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A Comparative Study of Tumor Regression Efficiency under the Impact of Cytokines Interleukin-21 and Interleukin-2 for Cancer Treatment Cultured with Chemo - Immunotherapy: A Mathematical Modeling Approach

Muhammad Suleman
Department of Computer Science & Information Technology,
Superior University,
Lahore, Pakistan.
Email: muh_sul@yahoo.com

Muhammad Usman Hashmi
Department of Applied Science,
Superior University,
Lahore, Pakistan.
Email: usmanhashmi06@hotmail.com

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Abstract. In our study we have developed a new mathematical model in the form of system of ordinary differential equations governing the interactions among the cellular populations NK cells, CD8+T cells, tumor cells and cultured with chemo-immunotherapy under the impact of newly characterized cytokine InterleukinIL-21. We have compared our formulated model under the impact of IL-21 to that with de Pilli's model under the impact of IL-2 with same cellular populations in order to investigate which Interleukin is more efficient to eradicate tumor. Theoretical interpretation shows that our developed model is more efficient than the de Pillis model for better tumor regression. We have also simulated both models for tumor reduction efficiency using MATLAB. Our simulations demonstrate that IL-21 is more efficient for tumor reduction than IL-2. Thus our experimental results agree with theoretical interpretations. In future IL-21 may be combined with IL-2 or any other antitumor agent for better tumor reduction.

AMS (MOS) Subject Classification Codes: 92-XX; 92-BXX; 92B05
Key Words: Tumor, Immunotherapy, Chemotherapy, Interleukin IL-21, Interleukin IL-2, Cancer model.

1. INTRODUCTION

Cancer is known as multi-faceted disease that contains complicated interactions between tumor cells and the neighboring micro-immune system [1]. It arises due to uncontrolled growth of abnormal cells in the body [2, 3]. The current available cancer treatment techniques like, chemotherapy, radiotherapy and surgery carry the prominent side effects on the patients. These facts produce great interest for the development of new therapeutic techniques for cancer treatment one such approach is to strengthen the body's own natural defense system in the form of immunotherapy to combat cancer [4, 5]. Immunotherapy targets the tumor cells only despite killing normal cells of the immune system and it becomes prominent promising technique against this fatal disease [1, 4]. Over the past 20 years mathematical modeling of tumor growth and treatment by a number of researchers, experimentalists and clinicians has revolutionized our understanding about this phenomenon for both quantitative and predictive purposes [4, 5, 6, 7].

IL-21 is recently discovered cytokine [8, 9] and is the youngest member of γ-chain receptors cytokine family that now includes IL-2, IL-4, IL-7, IL-9, and IL-15 [10]. It is the product of CD4+T cells [1, 11, 12, 13]. It has pleiotropic effects on T cells and NK cells [14]. It is extensively used as immunotherapeutic agent against cancer [12]. It has antitumor activity and promotes to activate immune system against cancer [1, 12, 15]. Clinical studies show that IL-21 has appreciable antitumor responses in solid cancers [1, 16]. It promotes the functions like enhancing proliferations, maturation and cytolysis activity of NK and CD8+T cells [1, 9, 17, 18, 19]. This novel cytokine has been declared as promising immunotherapeutic agent against tumor mass and its attenuation and regression owing to its strong exertion of tumor rejection [6, 20]. The cytokine Interlukin-2 (IL-2) has also four bundles α-helical structure [21] and belongs to the same family as of IL-21. It was identified in 1976 and was clinically used in 1992 [9]. It is known as subpopulation of CD4+T cells. IL-2 suppresses responses of T cells and activates immune responses. Despite stimulating the CD8+T cells it regulates the immune system. IL-2 offers prominent role for the treatment of metastatic melanoma and renal cell carcinoma [22]. Its presence stimulates NK cells and potently activates CD8+T cells to kill tumor cells [9, 23]. IL-2 is more effective for low dose as compared to high dose that causes serious hematologic violations [7].

