own in patient 1. Healthy immune system conditions that killed the tumor in patient 1 are ineffective at treating the same size tumor in patient-2 (see Fig.4 (A)). Patient 2's immune system is able to handle a tumor of size 10^5 under the same immune cell count, as we show in Fig.4 (B). Unfortunately, the immune system's tumor handling capacity appears very patient specific, which should be unsurprising since the combination therapy administered to 13 patients in Rosenberg's study [20], was only effective at treating two patients.
In addition to the differing results of the immune system alone, we examine the initial conditions where chemotherapy was effective at treating a tumor of size 10^6 with a weak immune system for patient1. This same simulation with patient 2's parameters yields a different result. Again, the tumor is not killed in this

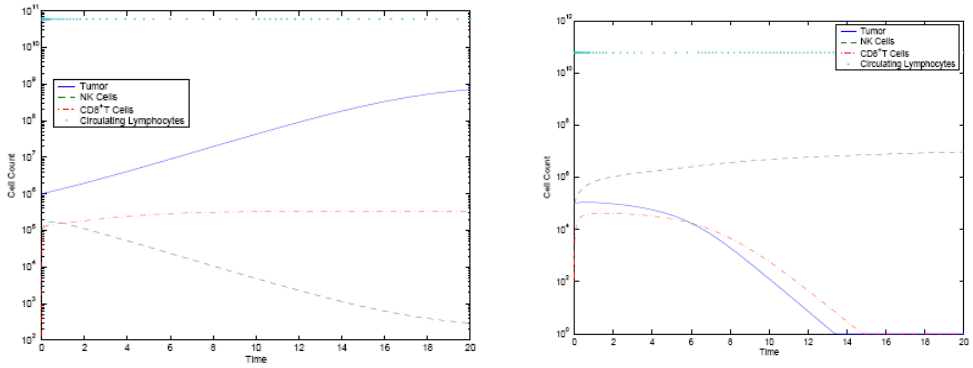
situation, shown in Fig.5. We also perform simulations of immunotherapy and combination therapy on patient 2 for a tumor of size 10^6 for the weak immune system. As shown inFig.6, immunotherapy is ineffective at killing this tumor burden. In fact, patient-2 needs combination therapy with pulsed chemotherapy for 100 days before the tumor is eliminated (see Fig.7). In this case it is a good idea to administer more immunotherapy treatment, involving additional doses of IL-2. This expansion in treatment is effective at speeding tumor death. For example, if we allow for three additional days of IL-2 doses of immunotherapy, with drug treatment, the tumor will die in less than thirty days (see Fig.8).



(A) (B)

Fig.3 (A):- Immunotherapy is able to kill a tumor burden of size 10^6 cells. 10^9 TILs are administered from day 7 through 8. IL-2 is administered in 6 pulses from day 8 to day 10.
(B):- Immunotherapy is unable to kill a tumor burden of size 10^9 cells. 10^9 TILs are administered from day 7 through 8. IL-2 is administered in 6 pulses from day 8 to day 11.
Parameters for this simulation are provided in Table 2.

.



(A) (B)

Fig.4 (A):- Patient -2 cannot kill a 10^6 cell tumor with a healthy immune system of 10^5 NK cells, 100 CD8+T cells, and 6×10^{10} circulating lymphocytes. Parameters for this simulation are provided in Table 2.
(B):- Patient -2 kills a 10^5 cell tumor with a healthy immune system of 10^5 NK cells, 100 CD8+T cells, and 6×10^{10} circulating lymphocytes.

