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Modeling the Tumor-Immune Interaction Cultured with Chemotherapy and Cytokine Interleukin IL-2 Under the Influence of Immunodeficiency Viruses

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Abstract: The human immunodeficiency virus (HIV) is lentivirus hat causes the acquired immunodeficiency syndrome (AIDS). In this paper we have model the impact of this immunodeficiency virus on the cellular population of tumor-immune interaction cultured with chemotherapy and interleukin IL-2. This model comprises of six ordinary coupled differential equations. The study focused on the investigation of tumor regression efficiency under this immunodeficiency virsus. Theoretical interpretations show that the newly developed model has potential to reduce tumor. This model carries the theoretical interpretations and numerical justification is left for future. Finally we have given some future directions.

Key words: Effector Cells · Immunotherapy · Interleukin IL-2 · Chemotherapy · Cancer Model

INTRODUCTION

Cancer arises due to uncontrolled growth of abnormal cells in the body [1- 4]. It is also termed as malignant tumor with mass of tissue formed due proliferation of uncoordinated, autonomous and purposeless cells [5]. Dvorak said “It might be a wound that never heals” [6]. According to World Health Organization p
cancer kills about six million people every year [5, 7]. Tumors escape natural host immunity by the process known as cancer immune editing [8]. Tumor size increases due to up regulation of the cell division among malignant cells [9]. Its main causes are exposure to chemicals, excess alcohol drinking, excessive sunlight exposure and genetic differences [2].Cancer research has undergone radical changes in the last few decades [6]. It is most difficult disease to treat clinically and become main cause of death in developed western societies [10].

It is multi-faceted disease that involves complex interaction of neoplastic cells and surrounding environment [11].Among the current approaches of its treatment are surgery, radiotherapy, hormone therapy, chemotherapy (discovered in chemical warfare during World War I and firstly used to treat cancer in 1940s [12) and immunotherapy. The researches focus on the immunotherapy prominently because other treatment techniques carry the side effects on the normal cells of the body [3, 10, 13]. However chemo- immunotherapy enhances tumor regression and antitumor immune response [14]. Immunotherapy strengthens the body’s own natural system to fight against cancer [15]. It has emerged as a novel approach to treat cancer [16, 17]. It refers to the utilization of cytokines along with adoptive cellular immunotherapy [18]. Cytokines are used in immunotherapy against cancer with anti-tumor immune responses [19] and have pleiotropic effects on tumor cells [20]. Apparantly vaccines, monoclonal antibodies, lymphocytes and cytokines are main targets for tumor immunology [21].Treatment of tumor depends on many factors like severity of disease, treatment technique and strength of patient’s immune system [22, 23]. Immune system attacks an immunogenic tumor by the mechanism known as cell mediated cytotoxicity where the effector cells involved in anti-tumor immune response are macrophages having innate immunity cells and NK cells having adaptive immunity cells [24].

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Immune system is capable to recognize and kill tumor cells and is fundamental to understand the tumor growth and its decay [25, 26].Immunotherapeutic approaches enhance the immune response to kill tumors [27].Tumor antigens are presented on MHC (Major Histocompatibility Complex). T cells and NK cells destroy the tumor cells but when the immune system is weak enough then they required stimulations which are provided by external interventions like Cytokines IL-2 [5]. Cytokine Interleukin IL-2 is produced naturally from $CD4^+$ T cells which are responsible for lymphocyte activation, growth and differentiation [18, 11]. IL-2 is T cells derived cytokine which has antagonistic effects [28]. It is four bundle α-helical cytokine [29]. It is heterodimeric proinflammatory cytokine [30]. It delays tumor progression [31]. The $CD8^+$T cells are classified into Th1 and Th2 cells where Th1 cells mainly secrete cytokine interleukin IL-2 [32].$CD4^+$T cells based IL-2 proliferate the effector cells [5]. It proliferate NK cells and causes self-regulation of $CD8^+$T cells [25]. NK cells (part of the immune system) kill target cells within a few minutes after first stimulation where $CD8^+$T cells(part of the adaptive immune system) kill multiple target cells after TCR activation [33, 34]. IL-2 activated $CD8^+$ T cells lyses tumor targets [35]. Effector cells are activated immune system cells like T cells, NK cells and macrophages. They are cytotoxic to the tumor cells [18]. T cells mediate immune response against tumor [17]. When the tumor cells increases it interact with the neighboring cells like normal cells, immune cells or therapeutic agents. Biochemical and mechanical interactions show that tumor cells and normal cells are co-dependent [36]. Immune system's cells produce coordination and robust to target antigen through molecular messengers known as cytokines [37].