Many researchers [30-37] have applied the mathematical modeling approach to study the dynamics of different biological phenomeanon taking into consideration of fluid flows and some considered fractional derivatives. Recent cancer research includes the investigation of tumor-immune cellular interactions for tumor regression under the influence of external drugs through mathematical modeling approach. Firstly, De Boer model the anti-tumor immune response under the impact of exogenous IL-2 in the form of system of ordinary differential equations [7, 24] then Kirschner and Panetta modeled such interactions by considering both endogenous IL-2(naturally produced) and exogenous IL-2 (external intervention)[7, 25]. Later L. G. de Pillis and colleagues formulated the chemo-immunotherapy under the impact of exogenous IL-2 and did not consider the naturally produced endogenous IL-2 [5, 26]. Antono Cappuccio and colleagues in [20] model the tumor-immune interaction under the influence of newly discovered cytokine interlukin-21 but they did not consider the chemotherapeutic effect on their model. Then Mustafa Mamat extended the de

Pillis model by including Interferon-α (IFN-α) to enhance the tumor regression efficiency [2].We have developed a new mathematical model describing the tumor-immune interaction cultured with chemo-immunotherapy under the influence of a novel cytokine IL-21. We have adopted the same cellular populations as have been taken by de Pillis in his model. We are interested in comparing our developed model with that of de Pillis model. We want to investigate the behavior of same cellular populations cultured with same chemo-immune system under different cytokines for better tumor regression efficiency. Theoretically our formulated model under the impact of interleukin IL-21 shows better tumor regression efficiency as compared to the IL-2 influenced de Pillis model. We have simulated both models for tumor dynamics under the impact of both cytokines IL-2 and IL-21. Our simulations show that IL-21 is more efficient cytokine than IL-2 in order to get better tumor reduction efficiency. Thus our simulations verify theoretical interpretation.

2. METHODOLOGY

We start with some biological assumptions on which the structure of our models is based.

2.1. **Model Assumptions.**

(1) A tumor grows logistically in the absence of immune response [2, 5, 26, 27].
(2) Both NK cells and CD8+T cells can kill tumor cells [2, 5, 27].
(3) We consider both Endogenous and Exogenous IL-2 and IL-21 in our model [5, 26].
(4) Natural Killer (NK) cells being part of the immune system are always present even no tumor cells exist [2, 5, 27].
(5) Active tumor specific cells as being part of the immune system are present only when tumor cells are present [2, 5, 27].
(6) Each of the NK and CD8+T cells become inactive after some number of encounters with the tumor cells [2, 5, 27].
(7) Despite the activated CD8+T cells and NK cells, the action of all other lymphocytes including circulating lymphocytes C (t), has been neglected [26].
(8) Effects of IL-21 are considered only on NK and CD8+T cells and independent on other factors [20].
(9) Major focus of the model is on the contribution of IL-21 to the cellular immunity [20].
(10) CD4+T helper cells are also neglected because they have minor contribution to anticancer response and also have low secretion as compared to the other therapeutic doses [20].
(11) NK and CD8+T cells respond with tumor cells by expanding and increasing metabolic and catalytic activity [2, 5, 27].
(12) The fraction of the tumor cells killed by the chemotherapy depends on the amount of the drug in the system and this killed fraction is always less than one [2].
(13) Chemotherapy also kills some fraction of the NK cells and CD8+T cells [2].
(14) Immune system possesses self-regulatory nature because activated effector cell NK and CD8+T cells from the cyclic process of stimulation and decay [2].

2.2. **Model Populations.** Our new model, we call it as IL-21-Model carries the same cellular populations as were taken by de Pillis in his model such that each cellular population represents one state variable given below.

- T(t) Tumor cellular population
- N(t) Natural Killer cellular (NK cell) population
- L(t) CD8+T cellular population
- C(t) Circulating lymphocytes
- M(t) Chemotherapy concentration drug
- I(t) Immunotherapy concentration drug

and the second one is de Pillis model under the drug concentration IL-2, we call it IL-2-Model. Besides considering assumptions and populations our model carries the four types of actions which are described below.

- Natural growth
- Natural decay
- Death of mediated cells
- Recruitment
- Exogenous drug

Each term in the ordinary coupled differential equations represents a single action like reproduction of population growth, natural elimination death, and death of one cell population from another cell population, cell being recruited and external drug intervention [1]. The function and interaction of cell populations with drug concentrations are depicted in schematic diagram Fig.1.

The above discussion can be formulated in the form of two generalized equations (A-1) and (B-1) [27].

- A-1 Rate of change of tumor cell population = (growth and death rate term) - (cell-cell kill rate term).
- B-1 Rate of change of active effector cell population = (growth and death rate term) + (recruitment rate term) - (Inactivation rate term).

FIGURE 1. Schematic diagram of the tumor-immune interaction with external intervention. NK cells, CD8+T cells, and Circulating Lymphocytes are represented by brown filled circles and form the basic immune system. P cell acts as mediators between NK cells and CD8+T cells are represented by brown filled circle, Tumor cells are represented by red filled circle, Endogenous and exogenous IL-21 are represented by green filled circle and arrow, Yellow filled arrow represents IL-21 dose dependent product, dose of CD8+T cells is represented by brown filled arrow, chemotherapeutic effect is given by blue rectangles and all other cellular interactions are represented by thick blue arrows as shown in Fig 1.