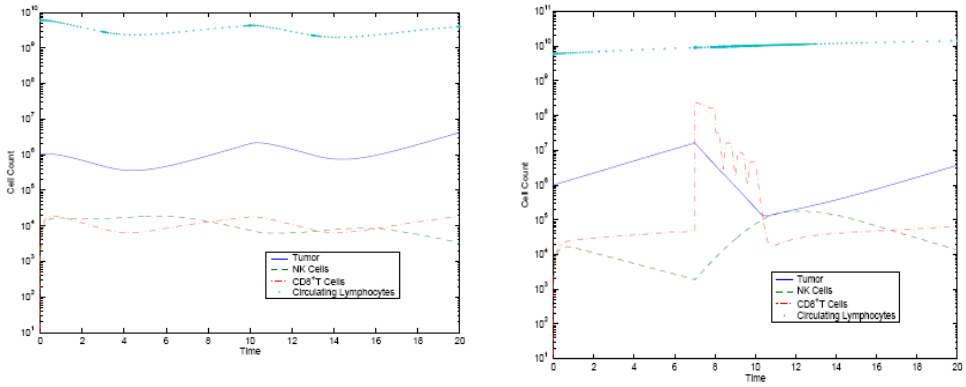


Fig.5: Pulsed chemotherapy fails to kill the 10^6 cell tumor in patient 10, even with a healthy immune system of 10^5 NK cells, 100 CD8+ T cells, and 6×10^{10} circulating lymphocytes. The parameters for this simulation are provided in Table 2.

Fig.6: TIL and IL-2 immunotherapy fails to kill the 10^6 cell tumor in patient 10, even with a healthy immune system of 10^5 NK cells, 100 CD8+ T cells, and 6×10^{10} circulating lymphocytes. 3×10^8 TIL cells are injected on day 7 through 8. IL-2 is pulsed 4 times between day 8 and day 10. The parameters for this simulation are provided in Table 2.

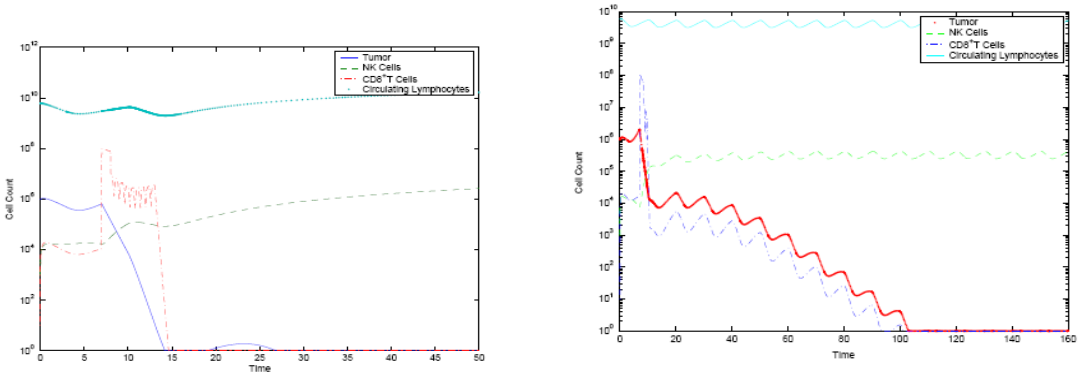


Fig.7: Combination therapy kills the 10^6 cell tumor in patient 10. The initial conditions for the immune system are 10^5 NK cells, 100 CD8+ T cells, and 6×10^{10} circulating lymphocytes. Chemotherapy is pulsed 3/10 days as in Fig.5 and immunotherapy is administered as in Fig.6. The parameters for this simulation are provided in Table 2.

Fig.8: Combination therapy kills the 10^6 cell tumor in patient 10 quicker than in Fig.7 the initial conditions for the immune system are 10^5 NK cells, 100 CD8+ T cells, and 6×10^{10} circulating lymphocytes. Chemotherapy is pulsed 3/10 days for 15 days. Immunotherapy is administered for longer: 10^8 TILs from day 7 through 8, and then pulses of IL-2 from day 8 through 13.5. The parameters for this simulation are provided in Table 2.

Since the tumor almost dies within 15 days, we ended the pulsed chemotherapy cycle at that point. However, we do see a relapse in tumor growth once we end chemotherapy. The tumor appears to arise out of nowhere after chemotherapy treatment ends in Fig.8; however the immune system is now strong enough to keep it in control.

5. Discussion and Conclusion -

We applied a model developed by de Pillis's *and* colleagues (2009) in the form of a system of coupled ordinary differential equation. Then we extended this model to include the presence of INF- . The model used to investigate effect of TIL, IL-2, and INF- on dynamics of tumor cells under the influence of immunotherapy, chemotherapy and biochemotherapy. Our simulation shown that the treatments play important role to remission or even to kill the tumor cells completely.