The human immunodeficiency virus (HIV) being lentivirus causes the acquired immunodeficiency syndrome (AIDS) [38, 39]. It historically dates back to 1981, identified as result of homosexual men first described in Los Angeles and New York. The patients were identified with apparent decrement of CD4 cells being an important part of the immune system. Later this disease was found throughout the United States, Western Europe and Africa. In 1983, researchers in the United States and France described the virus HIV that causes AIDS, belonging to the group of viruses called retroviruses. While HIV infection develop AIDS, complications of HIV infection ranging from a variety of opportunistic infections, cancers, neurologic symptoms and wasting syndromes [40]. Human Immunodeficiency Virus (HIV) is a virus that attacks the body's natural defense system and both the virus and the infection it causes are called HIV. If the immune system is week then body faces much difficulty in fighting against this virus [41].Endogenous human immunodeficient virsus possesses soluble-mediated suppression. Active human immunodeficient virsus have multifaceted deleterious effects on immune system. Virsus has negative impact human immunodeficient virsus specific cellular and humoral immune responses [42]. They devlop a number of malignancies like Kaposi's sarcoma and non-Hodgkin's Lymphoma [43]. Human immunodeficient virsus type-1(HIV-1) is casual agent of AIDS [44] and posseses several regulatory genes.

The role of quantitative and predictive mathematical modeling is increasing rapidly [10]. Mathematical models are becoming instrumental in planning treatment strategies and give deep insight in understanding complex biological processes [45, 46]. Mathematical models link experimental to computational biology [12].They have played an active role in providing non-intuitive insights into tumor growth and progression [47]. Cancer modeling is typical divided into two phases, the first is to have a concept of system without treatment and the second is its treatment in descriptive form [48].With every day passing new features and developments of new methods are becoming large [36]. Many clinicians and experimentalists have enough research on immune systems response to the cancer from mathematical perspective [10].Historically, De Boer was the first to model the anti-tumor immune response under the impact of exogenous IL-2 in the form of system of ordinary differential equations[49, 50]. Then Kirschner and Panetta model such cellular interactions by considering both endogenous IL-2 and exogenous IL-2 [50, 51]. Later L. G. de Pillis and colleagues formulated their model cultured with chemo-immunotherapy and under the impact of exogenous IL-2 and also with naturally produced endogenous IL-2 [15, 52]. Then Antono Cappuccio and colleagues in [53] model the tumor-immune interaction under the influence of newly discovered cytokine interlukin-21 but they did not consider the chemotherapeutic effects on their model. Then in 2013 Mustafa Mamat extended the de Pillis model by including Interferon-α (IFN-α) to enhance the tumor regression efficiency [1]. We have developed a new mathematical model for tumor regression by incorporating the Effector cell population, Tumor cell population,

Normal cells and Interleukin IL-2 under the impact of immunodeficiency viruses. The objective of this study is to investigate the role of immunodefficiency viruses on tumor reduction model. Our developed model may enhance the tumor regression efficiency and interpreted this model theoretically. This model needs experimental verification which is devoted to future work.

MATERIALS AND METHODS

This model comprises of six ordinary coupled differential equations formulating the immune response to the tumor growth under some treatments and external interventions. Model is based on some biological assumptions given below.