Now we are able to develop the growth equations and explaining core theory involved in our models.

3. THEORY AND CALCULATIONS

All the above stated physical assumptions, cellular populations, schematic representation, generalized equations and [5, 20, 25, 26, 27] constitute concise mathematical models in the form of coupled ordinary differential equations given below

3.1. **IL-21 Model.**

$$\dot{T(t)} = r_3 T\left[1-(T/K)^w\right] - k_1 pNT - k_2 pLT - k_T(1-\exp(-M)T \tag{3. 1}$$

$$\dot{N(t)} = eC - r_1 N\left[1 - \frac{N(I_{21}+q_1)}{p_1 I_{21}+p_2}\right] - pNT - k_N(1-\exp(-M)N \tag{3. 2}$$

$$\begin{aligned}\dot{L(t)} = r_2 L\left[1 - \frac{L}{h_2(0)+\frac{\sigma m}{1+(\frac{m}{D})}}\right] + \frac{jTL}{k+T} - qLT \\ +(r_1^{'}N + r_3 C)T - k_L(1-\exp(-M)L + V_L(t)\end{aligned} \tag{3. 3}$$

$$\dot{C(t)} = \alpha - \beta C - k_C(1 - \exp(-M)C \tag{3. 4}$$

$$\dot{m(t)} = -\alpha I_{21} - \mu_2 \tag{3. 5}$$

$$\dot{p(t)} = \frac{b_1 I}{b_2 + I} - \mu_3 p \tag{3. 6}$$

$$\dot{I_{21}(t)} = hn - \mu_1 I_{21} \tag{3. 7}$$

$$\dot{M(t)} = -\gamma M + V_M(t) \tag{3. 8}$$

Where $D = \frac{d(L/T)^l}{s+(L/T)^l}$
And de Pillis model, we call it IL-2 model is taken from [26, 28]. Brief description of the terms in the above model is given in Table 2. and the parametric values involving in the model are given in Table 3.

3.2. **IL-2 Model.**

$$\dot{T(t)} = aT(1 - bT) - cNT - DT - k_T(1 - \exp(-M)T \tag{3. 9}$$

$$\dot{N(t)} = f(\frac{e}{f}C - N) - pNT + \frac{p_N N I_2}{g_N + I_2} - k_N(1 - \exp(-M)N \tag{3. 10}$$

$$\dot{L(t)} = \frac{\theta m L}{\theta + I} + \frac{jTL}{k+T} - qLT + (r_1^{'}N + r_3 C)T - \frac{uL^2CL}{k+L} - k_L(1 - \exp(-M)L + \frac{p_I L I_2}{g_I} \tag{3. 11}$$

$$\dot{C(t)} = \beta(\frac{\alpha}{\beta}C - N) - k_C(1 - \exp(-M)C \tag{3. 12}$$

$$\dot{m(t)} = -\gamma M + V_M(t) \tag{3. 13}$$

$$\dot{I_2(t)} = -\mu_I I + \phi C + \frac{\omega L I}{\xi + I} + V_{I_2}(t) \tag{3. 14}$$

$$\dot{m(t)} = -\gamma M + V_M(t) \tag{3. 15}$$

Where$D = \frac{d(L/T)^l}{s+(L/T)^l}$
The parameters used in above model is given in Table-1. Now we justify our models as follows.

4. JUSTIFYING IL-21 MODEL

4.1. **Tumor cell dynamics Eq (3.1):** Following the Equation (A-1) the term $g(t) = r_3T(1-(T/K)^w)$ in equation (A) represents the tumor growth that follows the logistic law under the influence of IL-21[6]. The above term satisfies the experimental data for melanoma B16. Tumor growth is influenced by the cytotoxic, p-mediated, NK cells and CD8+T cells exhibiting antitumor response.k_1 represents the affinity of tumor with NK cells interaction while k_2 represents affinity of tumor with CD8+T cells interaction. p represents the mediator of the NK cells/CD8+T cell cytotoxicity and -N T is the tumor cells killed by the activated NK cells. The term -L T is the tumor cells killed by the activated CD8+T cells. The term $-k_T(1 - \exp(-M)T$ indicates the chemotherapeutic effect on tumor. It represents the fraction of the tumor cells killed by the chemotherapy M(t). The additions of growth term and cell kill terms along with chemotherapeutic gives net tumor growth. Thus all the terms involved in equation (A) justify Eq (A-1). Similarly we justify the other equations of our IL-21-Model as follows.