In the first our simulation, we examine an initial size of tumor cells is10^6. This simulation shows the immune system has not become activated to kill the tumor cells. For this tumor, immune system strength is very important in determining whether or not the immune system alone can kill a tumor. The first specifies what we will denote as an initially immune system with10^5, natural killer cells, 10^2 CD8+ T-cells, and 6×10^{10} circulating lymphocytes [6]. As seen in Figure 1A, the innate immune response is sufficiently strong to control the tumor. However, when the immune system is weakened, a tumor of the same size grows to a dangerous level in the absence of treatment interventions. Simulated results for this weakened immune case, with initial conditions set to 10^3 natural killer cells, 10 CD8+ T-cells, and 6 $\times 10^8$ circulating lymphocytes, are shown in Figure 1B. Similar with the case patient 1, our simulation for patient 2 shown that biochemotherapy able to kill tumor cells 10^6 until 10^7, are shown in Figure 5. But immunotherapy and chemotherapy is unable to kill tumor cells 10^6. As shown in Figure 3 (B), immunotherapy cause reduction the tumor cells until clean completely on day 10 and then relapsed on day 30 to level dangerous, instead chemotherapy is unable to kill this tumor size, as shown in Figure 4(B).

This work is still necessary to investigation on how the effect of drug injection for another cells or how the effect another cytokines such as IL-4, IL-10 and IL-12 in future.

6. References -

[1] P. Anand and A.B. Kunnumakara, "Cancer is a preventable disease that requires major lifestyle changes", Pharm. Res. 25 (9) (2008), 2097-2116.

[2] P. Calabresi and P. S. Schein, "Medical Oncology: Basic Principles and Clinical Management of Cancer", 2nd ed., McGraw-Hill, New York, 1993.

[3] J.A. Adam and N. Bellomo, "*A survey of models for tumor-immune system dynamics"*, Birkhäuser, Boston, MA, 1996.

[4] J.C. Arciero, D.E. Kirschner and T.L. Jackson, "*A mathematical model of tumor immune evasion and siRNA treatment"*, Disc. Cont. Dyn. Syst-B, 4 (2004), pp. 39-58.

[5] W Chang, L Crowl, E Malm, K Todd-Brown, L Thomas, and M Vrable, "Analyzing Immunotherapy and Chemotherapy of Tumors through Mathematical Modeling", Harvey Mudd College, Claremont, 2003.

[6] L. G. de Pillis, W. Gu and A. E. Radunskaya, "Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations", J. Theoret. Biol. 238(4) (2006), 841-862.

[7] O. G. Isaeva and V. A. Osiopov, "Different strategies for cancer treatment: Mathematical modelling, Computational and Mathematical Methods in Medicine" 10(4) (2009), 253-272.

[8] G. Rosen and Leo, Advancing the Global Fight against Cancer, American Science Society, 2008.

[9] P. CALABRESI AND P. S. SCHEIN, eds., "Medical Oncology: Basic Principles and Clinical Management of Cancer", McGraw-Hill, New York, second ed., 1993.

[10] L. BANNOCK, Nutrition. Found at http://www.doctorbannock.com/nutrition.

[11] M. CHAPLAIN, M. GANESH, AND I. GRAHAM, "Spatio-temporal pattern formation on spherical surfaces: numerical simulation and application to solid tumor growth", Journal of Mathematical Biology, 42 (2001), pp. 387–423.

[12] J. O. E. CLARK, ed., "A Visual Guide to the Human Body: A Comprehensive Atlas of the Structures of the Human Body, Barnes and Noble", 1999.

[13] L. DE PILLIS, A. RADUNSKAYA, AND C. WISEMAN, "A validated mathematical model of cell-mediated immune responses to tumor invasion and vaccine therapy in mice and humans", Presentation poster, 2003.