Model Assumptions:

- A tumor grows logistically in the absence of immune response [1, 15, 52, 54, 61].
- Both NK cells and CD8+T cells can kill tumor cells [1, 15, 54].
- Both Endogenous IL-2 (naturally produced) and ExogenousIL-2 (external intervention) are considered in this model [15, 52].
- Natural Killer (NK) cells being part of the immune system are always present even no tumor cells exist [1, 15, 54].
- Active tumor specific cells as being part of the immune system are present only when tumor cells are present [1, 15, 54].
- Each of the NK and CD8+T cells become inactive after some number of encounters with the tumor cells [1, 15, 54].
- Despite the activated CD8+T cells and NK cells, the action of all other lymphocytes including circulating lymphocytes C(t), has been neglected [52].
- 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 [53].
- NK and CD8+T cells respond with tumor cells by expanding and increasing metabolic and catalytic activity [1, 15, 54].
- 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 [1].
- Chemotherapy also kills some fraction of the NK cells and CD8+T cells [1].
- Immune system possesses self-regulatory nature because activated effector cell NK and CD8+T cells from the cyclic process of stimulation and decay [1].

Model Populations: Our model carries the following state variables for each cellular populations involved in the model.

- $T(t)$ Tumor cell population
- $N(t)$ Natural Killer cell (NK cell) population
- $E(t)$ Effector cell population
- $V(t)$ Immunodeficiency Viruses
- $M(t)$ Chemotherapy concentration drug
- $I(t)$ Interleukin IL-2

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 [52]. The function and interaction of cell populations with drug concentrations are depicted in schematic diagram Fig.1.

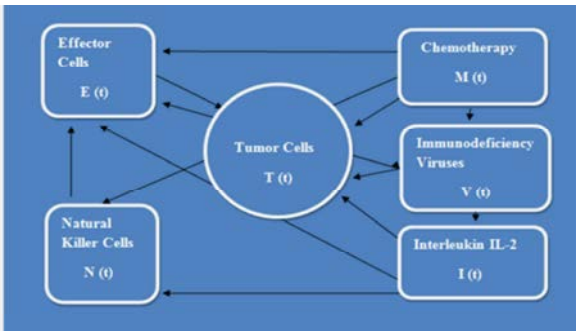

Fig. 1: Schematic diagram showing the interaction among the cellular populations of the Tumor cells, Natural Killer cells and Effector cells cultured with chemo-immunotherapy and Interleukin IL-2 under the impact of Immunodeficiency Viruses.

RESULTS

The above discussion can be formulated in the form of two generalized equations (A-1) and (B-1) [54].

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).

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

Mathematical Model:

$$(1)\quad \frac{dT}{dt} = r_1 T(1-bT) - \frac{aET}{g_2+T} - k_T\left(1-e^{-\xi M}\right)T$$

$$(2)\quad \frac{dN}{dt} = r_2 N(1-eN) + kT\left(1-\frac{T}{T^c}\right) - k_N\left(1-e^{-\xi M}\right)N$$

$$(3)\quad \frac{dE}{dt} = cT - \mu_1 E + \frac{p_1 EI}{g_1+I} - \alpha VE - k_E\left(1-e^{-\xi M}\right)E$$

$$(4)\quad \frac{dI}{dt} = \frac{p_2 TE}{g_2+T} - \mu_2 I$$

$$(5)\quad \frac{dV}{dt} = \frac{fV}{h+V} - \beta VE - \mu_3 V$$

$$(6)\quad \frac{dM}{dt} = -\gamma M + V_M(t)$$

The values of the parameters used in our model are given in Table 1.

Justification of Model Dynamics: Now we justify the dynamics involved in our developed model.