4.2. **Natural Killer (NK) cell dynamics Eq (3.2):** NK cell population follows the logistic growth law $r_1N(1 - \frac{N(I_{21}+q_1)}{p_1I_{21}+p_2})$ where r_1 is growth rate. The carrying capacity $\frac{p_1I_{21}+p_2}{(I_{21}+q_1)}$ being linear function shows the effect of IL-21 on the NK cell population. p_1, p_2 and q_1 being constants having values given in [6]. The inactivation term -pNT represents the NK cell death by tumor killing and the last term of this equation $-k_N(1-\exp(-M)N$indicates the NK cell death by chemotherapy. Thus the sum of self growth, decay rates and inactivation terms constitute the net growth of NK cells.

4.3. **CD8+T cell dynamics Eq (3.3):** Here r_2 is the logistic growth rate, h_2 is the carrying capacity which is the function of memory factor m and ? establishes the relation between memory factor and growth of the carrying capacity. D contains the constraints for CD8+T cells, inhibitory functions of T regulatory cells and Th2 cytokines [20]. The activated CD8+T cells recruitment term is given by $\frac{jTL}{k+T}$[26]. CD8+T cells death by tumor killing resources is given by the inactivation term $-qLT$. The cells killed due to recruitment are proportional to $r_1^{'}N$. The chemotherapeutic effect on CD8+T cells is given by $-k_L(1 - \exp(-M)L$ and $V_L(t)$ gives the CD8+T cell injected drug concentration.

4.4. **Circulating Lymphocytes dynamics Eq (3.4):** Circulating lymphocytes are generated at constant rate such that each cell possess natural life span is represented by the term $\alpha - \beta C$. The chemotherapeutic impact on $C(t)$ is given by $k_C(1 - \exp(-M)C$.

4.5. **Dose dependent product dynamics Eq (3.5):** IL-21 dose dependent product expands the adaptive response of CD8+T cells even after complete removal of IL-21. Here a is proportionality constant and μ_2 is clearance rate that's reciprocal is the time measure of CD8+T cells response. It acts like a member which facilitate the memory of CD8+T cells [20].

4.6. **Cytotoxic Protein dynamics Eq (3.6):** Our model also assumes cytotoxic protein like perforin that causes IL-21 mediated increase in the killing of effector cells potential. This is known as IL-21 dose dependent phenomena. Since NK cell and CD8+T cells share the same cytotoxic factor we call this factor as general protein p known as average effector cytotoxicity , a cytotoxic protein that affect tumor lysis given by Eq (E). $\mu_3$is termed as natural degradation of p and b_1, b_2 are variables of selected function [20].

4.7. **IL-21 dynamics Eq (3.7):** The route of intervention of exogenous IL-21 is through function input which is proportional to n number of genetically engineered tumor cells. Here h is constant of proportionality and μ_1 is clearance rate [20].

4.8. **Chemotherapeutic dynamics Eq (3.8):** Here $-\gamma m$ represents decay or elimination of chemotherapy drug after concentration and $V_M(t)$ is injected chemotherapeutic drug [2].

5. JUSTIFYING IL-2-MODEL:

In this model justification of all terms are given in [24, 26] by de Pillis and colleagues.

6. SIMULATIONS OF MODELS

In this section we have simulated both models for tumor regression. For IL-2 model we have taken the initial conditions: $T_0 = 2 \times 10^7$,$N_0 = 2.5 \times 10^8$,$L_0 = 5.268 \times 10^5$,$C_0 = 2.25 \times 10^9$,$M_0 = 2.3869$,$I_0 = 1073$. We have taken the x-axes as time in days and y-axes as number of tumor cells. We have ran the simulation for 30 days. We have also applied the doses of CD8+T cells 1.77×10^{10}, chemotherapy(2.3869) and IL-2(2.7859×10^6). We have plotted only tumor cells versus time because at this stage our main focus is on tumor reduction output. Plot for Tumor cells for IL-2 model has been indicated by red dotted line as shown in Fig 2. We have then simulated IL-21 model for tumor cells versus time. Here we have taken the same initial conditions as in previous case but with change of value of IL-21 to $T_0 = 2 \times 10^7$,$N_0 = 2.5 \times 10^8$,$L_0 = 5.268 \times 10^5$,$C_0 = 2.25 \times 10^9$,$M_0 = 2.3869$,$I_0 = 500$. In case of IL-21 model we have applied the IL-21 dosages. 10×500 and other dosages remain same i.e. CD8+T cells (1.77×10^{10}) and chemotherapy(2.3869). Simulation for tumor dynamics has been demonstrated by blue circled line imbedded on the previous plot for IL-2 in order to make comparison which interleukin reduces more tumor cells. Comparison from Fig 2. Show that using IL-2 tumor reduces in 2-3 days. But more reduction can be obtained within one day by using IL-21. Thus our experimental results agree with theoretical justifications that IL-21 is more efficient to eradicate tumor cells as compared to IL-2.