[15] R. J. Motzer and W. J. Berg, "Role of Interferon in Metastatic Renal Cell Carcinoma", Humana Press, 2000.
[14] Hannah Savage, "A Nonlinear ODE Model of Tumor Growth and Effect of Immunotherapy and Chemotherapy Treatment in Colorectal Cancer", May, 2010.
[16] The immune system - second of two parts, The New England Journal of Medicine, 343 (2000), pp. 108–117.
[17] A. DIEFENBACH, E. R. JENSEN, A. M. JAMLESON, AND D. H. RAULET, Rae1 and H60 ligands of the NKG2D receptor simulate tumour immunity, Nature, 413 (2001),pp. 165–171.
[18] M. S. DORDAL, J. N. WINTER, AND A. J. ATKINSON, JR., "Kinetic analysis of Pglycoprotein-mediated doxorubicin efflux, The Journal of Pharmacology and Experimental Theraputics", 263 (1992), pp. 762–766.
[19] J. R. DRISCOLL AND D. M. HEALY, JR., "Computing Fourier transforms and convolutions on the 2-sphere, Advances in Applied Mathematics", 15 (1994), pp. 202–250.
[20] M. E. DUDLEY, J. R. WUNDERLICH, P. F. ROBBINS, J. C. YANG, P. HWU, D. J. SCHWARTZENTRUBER, S. L. TOPALIAN, R. SHERRY, N. P. RESTIFO, A. M. HUBICKI, M. R. ROBINSON, M. RAFFELD, P. DURAY, C. A. SEIPP, L. ROGERSFREEZER, K. E. MORTON, S. A. MAVROUKAKIS, D. E. WHITE, AND S. A. ROSENBERG, "Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes", Science, 298 (2002), pp. 850–854.
[21] Mustafa Mamat, subiyanto and Agus Kartono, "Mathematical Model of Cancer Treatments Using Immunotherapy, Chemotherapy and Biochemotherapy", Applied Mathematical Sciences, Vol. 7, 2013, no. 5, 247 – 261.
[22] M. L. DUSTIN AND D. R. COLMAN, "Neural and immunological synaptic relations", Science, 298 (2002), pp. 785–789.
[23] B. HAUSER, "Blood tests, tech. rep.", International Waldenstrom's Macroglobulinemia Foundation, Jan. 2001.
[24] D. KIRSCHNER AND J. C. PANETTA, "Modeling immunotherapy of the tumor-immune interaction", Journal of Mathematical Biology, 37 (1998), pp. 232–252.
[25] H. KNOLLE, "Cell kinetic modeling and the chemotherapy of cancer", Springer-Verlag, Berlin, 1988.
[26] V. KUZNETSOV, I. MAKALKIN, and M. TAYLOR, AND A. PERELSON, "Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis", Bull. Of Math. Bio. 56 (1994), pp. 295–321.
[27] M. C. PERRY, ed., "The Chemotherapy Source Book", Lippincott Williams & Wilkins, third ed., 2001.
[28] L. PREZIOSI, "from population dynamics to modeling the competition between tumors and immune system, Mathematical and Computer Modeling", 23 (1996), pp. 135–152.

The IISTE is a pioneer in the Open-Access hosting service and academic event management. The aim of the firm is Accelerating Global Knowledge Sharing.

More information about the firm can be found on the homepage:
http://www.iiste.org

CALL FOR JOURNAL PAPERS

There are more than 30 peer-reviewed academic journals hosted under the hosting platform.

Prospective authors of journals can find the submission instruction on the following page: http://www.iiste.org/journals/ All the journals articles are available online to the readers all over the world without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. Paper version of the journals is also available upon request of readers and authors.

MORE RESOURCES

Book publication information: http://www.iiste.org/book/

Academic conference: http://www.iiste.org/conference/upcoming-conferences-call-for-paper/

IISTE Knowledge Sharing Partners

EBSCO, Index Copernicus, Ulrich's Periodicals Directory, JournalTOCS, PKP Open Archives Harvester, Bielefeld Academic Search Engine, Elektronische Zeitschriftenbibliothek EZB, Open J-Gate, OCLC WorldCat, Universe Digtial Library , NewJour, Google Scholar