Tumor Cell Dynamics (1): First term on R. H. S. $r_1T(1-bT)$ follow the Logistic G rowth Law [9, 46]. The tumor cells independently grow according to this law. Here r_1 is proliferation rate. The interaction between tumor cells and immune system is given by Michalelis-Menten interaction, $\frac{aET}{g_2+T}$ where α is rate of clearance of tumor cell and g^2 is half saturation of cancer clearance. The last term in this dynamics is $k_T(1-e^{-\xi M})T$ which gives the chemotherapeutic effect on tumor cells. Where ξ =1 (usually) for good fitting of experimental data. Thus following the equation (A-1) rate of change of tumor dynamics $\frac{dT}{dt}$ equals to the Kirschner dynamics.

Natural Killer (NK) Cell Dynamics (2): Here $r_2N(1-eN)$ is natural growth of NK cells under Logistic Growth Law. T^c is Interaction rate of tumor- normal cells or coupling constant. $T>T^c$ is critical number of tumor cells and if the tumor cells increase their ability to inhibit normal cell growthand the last term of this equation $-k_N(1-e^{-M})N$ gives the NK cell death by chemotherapy. Thus the sum of self-g rowth, decay rates and inactivation terms constitute the net growth of NK cells.

Table 1: Parametric values used in model

Parameter	Description	Values	Source
r_1	Tumor growth rate	0.18	[5]
b	Carrying capacity of tumor	1×10^{-9}	[5]
a	Tumor cell strength	1	[5]
g_2	Half saturation constant	1×10^{5}	[5]
k_T	Tumor cell decay by chemotherapy	0.9	[5]
r_2	Growth rate for the normal cells	0.4	[36]
e	Carrying capacity of normal cells	1×10^{-6}	[36]
k	Interaction rate of tumor normal cells	0-0.028	[36]
k_N	Carrying capacity of normal cells	10^{6}	[36]
c	Antigen city of tumor	0-0.035	[5]
μ_1	Effectors cell growth rate	0.03	[5]
p_1	Proliferation rate of effectors cells	0.1245	[5]
g_1	Half saturation constant	2×10^{7}	[5]
α	Effectors cell virus interaction rate	2.5×10^{-4}	[5]
k_E	Effectors cell decay by chemotherapy	0.6	[5]
p_2	Production rate of effectors molecule	5	[36]
g_2	Half saturation production constant	30 10^{3}	[36] [5]
μ_2	Decay rate of IL-2	10	[5]
f	Production rate of viruses	3×10^{4}	[36]
h	Half saturation of virus population	5	[36]
β	Virus effectors cell interaction rate	0.005	[36]
μ_3	Death rate of viruses	0.03	[36]
ξ	Pharmacokinetics parameter	1	[36]
γ	Decay rate of chemotherapy	6.4	[5]

Effector Cell Dynamics (3): Here C is antigenicity, μ_1 is death rate of im mune cells. $\mu_1 E$ represents natural death of effector cells. Effector cells includes T cells and other immune cells which are cytotoxic to tumor cells. The decay to tumor cells due to effector cells is model as Michaelson Menten interaction $\frac{p_1 EI}{g_1 + I}$ which is activation due to IL-2 harmones. Here p_1 is proliferation rate of immune cells and g_1 is half saturation for proliferation term. $-\alpha VE$ model the effector cell virsus interaction at rate α. The last term $k_E(1 - e^{-\gamma t})E$ represents the impact of chemotherapy on the effector cells.

IL-2 dynamics (4): In our model we are considering both endogenous and exogenous IL-2. The decay rate of IL-2 is given by $-\mu_I I$ and $\frac{p_2 TE}{g_2 + T}$ represents IL-2 c oncentartion which is only activated when tumor is present. The IL-2 drug intervention is represented by $V_I(t)$.

Immunodeficience Virsus Dynamics (5): The production sources of virsus is formulated to $\frac{fV}{h + V}$ [55, 56] where f is production rate and h is saturation term. $-\mu_2 V$ is natural death of virsus at the rate of μ_2.The interaction between virsus and tumor cells which is model as $-\beta VE$. Where β is virsus-effector cells interaction rate. As the result of this interaction immune-effector cells decreases the population of virsus. Both populations have been decreased with different rates as the result of this interaction.