Table 1:Parametric values used in mathematical model of IL-2			
Parameter	Description	Values	Source
a	Growth rate of Tumor	$4.31 \times 10^(-1)$	[26]
b	Inverse of carrying Capacity	$1.02 \times 10^(-9)$	[26]
c	NK induced tumor death rate	$2.9077 \times 10^(-13)$	[26]
K_T	Chemotherapy induced tumor death	$9 \times 10^(-1)$	[26]
δ_T	Medicine efficacy coefficient	1.8328	[26]
$\frac{e}{f}$	NK synthesis rate over turnover rate	$1.11 \times 10^(-1)$	[26]
f	NK cell turnover rate	$1.25 \times 10^(-2)$	[26]
p	NK cell death rate due to tumor	$2.794.25 \times 10^(-13)$	[26]
p_N	IL-2 induced NK cell proliferation	$6.68 \times 10^(-2)$	[26]
g_N	IL-2 concentration for NK cell proliferation	$2.5036 \times 10^(5)$	[26]
K_N	NK depletion from toxicity	$6.75 \times 10^(-2)$	[26]
δ_N	Medicine efficacy coefficient	1.8328	[26]
m	Activated CD8+T cells turnover rate	$9 \times 10^(-3)$	[26]
θ	IL-2 concentration to halve CD8+T cell turnover	$2.5036 \times 10^(-3)$	[26]
q	CD8+T cell death due to tumor interaction	$3.422 \times 10^(-10)$	[26]
r_1	Rate of NK lysed tumor cells	$2.9077 \times 10^(-11)$	[26]
r_2	Rate of CD8+T cell production from Lymphocytes	$5.8467 \times 10^(-13)$	[26]
p_I	IL-2 induced CD8+T cells proliferation	2.971	[26]
g_I	IL-2 concentration for half maximum CD8+T cells proliferation	$2.5036 \times 10^(3)$	[26]
u	CD8+T cells feedback coefficient	$4.417 \times 10^(-14)$	[26]
k	IL-2 concentration to half CD8+T cells self-regulation	$2.5036 \times 10^(3)$	[26]
j	Rate of CD8+T lysed tumor cells	$1.245 \times 10^(-2)$	[26]
K_L	Rate of CD8+T depletion from medicine toxicity	$4.86 \times 10^(-2)$	[26]
δ_N	Medicine toxicity coefficient	1.8328	[26]
$\frac{\alpha}{\beta}$	Rate of Lymphocytes production to turnover rate	$2.25 \times 10^(-1)$	[26]
β	Rate of Lymphocyte turnover	$6.3 \times 10^(-3)$	[26]
K_C	Rate of Lymphocyte depletion from medicine toxicity	$3.4 \times 10^(-2)$	[26]
δ_C	Medicine toxicity coefficient	1.8328	[26]
γ	Rate of excretion and elimination of doxorubicin	$5.199 \times 10^(-1)$	[26]
μ_I	Rate of Excretion and elimination of IL-2	11.7427	[26]
ω	Rate of IL-2 production from CD8+T cells	$7.874 \times 10^(-2)$	[26]
ϕ	Rate of IL-2 production from CD4+T nave cells	$2.38405 \times 10^(-7)$	[26]
ξ	IL-2 concentration for half maximal CD8+T cells IL-2 production	$2.5036 \times 10^(3)$	[26]
d	Coefficient of immune system strength	2.34	[26]
l	Coefficient of immune strength scaling	2.09	[26]
s	Value of $(\frac{L}{T})^l$ necessary for half-maximal CD8+T cells toxicity	$8.39 \times 10^(-2)$	[26]

Table-2: Description of Terms used in IL-21 Model			
Equation	Terms	Brief Description	Source
3.1	$\frac{dT}{dt}$	Rate of change of tumor cell population	[27]
	$r_3T(1-(T/K)^w)$	Tumor growth Law	[20]
	$-k_1pNT$	NK induced tumor death	[26]
	$-k_2pLT$	CD8+T cell induced tumor death	[26]
	$-k_T(1-\exp(-M)T$	Tumor cell death by chemotherapy drug	[26]
3.2	$\frac{dN}{dt}$	Rate of change of NK cell population	[20]
	$r_1N(1-\frac{N(I_{21}+q_1)}{p_1I_{21}+p_2})$	NK cell logistic growth Law	[20]
	$-pNT$	Inactivation term, NK death by tumor killing	[26]
	$-k_N(1-\exp(-M)N$	NK cell death by chemotherapy drug	[26]
3.3	$\frac{dL}{dt}$	Rate of change of CD8+T cell population	[26]
	$r_2L(1-\frac{L}{h_2(0)+\frac{\sigma m}{1+(\frac{m}{D})}})$	CD8+T cell growth Law	[20]
	$\frac{jTL}{k+T}$	CD8+T cell recruitment term	[26]
	$-qLT$	CD8+T cell inactivation term	[26]
	$r_1^{'}N$	Cell killed due to recruitment	[5]
	$-k_L(1-\exp(-M)L$	CD8+T cells killed due to chemotherapy	[26]
	$V_L(t)$	Treatment intervention of CD8+T drug	[5]
3.4	$\frac{dC}{dt}$	Rate of change of circulating lymphocytes	[20]
	$-k_C(1-\exp(-M)C$	circulating lymphocytes cells killed due to chemotherapy	[26]
3.5	$\frac{dm}{dt}$	Rate of change of IL-21 dose dependent product	[20]
	αI_{21}	IL-21 clearance factor	[20]
	μ_2	Decay rate of IL-21 dose dependent product	[20]
3.6	$\frac{dp}{dt}$	Rate of change of mediator of the NK cell/CD8+T cell	[6]
	$\frac{b_1I}{b_2+I}$	Tumor lysis due to cytotoxic protein effectors	[20]
	$-\mu_3p$	Mediators decay	[20]
3.7	$\frac{dI_{21}}{dt}$	Rate of change of IL-21 dose	[20]
	hn	Genetically engineered tumor cells	[20]
	$-\mu_1I_{21}$	Decay of IL-21 drug after intervention	[20]
3.8	$\frac{dM}{dt}$	Rate of change of chemotherapy	[26]
	$-\gamma M$	Decay or elimination of chemotherapy drug	[26]
	$V_M(t)$	Chemotherapy drug intervention	[26]

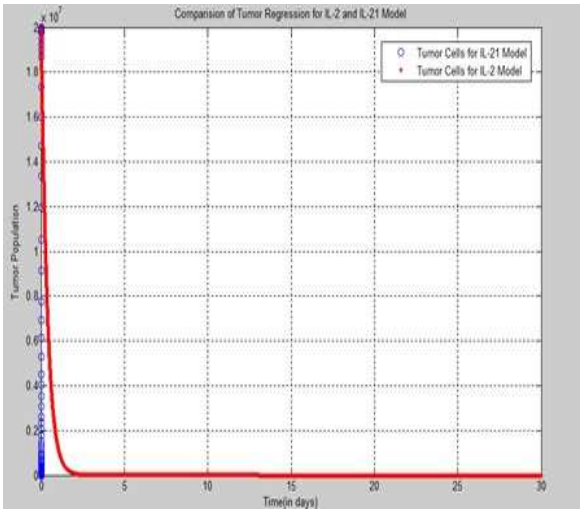

FIGURE 2. Comparison of Tumor cells reduction for IL-2 (red dotted line) and IL-21(Blue circled line) models.

Table-3: Parametric values used in IL-21 Model					
Parameters	Values	Source	Parameters	Values	Source
r_3	0.48	[6]	D	$0.91 \times 10^(3)$	[6]
w	1.5	[6]	j	$2.49 \times 10^(-2)$	[2]
k_1	$2.6 \times 10^(6) or 6.2 \times 10^(5)$	[20]	$j^{'}$	$3.36 \times 10^(-9)$	[2]
k_2	$2.0 \times 10^(-3) or 1.2 \times 10^(-3)$	[20]	$k^{'}$	$1.8 \times 10^(-8)$	[2]
p	$3.42 \times 10^(-6)$	[6]	r_2	0.26	[6]
r_1	0.095	[6]	p_I	$1.25 \times 10^(-1)$	[6]
$r_{1}^{'}$	$1.10 \times 10^(-7)$	[2]	g_I	$2.00 \times 10^(2)$	[2]
μ_1	10	[6]	a	0.57	[6]
p_1	0.01	[6]	μ_2	0.014	[6]
p_2	1.05	[6]	b_1	0.1	[6]
q_1	0.54	[6]	b_2	0.1	[6]
p_N	$6.68 \times 10^(-2)$	[2]	μ_3	0.08	[6]
g_N	$2.5036 \times 10^(5)$	[2]	h	$6.34 \times 10^(2)$	[20]
r_2	0.26	[6]	γ	$9.00 \times 10^(-1)$	[2]
$h_2(0)$	0.066	[6]	μ_I	10	[2]
σ	0.0071	[6]	g	1.7	[2]