Chemotherapeutic Dynamics (6): Here $V_M(t)$ is injected chemotherapeutic drug and☻represents decay or elimination of chemotherapy drug after concentration [1].

RESULTS AND DISCUSSION

Due to presence of tumor cells concentration of effector cells and IL-2 is increased due to interaction b/w tumor and NK cells with effector cells. The population of tumor cells decreases and normal cells increases. Chemotherapeutic agent kill the tumor cells along with normal and effector cells but the killing rate of tumor cells is higher as compared to other normal cells of immune system. As the tumor cells decreased, effector cells and IL-2 concentration also decreased. As the population of the tumor cells decreases, both tumor cells and normal cells state to oscillate and their equilibrium during the chemotherapeutic interaction and amplitude of oscillate increases until it reaches a steady state. In this way for small amplitude their size decreases significantly.

In order to control the size of tumor cells. Either we must need a significant larger immunotherapeutic agent or the level of chemotherapeutic agent with some immunotherapeutic agent should increase in absence of immunodeficient virsus but toxicity of chemotherapy weakens the immune system which leads to patient death. Immunodeficient virsus on immune system which directly affected the behavior of tumor and immune cells and its component.

NK cells are also capable to control immuondeficient virsus replication. NK cells play a vital role for host innate immunity to immunodeficient virsus. Regarding human immunodeficient virsus, NK cells non-specifically maintain the antiviral activity [42]. CD8+T cells play an active role to overcome the human immunodeficient virsus infected people and are potent to control human immunodeficient virsus replication. NK cells and CD8+T cells both may suppress human immunodeficient virsus replication. but NK cells play important role in protection against both infection and progression of human immunodeficient virsus.

White blood cells are vital component of the immune system. Human immunodeficient virsus infects and destroys certain CD4+ cells being part of these white blood cells. Great number of setruction of CD4+ cells results in the body that it can no longer defend itself against infection. The studies show that the immunodefcient virsus in retroviral therapy (HAART) has less survival chances in lung cancer. Individual affected by human immunodeficient virsus have poor outcomes. Dr. Ramalingam in [57] states that *"There is clear need to study the tolerability and efficiency of commonly used anticancer agents in the human immunodeficient virsus patient population"*. Dr. Ramalingam also says *"There are significance biological differences between human immunodeficient virsus - infected and non-infected human immunodeficient virsus lung cancer patient population"*.

Usually chemotherapy was used in human immunodeficient virsus epidemic but it produces detriemental effects that ultimately have detrimental effects on tumor response produces poor outcomes. Human immunodeficient virsus are usually induced by cytokines for example it is induced by monocyte derived cytokines (TNF-α). Cytokines may also play an acute role in the mechanism of pathogenesis of human immunodeficient virsus infection [58]. Human immunodeficient virsus requires interaction b/w components of virsus and CD4 on plasma membrane of

target cells [59]. Human immunodeficient virsus may results in severe abnormalities including dementia, ataxia and memory loss [60].

The main focus here is to develop mathematical model of tumor-immune interaction cultured with chemotherapy under external intervention. We have also interpreted and discussed this model theoretically however after simulation of this model and can interpret it on some technical basis but left the simulation to future work.

CONCLUSION

This study developed a new mathematical model describing the tumor-immne interaction cultured with chemotherapy and cytokine interlukin IL-2 under the influence of immunodeficient virsus was devolped. This model focused on the investigation of tumor regression under the influence of external immunodeficeint virsus mathematical model describing the tumor-immne interaction cultured with chemotherapy and cytokine i-nterlukin IL-2 under the influence of immunodeficient virsus. Theoretcal interpretions show that this model may give better tumor regression efficiency and left the numerical verification to future work. Among the future research may be to investgate the impact of immunotherapeutic agent on this tumor-immune mathematical model for tumor reduction.

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