7. Discussion and Analysis

For analysis we consider our model in the absence of treatment [5] i.e. we delete chemotherapy, immunotherapy and external concentration from IL-21 model. After this modification model becomes

$$\dot{T(t)} = r_3 T(1-(T/K)^w) - k_1 pNT - k_2 pLT \tag{7. 16}$$

$$\dot{N(t)} = eC - r_1 N - pNT \tag{7. 17}$$

$$\dot{L(t)} = r_2 L(1 - \frac{L}{h_2(0) + \frac{\sigma m}{1+(\frac{m}{D})}}) + \frac{jTL}{k+T} - qLT + (r_1^{'} N + r_3 C)T \tag{7. 18}$$

$$\dot{C(t)} = \alpha - \beta C \tag{7. 19}$$

For equilibria, setting all the equations simultaneously equal to zero [5]. Then the above models implies

$$0 = r_3 T(1-(T/K)^w) - k_1 pNT - k_2 pLT \tag{7. 20}$$

$$0 = eC - r_1 N - pNT \tag{7. 21}$$

$$0 = r_2 L\left[1 - \frac{L}{h_2(0) + \frac{\sigma m}{1+(\frac{m}{D})}}\right] + \frac{jTL}{k+T} - qLT + (r_1^{'} N + r_3 C)T \tag{7. 22}$$

$$0 = \alpha - \beta C \tag{7. 23}$$

Equilibria are found by solving equations (7.20)-(7.23) simultaneously. Solving equation (7.21) for N, we get

$$N = \frac{eC}{r_1 + pT} \tag{7. 24}$$

Solving equation (7.20) for Land substituting the value of N from equation (7.24).

$$L_1 = \frac{1}{pk_2}\left[r_3(T(1-(\frac{T}{K})^w) + \frac{k_1 peC}{r_1 + pT}\right] \tag{7. 25}$$

Solving equation (7.22) for L, and substituting the value of N from equation (7.24), we get

$$L_2^2 + \left[qT - \frac{jTL}{k+T} - r_2\right]\left[\frac{h_2(0) + \frac{\sigma m}{1+(\frac{m}{D})}}{r_2}\right] L_4 - r_1^{'} T\left[\frac{eC}{r_1 + pT}\right]\left[\frac{h_2(0) + \frac{\sigma m}{1+(\frac{m}{D})}}{r_2}\right] = 0 \tag{7. 26}$$

Which is quadratic in L. The intersection of equations (7.25) and (7.26) will give the equilibrium points. Tumor is considered to be consisting of homogenous spherical shape in which tumor cells grow according to scale law i.e. number of tumor cells n is proportional to $z^(3/2)$ [20]. It is usually measured by calculating the perpendicular diameters and multiplying them using digital caliper in the form of mm2 [30]. In order to eradicate such

type of tumors we use different types of external drugs to strengthen the immune system to fight against cancer. The impact of variety of cytokines on tumor-immune interactions cultured with chemo-immunotherapy is used extensively in modern era. For such purposes, the impact of IL-21 or IL-2 on tumor size can produce constructive results for tumor eradication. However the impact of IL-21 may be more dominant than IL-2. Our major focus will be to compare the tumor dynamics because we are interested to eradicate the tumor by utilizing different cytokines. When we put the values of constants in the equations (3.1) and (3.9). They imply

$aT(1-bT) - cNT - DT - k_T(1-\exp(-M)T < r_3T(1-(T/K)^w) - k_1pNT - k_2pLT - k_T(1-\exp(-M)T$

Chemotherapeutic effect on both dynamics has same effect and by substituting other constants and neglecting other very small terms. L.H.S is approximately 0.031 times of T but on R.H.S we get 0.45 times of T. Which shows that the IL-21 causes more eradication of tumor as compared to the IL-2. This theoretical interpretation shows that IL-21 proved to be more effective for controlling tumor progression as compared to IL-2. Further if we compare the CD8+T cells dynamics we reach at the result that under the impact of IL-21, CD8+T cells are produced more than the IL-2 influenced CD8+T cells. Similarly we can investigate the influence of IL-21 and IL-2 on other cellular dynamics. For tumor dynamics we can take initial tumor burden of 2×10^7 cells and initially healthy immune system with 2.5×10^8 NK cells, 5.268×10^5 CD8+T cells and 2.25×10^9 circulating lymphocytes. We are interested only in the comparison of tumor regression under the impact of cytokines IL-21 and IL-2. IL-21 cytokine therapy may prove to be more important strategic component for effector tumor immunotherapy than IL-2 cytokine therapy. Now we prove our theoretical hypothesis through experiments. We simulate both IL-2 influenced and IL-21 affected models using MATLAB. Simulations show that our developed model reduce tumor cells earlier than IL-2 influenced model. Thus IL-21 possesses better tumor reduction efficiency than IL-2 which confirms our theoretical interpretations. The saturation factor $k_T(1-\exp(-M)T$ represents the tumor cell death due to concentration of chemotherapeutic drug effect. Low concentration of chemotherapy results in linear drug response while at higher concentration death rate becomes independent of the term M. Increment in the IL-2 concentration also causes to grow the CTL cells and when the concentration decrease the CTL population also decreases. Ultimately contribute to eradicate tumor cells. In fact IL-2 treatment is less toxic. IL-21 and IL-2 also have opposite effects on the differentiation of the CD8+T cells. IL-21 reduces the NK cell population and potently enhances the magnitude and antitumor efficacy of CD8+T cells. IL-2 induces the tumor killing lymphocytes in cancer patients. De Pillis in [26, 27, 28] used the CD8+T cell-induced tumor death by the term -DT where D is given by equation (7.15). In this expression de Pilli used constants d,l and s constants for good fitting of his curves with experimental data. However for simulation purposes this term may be taken as -LT expression for simplicity. We have constructed our model by incorporating the latest research based on CD8+T and NK cells concentrations in cancer patients. Effective immunotherapy in conjunction with chemotherapy is highly dependent on aid of CD8+T cells taken from the peripheral blood. NK cells and CD8+T cells also expected to reduce in lesser quantity. Tumor progression

is affected by CD8+T cells having affinity $k_1.CD8 + T$ cells are more dominant in intensified immunogenic tumors. NK cells may contribute to aid CD8+T cells through indirect mechanism. IL-21 demonstrates therapeutic promise for antitumor activity. In the recent era bio mathematical models are being used as effective tool for cancer treatment strategies where our formulated model and its implications may pave the way for its clinical recommendations because simulations of IL-2 affected model and IL-21 affected model confirms our theoretical interpretation.

7.1. **Remarks.** Our simulations reveals that IL-2 is able to kill tumor cells in 2-3 days and IL-21 can kill within ours. Our objective was to investigate which interleukin among IL-2 and IL-21 reduces more tumor cells. Although simulations of models meet our objective that IL-21 is more efficient than IL-2 for tumor regression yet these simulation carry some reservation that it may not fully agree with biological interpretations or clinical data because we have taken arbitrary scales and initial burden of tumor cells, immune system and external doses. Therefore by taking exact clinical data these simulation may need some minor modifications in order to agree with exact data.

8. Conclusion

We have developed a new mathematical model for tumor regression by incorporating cellular population and chemo-immunotherapy under the impact of IL-21. We have compared the dynamics involved in our model to that with de Pilli's model under the impact of IL-2 from theoretical perspective. Our analysis shows that our developed model is more effective as compared to the de Pilli's model for better tumor regression. This supports the active utilization of IL-21 as compared to IL-2 to maintain high number of antitumor CD8+T cells to sustain long term tumor regression activity. In short the analysis of our study suggests that IL-21 cytokine may play a major role to eradicate the tumor by providing an important strategy for effective cancer immunotherapy. We have also simulated our model for validation of theoretical interpretations and making comparison with IL-2 influenced de Pilli's model. Our experimental results agree with theoretical interpretation that IL-21 is more efficient for tumor reduction than IL-2. In future IL-21 may be used as combination therapy with other cytokines to eliminate tumor and the study of interaction of tumor cells and CD8+T cells will also be the active research topics in the near future. .

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10. Conflict of Interest

Both the authors have no conflict of interest to disclose.

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